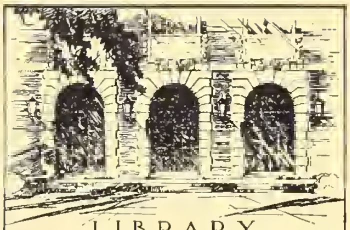

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SEMINAR TOPICS

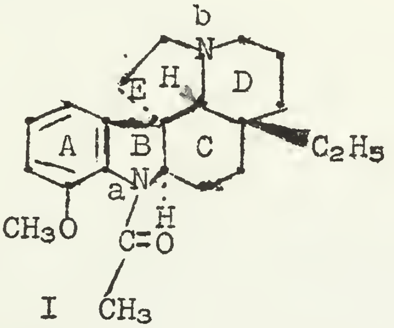
I Semester 1960-1961

STRUCTURE OF ASPIDOSPERMINE

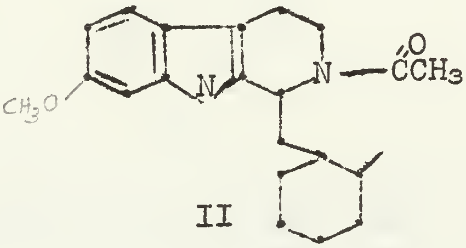
Reported by D. B. Borders September 22, 1960

Introduction

Structure studies on the alkaloid aspidospermine (I) have involved many techniques other than classical degradative studies. The classical methods were frequently hampered by the fact that the degradative products were complex or inseparable mixtures. Finally, in order to obtain an unequivocal structure proof, X-ray analysis was used.



I



II

Aspidospermine is a member of the quebrancho alkaloid family (1). It was first isolated by Fraude in 1878 from the bark of aspidosperma quebrancho (2,3,4). It has also been isolated from the leaves of Vallesia glabra and the bark of aspidosperma australe (5,6,7). The alkaloid has only a few relatively unimportant physiological effects (8). Bark extracts have been used, however, as a respiratory stimulant for asthma.

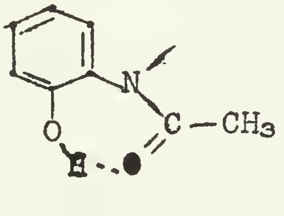
Nature of Functional Groups and Dihydroindole Nucleus

The first structural work on aspidospermine was reported in 1914 by Ewins (9). He found that the alkaloid contained an N-acetyl group and an aromatic methoxy group. In 1934 Scholtz postulated structure II based on the limited findings of Ewins and the fact that the alkaloid occurred in nature with yohimbine which contains an indole nucleus (10). Later studies involving comparisons of the ultra violet spectra of aspidospermine to those of other alkaloids suggested a closer relation to some derivative of N-acetyltetrahydronorharman (11).

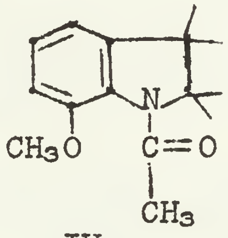
Attempts to isolate indole or its derivatives by zinc dust distillation were not very successful. The product was a mixture which could not be separated by crystallization but its infrared spectrumdisplayed bands expected of an indole (12). However, aspidospermine and its deacetylated derivative (obtained from acid hydrolysis) gave no typical indole color reactions. It was also known that neither aspidospermine nor deacetylaspdiospermine absorbed hydrogen in the presence of platinum as would be expected of an indole derivative (13).

The ultraviolet spectra of aspidospermine and deacetylaspidospermine were considerably different indicating that the acetylated nitrogen was probably attached directly to the aromatic ring (13). Additional support for this concept was obtained from electrometric titrations of deacetylaspidospermine. The dissociation constants for the two nitrogens showed one to be a rather strong base

(K_b 10^{-6}) and the other a weak base (K_a 10^{-11}) as expected for a nitrogen attached to an aromatic ring. Aspidospermine can be demethylated to obtain a phenolic derivative which displays no N-H or O-H stretching bands in the infrared (14). This phenomenon can be explained in terms of phenolic hydroxyl group being ortho to the N-acetyl group. The hydrogen bonding between the two groups as indicated in structure III would explain the missing hydroxyl absorption. The evidence mentioned thus far suggests a 7-methoxydihydroindole structure IV.

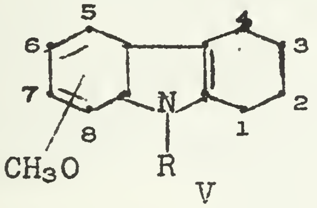


III

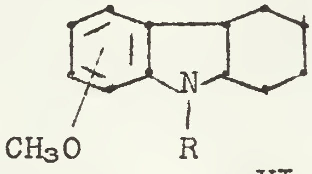


IV

Further confirmation of this structural unit was obtained by comparison to ultraviolet spectra of model compounds. A comparison of spectra of aspidospermine and deacetylaspidospermine to the tetra- and hexahydrocarbazoles, acetylated and non-acetylated (structures V and VI where R = -H or $-\overset{O}{C}CH_3$), showed the 8-methoxy-



V

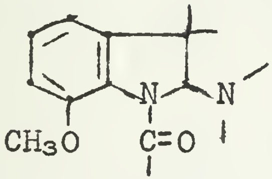


VI

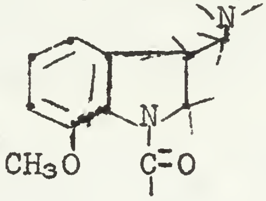
hexahydrocarbazole, acetylated and non-acetylated, to have an ultraviolet chromophore almost identical to the corresponding aspidospermine and deacetylaspidospermine. This observation was especially significant since the 5-, 6-, 7- and 8-methoxy- substituted hexahydrocarbazoles displayed ultraviolet absorption curves that were significantly different (15,17).

<u>Relationship of the Nitrogens</u>

The nitrogens of aspidospermine were originally thought to be involved in an eserine type of structure VII. Benzoylation of the related deformylvallesine* was reported to yield a neutral substance in addition to the expected benzoyldeformylvallesine (16).



VII



VIII

The neutral compound was thought to result from an eserine ring cleavage. However, the neutral compound from the aspidospermine

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*Deformylvallesine and deacetylaspidospermine have identical melting points, $[\alpha]_D^{23}$, infrared spectra, and Röntgen powder diagrams. This is also true for their acetyl- and formyl- derivatives, however, elementary analysis shows these compounds and their derivatives to differ by a CH_2 unit (16.5).

reaction was later found to be the chloroform soluble hydrochloride salt of benzoyldeacetyl-aspidospermine (14).

Further disproof of the eserine type of structure and an insight into the separation of the two nitrogens was obtained by pK_a studies. The increase in basicity observed in conversion of aspdiospermine (pK=7.36) to deacetylaspidospermine (pK=7.30) is too small to substantiate an eserine structure (14). The pK_a difference between the N_a of deacetylaspidospermine and hexahydro-8-methoxycarbazole is about 2.63. This difference can be attributed to a positive charge on the N_b nitrogen of deacetylaspidispermine. A comparison of this pK_a difference with those recorded for diamines $H_2N(CH_2)_nNH_2$ suggests that the N_a and N_b are separated by three carbon atoms as in structure VIII (19).

Also, compounds with the unit N-C-N are sensitive to lithium aluminum hydride reduction but deacetylaspidospermine is stable to this reduction (20). The tertiary nature of N_b was deduced from the relatively strong basic nature of aspidospermine and the fact that it contained no active hydrogens by Zerewitinov's estimations (13). Deacetylaspidospermine and aspidiosine contained one and two active hydrogen atoms respectively.

The initial nuclear magnetic resonance studies on aspidospermine caused considerable confusion as to the nature of the second nitrogen atom. The spectra strongly suggested an $-N-CH_3$ group (τ=7.6*), three $>N-C-H$ groups, and a lack of methylenes adjacent to the nitrogen (21). Support of the $>N-CH_3$ group was obtained by Herzig-Meyer determinations based on the following reaction sequence:

$$>N-CH_3 + HI \dashrightarrow >NCH_3\cdot HI \dashrightarrow >N-H + CH_3I$$

The number of N-methyl groups is estimated from iodometric determination of the amount of methyl iodide formed. In one instance, 94% of the theoretical value for one $>N-CH_3$ group was obtained (21). However, on other runs the values were much lower (9,22). In contrast with these results, aspidospermine did not undergo the expected von Braun degradation to yield methyl bromide (20,21).

Finally, labeling experiments attempting to exchange the N-methyl with a C^{14} labeled methyl group showed that the N-methyl group probably did not exist in aspidospermine (20). The quaternary methyl salt of aspidospermine (at N_b) was prepared using C^{14} labeled methyl iodide. This salt was easily pyrolyzed to aspidospermine. Assuming two equivalent methyl groups on the N_b of the salt, the recovered aspdiospermine should have contained C^{14} if an N-methyl group were present. Only a 3% incorporation of C^{14} was observed and this was attributed to O-methyl exchange.

With the conclusion that the N-methyl group is not present in aspidospermine, it is necessary to account for the NMR spectra and the Herzig-Meyer determinations. The latter can be dismissed on the grounds that other compounds such as yohimbol, a compound known to contain <u>no</u> N-methyls, have given high blank values (23). The NMR spectra probably show methylenes adjacent to nitrogen with atypical τ values (20). The expected splittings for the $N-CH_2$

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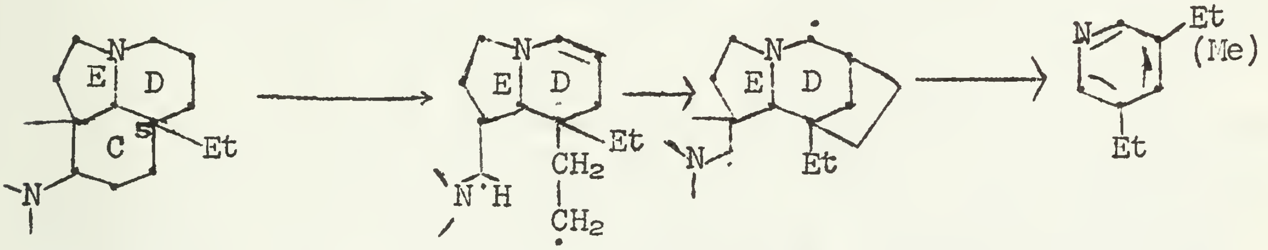
*This value has been estimated from original values given for spectrum run in chloroform with toluene as an external standard.

groups was not observed due to poor resolution.

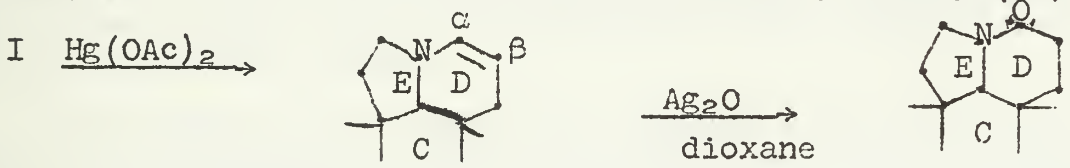
Chemistry of the D and E Rings

Zinc dust distillation studies by Witkop on aspidospermine and deacetylaspidospermine yielded pyridine derivatives in addition to the indoles mentioned before (12). One of the products was quite similar but not identical to 3,5-diethylpyridine as shown by an analysis for $C_9H_{13}N$, melting points of derivatives, and ultraviolet and infrared spectra comparisons. The infrared spectra of the unknown and the 3,5-diethylpyridine showed only minor differences. The picrate of the unknown gave a lower melting point (159° vs. 180-2°) but would not depress that of the 3,5-diethylpyridine. Smith and Wrobel later showed that these results could be explained in terms of a mixture of 3-ethyl-5-methylpyridine and 3,5-diethylpyridine (18). The formation of 3,5-dialkyl substituted pyridines from structure I is difficult to explain but may be a consequence of a 1,3-migration proposed by Smith and Wrobel (18).



In the above scheme, simple aromatization of the D ring is prevented by the quaternary nature of C_5. Consequently elimination or migration of the blocking group at C_5 is necessary.

Further confirmation of the 6-membered nitrogen-containing D-ring was obtained from oxidation studies by Conroy (24).



IX

X

Aspidospermine was converted into the lactam X by the above sequence of reactions. Reduction of lactam X by lithium aluminum hydride produced N_a- ethyldeacetylaspidospermine* thus showing that structural rearrangement had not occurred. Lactam X was hydrolyzed to the corresponding deacetyl derivative which displayed carbonyl absorption near 1621 $cm.^{-1}$ characteristic of 6-membered ring lactam.

The following sequence of reactions showed that the β- and γ-positions of the D-ring were also not substituted.

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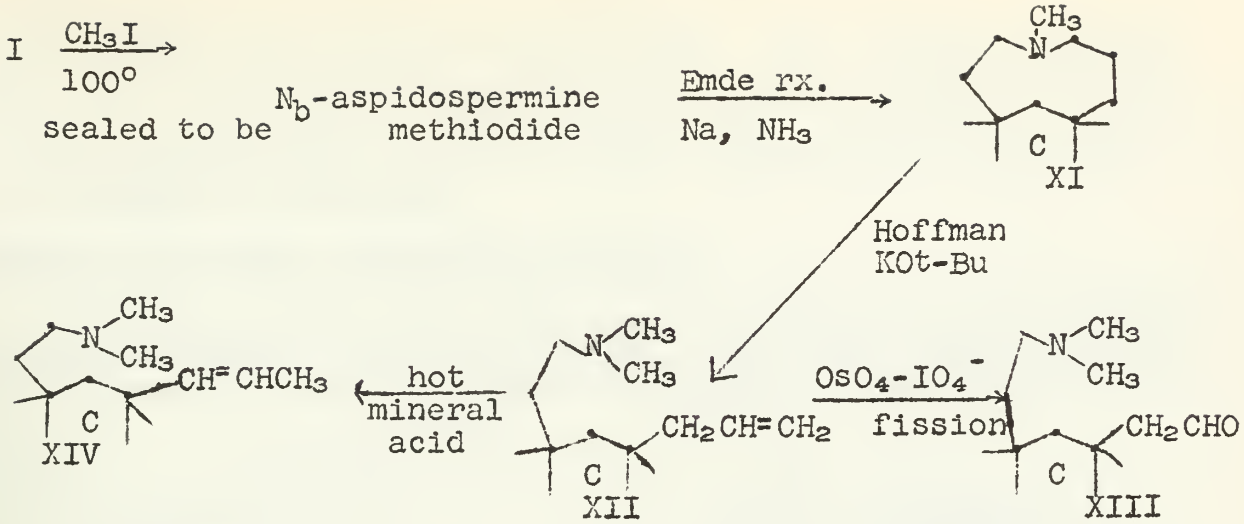
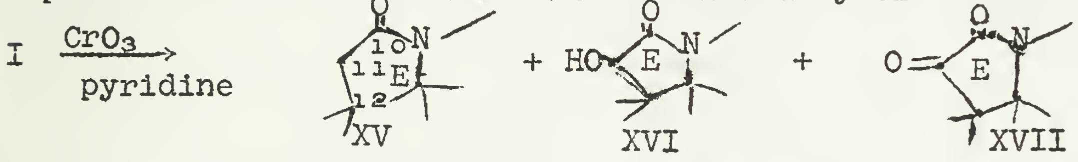
*N_a-ethyldeacetylaspidospermine can be obtained directly from aspidospermine by lithium aluminum hydride reduction (14).



Structure XI was consistent with elemental analysis, nuclear magnetic resonance and infrared spectra, C-methyl determinations (no new C-methyls were detected), and knowledge of the E-ring structure** and the 6-membered nature of the D-ring. The assignment of the direction of the ring opening in the Hoffman reaction to give compound XII was based on the nuclear magnetic resonance spectrum of the compound (the spectrum was more complex than expected for a vinyl group attached to a quaternary center). The structure was also supported by the infrared spectrum and elemental analysis. The aldehyde XIII obtained from the osmium tetraoxide-periodate reaction gave a nuclear magnetic resonance spectrum expected for a compound having a methylene group adjacent to an aldehyde grouping. The aldehyde proton was at τ=0.17 and was split into a symmetrical triplet with J=2.9 cycles per second. The isomerization of olefin XII to structure XIV -- identified by elemental analysis, nuclear magnetic resonance spectra, and infrared spectra -- and not further to a trisubstituted olefin suggests the position of the quaternary center.

The nature of the E-ring was studied by chromic oxide oxidations of aspidospermine (24). The products from the reaction were separated on florisil and then identified by elemental analysis,



nuclear magnetic resonance spectra, and infrared spectra. The products were also interrelated by conversion of XVI to XV and XVII to an epimer of XVI. Reduction of lactam XV with lithium aluminum hydride yield N_a-ethyldeacetylaspidospermine showing that skeletal rearrangement had not occurred in the course of oxidation. The infrared spectrum of lactam XV showed an infrared absorption band at 1680 cm.$^{-1}$ indicative of the carbonyl of a 5-membered ring lactam. In addition, lactam XVII showed carbonyl absorptions in the infrared at 1721 cm.$^{-1}$ and 1770 cm.$^{-1}$ which are very typical for α-keto-γ-lactams. The nuclear magnetic resonance spectrum of lactam XV showed a well resolved 2-proton nonequivalence quartet centered at τ=7.63 with J=16.2 cps which is absent in

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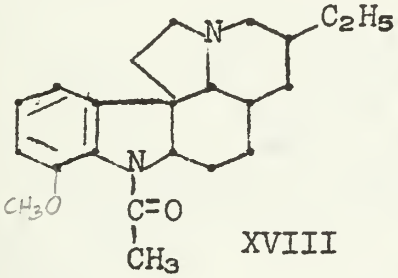
**See next paragraph.

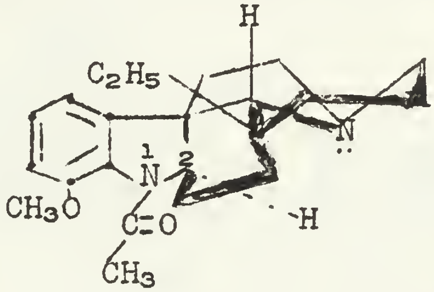
aspidospermine and lactams XVI and XVII. This effect was attributed to -CH$_2$- adjacent to the carbonyl. The 11-hydroxy-lactam XVI showed the expected singlet for one proton at $\tau=4.90$ due to the methine hydrogen of the 11-carbon atom. From these observations it was concluded that the E-ring was 5-membered and contained the $\rangle N\text{-}CH_2CH_2\text{-}\overset{|}{\underset{|}{C}}\text{-}$ grouping.

Complete Structure and Stereochemistry

Previous to the X-ray study, one of the structures proposed for aspidospermine was XVIII (14,17). This was originally based on evidence for the substituents on the dihydroindole nucleus,



XVIII



XIX

the presumed degradation products of 3-ethylindole and 3,5-diethylpyridine from zinc dust distillations, and C-methyl determinations (13,16). Modification of the C-methyl determination later confirmed the hypothesis that the C-methyl was actually involved in a C-ethyl group (19). A three dimensional X-ray analysis showed that structure XVIII was in error only in the position of the ethyl group (25,26). The X-ray analysis was conducted on the aspidospermine-N$_b$-methiodide. The analysis was of low accuracy; however, the salt was noted to have the chair conformation for ring C and the boat for ring D. In this particular conformation the N-methyl group of the salt is cis to the methine hydrogen of the 13-carbon atom.

In contrast to the stereochemistry of the methiodide salt of aspidospermine, the free base has the chair conformation for both the C and D rings (18). All aspidospermine derivatives with the tertiary N$_b$ show a medium well defined band at 2750-2800 cm.$^{-1}$ which is characteristic of $:N\text{-}\overset{/}{\underset{\backslash}{C}}\text{-}H$ where the proton and the p-electrons of the nitrogen are trans and coplanar with the carbon and nitrogen. If the C-ring was the chair form and the D-ring the boat in aspidiospermine, the p-electrons would be cis to the methine hydrogen and the 2750-2800 cm.$^{-1}$ band would be absent. This structure (XIX) for aspidospermine explains the failure of the alkaloid to react with methyl iodide at room temperature but to give almost a quantitative yield of the methiodide at higher temperatures (19,20). With both the C and D rings in the chair conformation, the approach to the p-electrons of the nitrogen is sterically hindered mainly by the axial 2-hydrogen (structure XIX). At higher temperature ring D goes into a boat form which provides a less hindered nitrogen.

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NB: "Scheehan" should read Sheehan

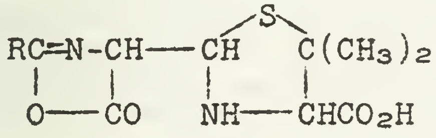
THE SYNTHESIS OF NATURAL AND SYNTHETIC PENICILLINS

Reported by J. L. Foght September 29, 1960

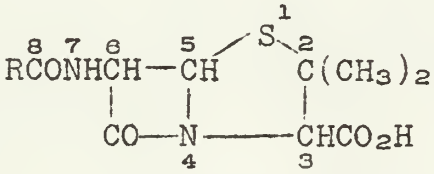
INTRODUCTION

Penicillin was discovered by Fleming in 1929 (1). Significant *in vivo* activity was shown by Chain and Florey (2). This antibiotic has since found numerous applications of therapeutic nature, due to its high bactericidal activity and relatively low toxicity.

Concerted efforts were made during World War II, by teams in Great Britain and this country, to elucidate the structure of penicillin. These structural studies have been well summarized (3,4), so only brief mention will be made here. Two alternate structures were proposed, a thiazolidineoxazolone (I) and a B-lactamthiazolidine (II). The β-lactam was verified by lack of a basic group in penicillin, sulfur hydrogenolysis of sodium benzylpenicillinate to give desthiopenicillin (III) and phenylacetyl-L-alanyl-D-valine (IV), and electron density projections. Also, the distinctive I.R. spectra of β-lactam model compounds resembled that of naturally occuring penicillins.



(I)



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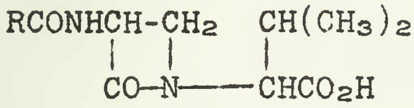

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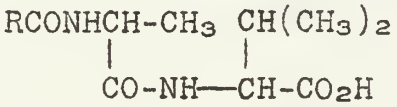
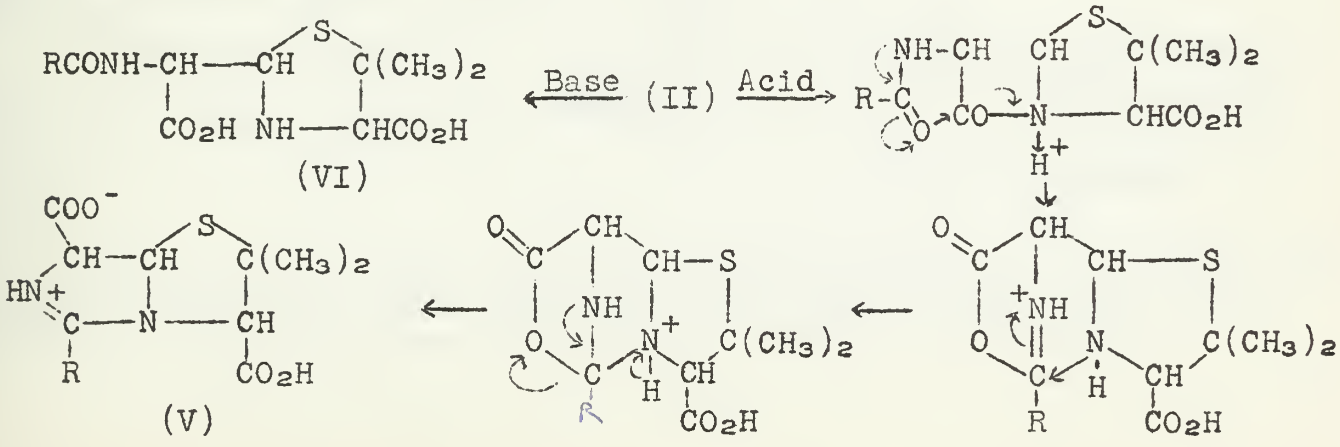


$$\begin{array}{l} RCONHCH\text{-}CH_3\quad CH(CH_3)_2 \\ \quad CO\text{-}NH\text{—}CH\text{-}CO_2H \end{array}$$

(IV)

It was then shown that there were at least six penicillins resulting from natural mold growth (5), --benzylpenicillin, p-hydroxybenzylpenicillin, 2-pentenylpenicillin, 3-pentenylpenicillin, n-amylpenicillin, and n-heptylpenicillin. These are all stable in aqueous solution at pH 5-8, but rearrange at lower pH to give penillic acids (V) and at higher pH to give penicilloic acids (VI). The acid rearrangement may occur through formation of an intermediate oxazolone, followed by attack of the thiazolidine nitrogen on carbon 8, with subsequent proton loss and simple electronic shift (4).

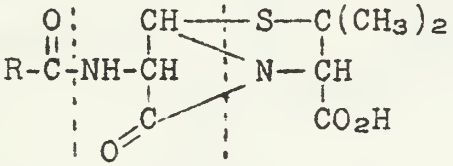


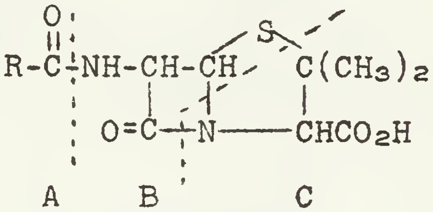
These natural penicillins, despite their excellent applicability, have certain inherent drawbacks, such as rapid excretion, low stability, poor biological spectrum, and sensitivity to penicillinase (6). These drawbacks may be overcome by chemical change of natural products, addition of new precursors to the medium, and total synthesis

BIOLOGICAL SYNTHESIS

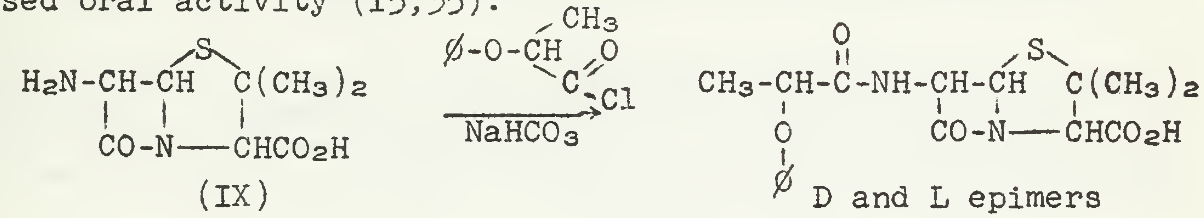
The most rewarding approach to new penicillins has been the biological method, i.e. addition of unatural precursors to enrichment media. Behrens quite early suggested that penicillin could be biosyntheticaly viewed as 3 moieties (3)--phenylacetic, aminomalonsemialdehyde, and penicillamine (VII). Following this concept, addition of phenylacetic acid to the fermentation broth increased the yield of benzylpenicillin (7). Similarly, additions of p-hydroxyphenylacetamide, p-methoxyphenylacetamide, and N-(2-hydroxyethyl)-phenoxyacetamide gave the corresponding biosynthetic penicillins in significant yield. In this manner, at least 29 new penicillins have been synthesized. It may be noted that mixtures of penicillins are generally obtained in these brews and chromatography on cellulose colums is necessary (8).

Elucidation of the actual penicillin precursors has led to a revised picture of the moiety makeup (VIII) (9). The A group can result from various acids or amides, the B from L-cystine, and the C from D-valine, as shown by radiotracer studies (9,10). The pathway of biosynthesis awaits further clarification.


(VII)


(VIII)

Recently, Beecham Lob has been able to obtain bulk quantities of 6-aminopenicillanic acid (IX) from fermentation, without addition of side-chain precursors (11,12). This compound has also been successfully prepared by the action of various "acylases." An enzyme from freeze-dried gram-negative cells, when reacted with sodium benzylpenicillin, gave yields as high as 80 percent (13,14). Since this compound is relatively acid stable (no possibility of azlactonization), many new N-derivatives may be prepared. The first of these is 6-(-α phenoxypropionamido)penicillanic acid (X) which shows increased oral activity (15,35).


(IX)

(X)

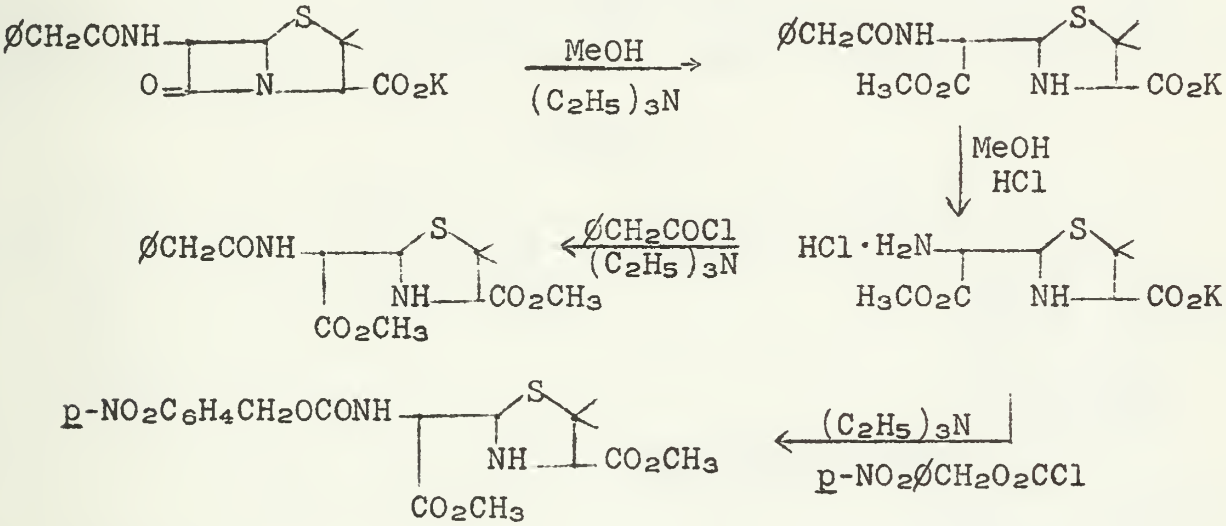
Unfortunately, most of the penicillins biologically prepared have showed little improvement over the natural penicillins. Therefore, chemical synthetic methods have been intensely investigated.

SIMPLE CHEMICAL MODIFICATION

The biologically prepared penicillins may, in some cases, be altered by simple chemical reactions on various functional groups. Thus, p-hydroxybenzyl penicillin has been converted to the 3,5-diiodo derivative and also to various 3-azo coupled compounds (with aniline, halogenated anilines, etc.) (16). Again, p-aminobenzylpenicillin was converted to various N-derivatives by means of carboxylic acid halides, 2,4-dinitrofluorobenzene, and p-toluenesulphonyl chloride (17). It should be noted that these reactions must be run at controlled pH, as a consequence of the instability of penicillin under severe conditions.

Under more severe reaction conditions, natural penicillins may be converted to penicilloates, which can be used for further synthesis of new penicillins. Thus, Scheehan and Ferris converted potassium benzylpenicillinate to a deacylated penicilloate by methanolysis and carried out further conversions by Scheme I (18).

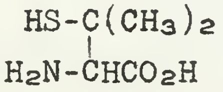
Scheme I



TOTAL SYNTHESIS

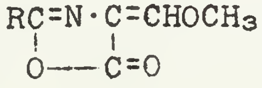
The most interesting and significant work in the field of penicillin chemistry has been the approach to total synthesis, mainly carried out by Scheehan and co-workers. As one considers the synthesis of penicillins, the main problems are the formation of thiazolidine ring, closure to the β-lactam structure, and incorporation of the various possible side chains.

The earliest attempts at total synthesis, which have been well reviewed (3,4), involved the condensation of penicillamine (XI) and an appropriate azlactone (XII). Obviously, since this approach was based on an incorrect structure for penicillin, yields were extremely poor.



$$\begin{array}{c} HS\text{-}C(CH_3)_2 \\ | \\ H_2N\text{-}CHCO_2H \end{array}$$

(XI)



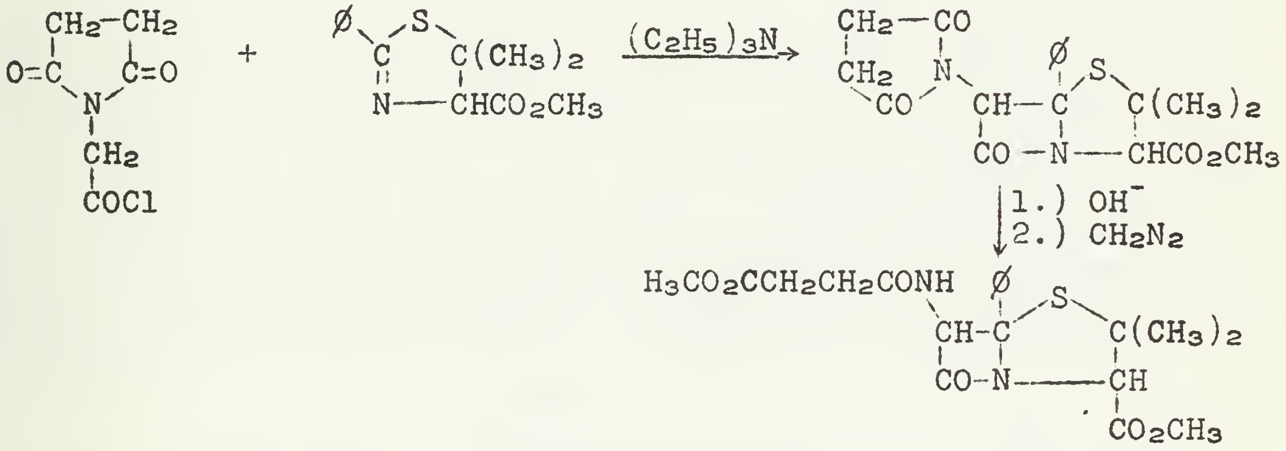
(XII)

When the true structure was determined, it was realized that β-lactamization would involve serious problems. The preferential

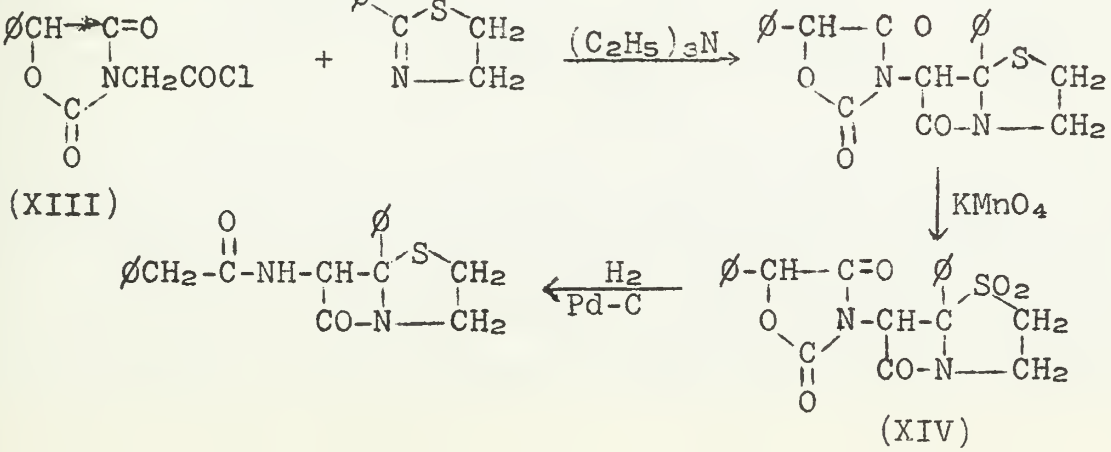
formation of a five-membered oxazolone ring invalidated ordinary methods in many cases. Scheehan and Corey have reviewed earlier methods of β-lactamization (19).

One method, which gave some success in the synthesis of certain specific penicillins, was the reaction of an acylamino halide with an imine (thiazoline), as shown in scheme II. This route had to be indirect, however, since attempted preparations of acylamino acid halides usually give the isomeric oxazolone hydrochloride. By using protected amino acid chloride derivatives with no free NH group and then regenerating the acylamino acid group after cyclization, this difficulty was circumvented. Thus, Scheehan and coworkers synthesized 5-phenylpenicillin by scheme II, using a succinimido group as blocking agent (20). A phthalimido blocking group also worked (21), but the succinimido group could be hydrolyzed to give typical acetylamino penicillins. This hydrolysis was carried out by careful titration with 0.1 N base to a phenolphthalein end-point. It is interesting that an imide is even more susceptible to hydrolysis than a β-lactam. This is probably a case of electronic considerations overriding strain factors. The I.R. spectrum of the product showed bands at 1770 cm^{-1} (β-lactam carbonyl), 1686 cm^{-1} (amide carbonyl), 3400 cm^{-1} (N-H stretch), 1508 cm^{-1} (N-H band), 1727 and 1748 cm^{-1} (ester carbonyls). Unfortunately, the configuration was unknown and no biological activity was shown.

Scheme II

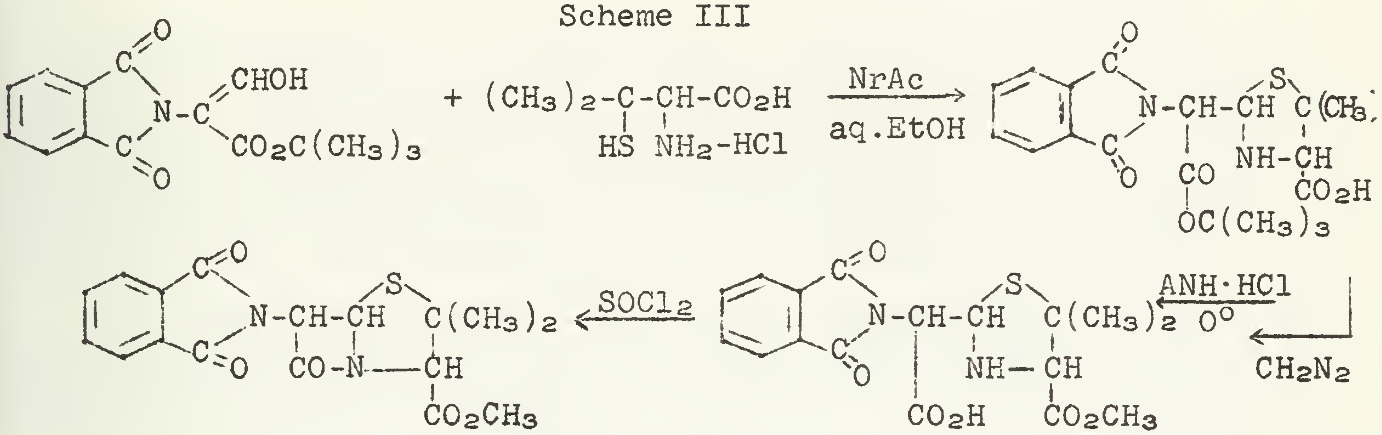


Another blocking group used in an analogous preparative scheme was an oxazolidine (XII). The sulfone (XIV) was reduced by hydrogenation with Pd on charcoal at atmospheric pressure to give a good yield of benzylpenicillin.



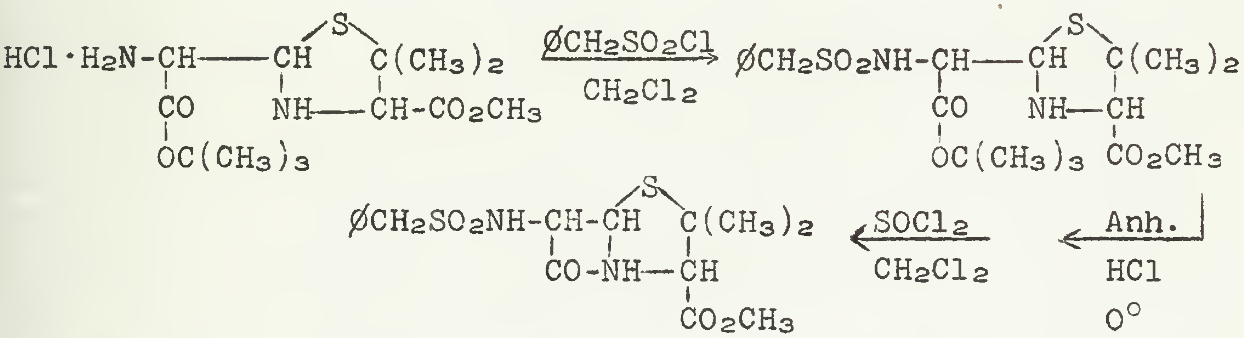
When optically pure penicillamine hydrochlorides were made available, by brucine resolution of isopropylidene-DL-penicillamine (22), a number of new routes leading to products with established configurations became possible. Scheehan and coworkers condensed phthalimimidomalonaldehydic esters with penicillamine to obtain various penicilloate derivatives by scheme III (23). The phthalimido penicilloate was cyclized with $SOCl_2$ to yield the corresponding penicillin in fairly good yield (24). Unfortunately, removal of the phthaloyl group to give the highly desired 6-aminopenicillanic acid proved impossible. The reactivity of the azetidinone carbonyl led to formation of an acetyl hydrazide when phthalimidopenicillin was treated with hydrazine.

Scheme III



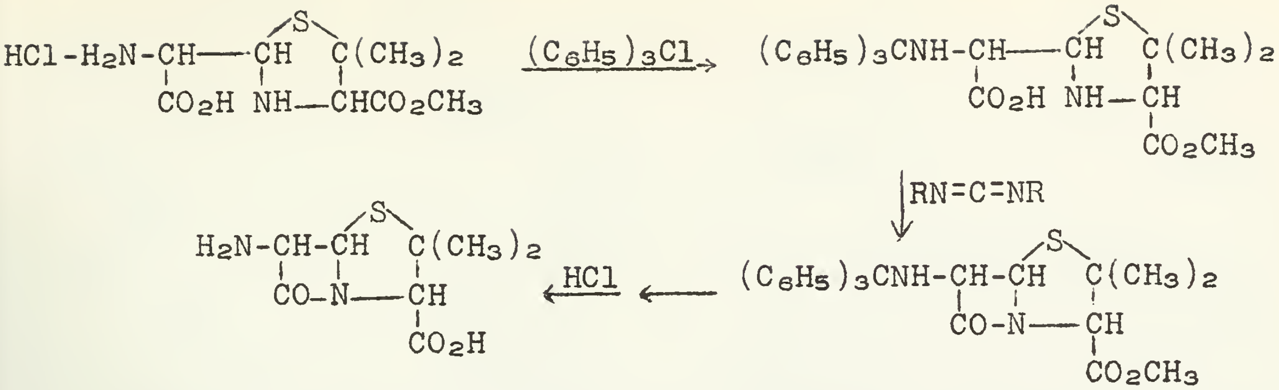
A benzylsulfonyl blocking group was also used by Scheehan (25,26). By reaction of the penicilloate prepared by scheme III with benzylsulfonyl chloride in methylene chloride and β-lactamization with $SOCl_2$, the α-isomer of penicillin was obtained in good yield (scheme IV). The I.R. spectrum showed the band at 1780 cm^{-1} characteristic of a β-lactam carbonyl. As in the case of the phthaloyl compounds, removal of the blocking group led to destruction of the azetidinone ring. The only methods available (hydroiodic acid or phosphonium iodide in glacial acetic acid) were too severe for retention of the penicillin structure. However, the benzylsulfonylpenicillin is resistant to acid rearrangement to penillic acid (V), which could be significant biologically.

Scheme IV



Recently, Scheehan has utilized a trityl group on the 7-nitrogen, which prevents azlactonization during cyclization (scheme V) (27). The trityl group was added to 6-aminothiazolidineacetate by use of trityl chloride and diethylamine (28). The trityl group may be removed without affecting the azetidinone ring, by employing one equivalent of dilute HCl in ethanol. The resultant 6-aminopenicillanic acid has been acylated to give several natural and synthetic penicillins.

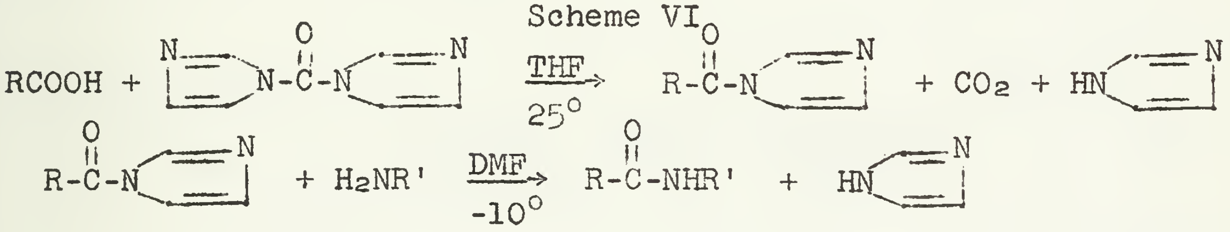
Scheme V



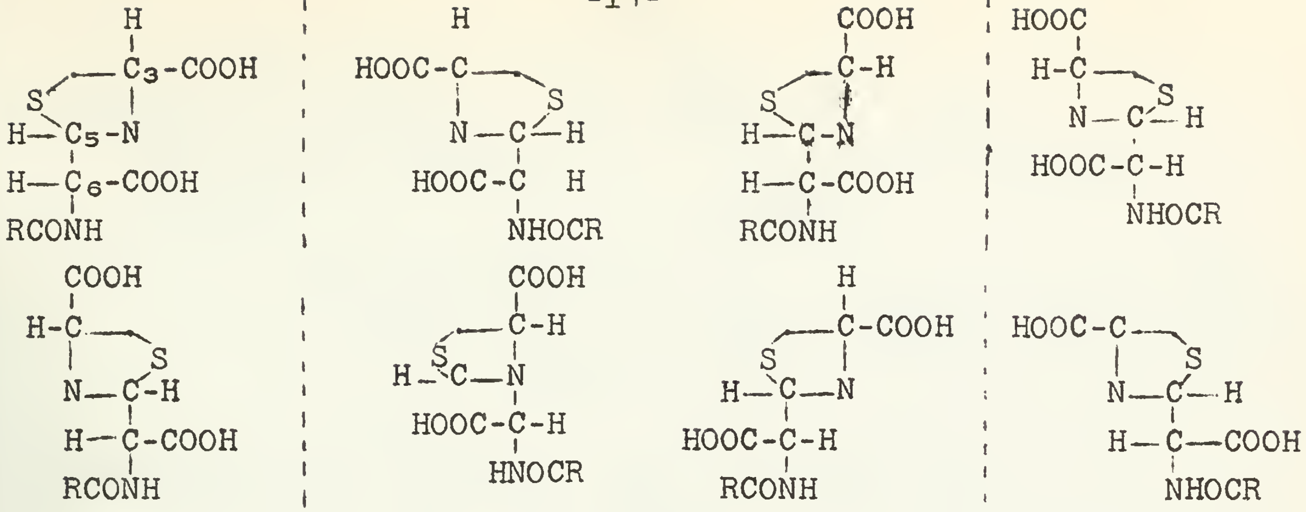
Since Scheehan and Corey reviewed β-lactamization, several new methods for ring closure under neutral conditions have been evolved. Methoxy- and ethoxyacetylene were found to facilitate amide formation, only slight warming of the reaction solution being required (29). Yields were nearly quantitative, with neutral byproducts. Since lactonization appears to be an acid catalyzed reaction, Scheehan suggests that no azlactonization would occur with this method.

N,N'-carbonyldiimidazole will react with an appropriate acid to give an acyl imidazole, which then reacts with an amine to form the desired amide (scheme VI) (31). β-lactamization without azlactonization should again be possible.

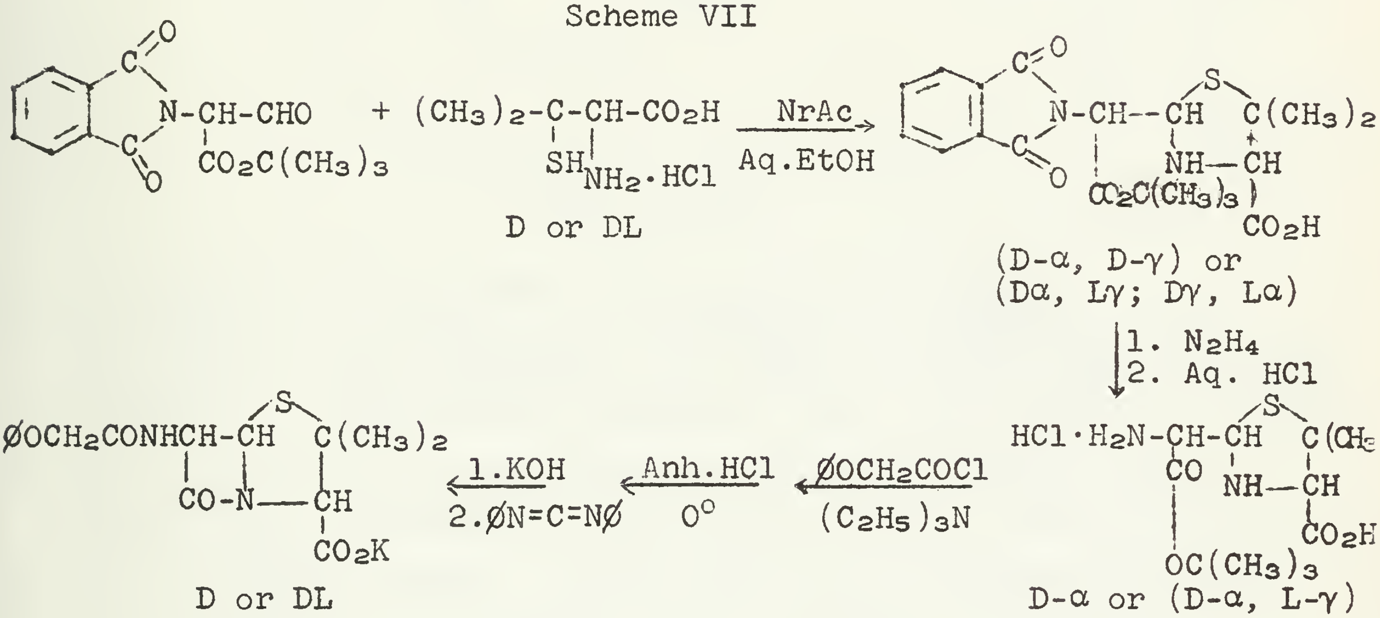
Scheme VI



Carbodiimides have been successfully used for cyclization, with no apparent azlactonization (32). By this method, penicillin V has been prepared in both D- and DL-configurations (Scheme VII) (33). The stereochemistry of this reaction sequence is rather complex. Scheehan's designation of the various isomeric penicilloates is quite arbitrary and, in fact, quite misleading. There are three asymmetric centers in a penicilloate (carbons 3,5, and 6) which can give eight possible isomers, as shown below. The configuration at carbon 3, designated as D- or L-, will depend upon the starting penicillamine. The synthetic incorporation of carbons 5 and 6 yields two of the four possible arrangements of these two centers. These arrangements are designated as α and γ by Scheehan, with α corresponding to the natural penicilloates. The γ isomer, which is the predominant synthetic product, is racemized to α by heating in pyridine solution. If D-penicillamine is used as starting material, the diastereoisomers D-α and D-γ penicilloate are easily separated by differential solubility. Then D-α penicilloate may be cyclized to give an optically pure penicillin. But if DL-penicillamine is employed in scheme VII, four penicilloates are obtained as two optically inactive racemic mixtures. These should be designated (D-α, L-γ) and (D-γ, L-α). Scheehan calls them DL-α and DL-γ, but this would indicate mixtures of diastereoisomers, which should certainly not be racemic in nature. Cyclization of racemic (D-α, L-γ) will yield a DL-penicillin, which is optically inactive. Interestingly enough, DL-penicillin V showed 51 percent of the bioactivity of natural penicillin V, indicating that only one configuration is bactericidal.

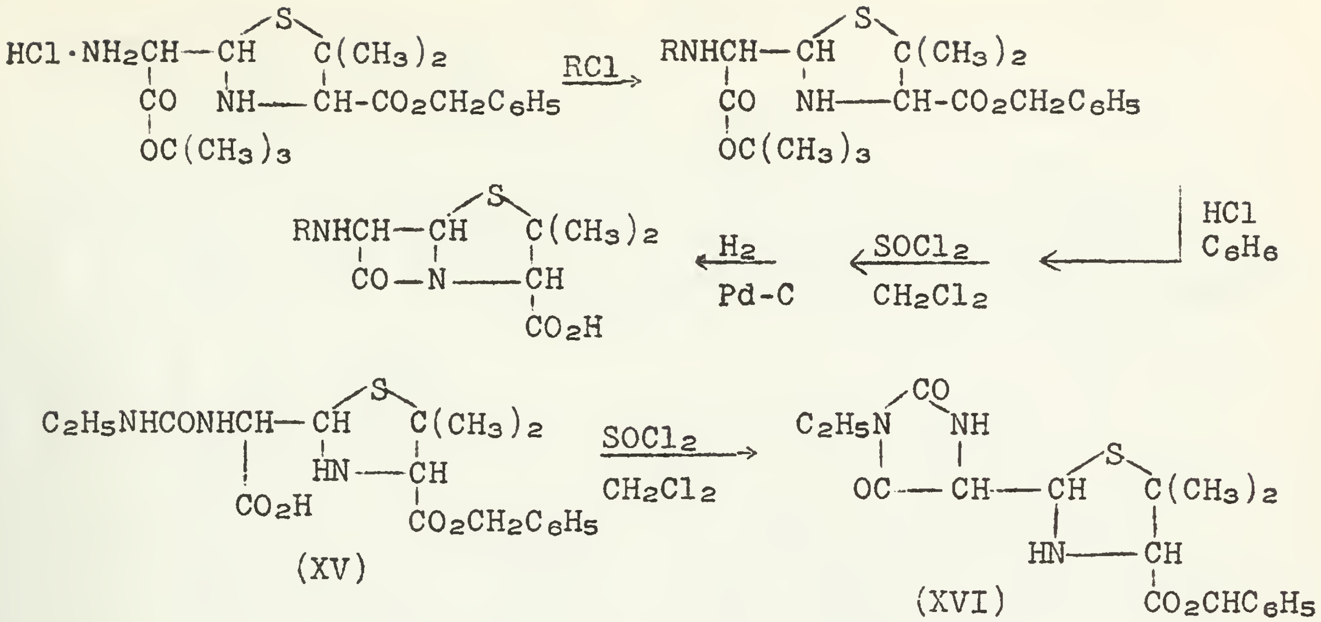


Scheme VII



Scheehan and co-workers have recently synthesized a whole series of "synthetic" penicillins, using scheme VIII (6). The α-aminothiazolidineacetate was the D-α-isomer, so that the configuration of products is clear. Acylation was carried out in methylene chloride or dioxane. The α-ester group was removed by hydrohalogenolysis, to which t-butyl ester groups are particularly susceptible. Cyclization by $SOCl_2$ worked on such R-groups as CH_3SO_2-, ØSO_2-, and CH_3OCO-. However, ethyl carbamyl (XV) gave a hydantoin (XVI), as might be expected. The catalytic hydrogenolysis of the benzyl group was carried out with Pd on Norite in dioxane solvent. Most of the penicillins were obtained as N-ethylpiperidine salts. Although these compounds showed increased resistance to rearrangement in acid solution, none were more biologically active than penicillin G.

Scheme VIII



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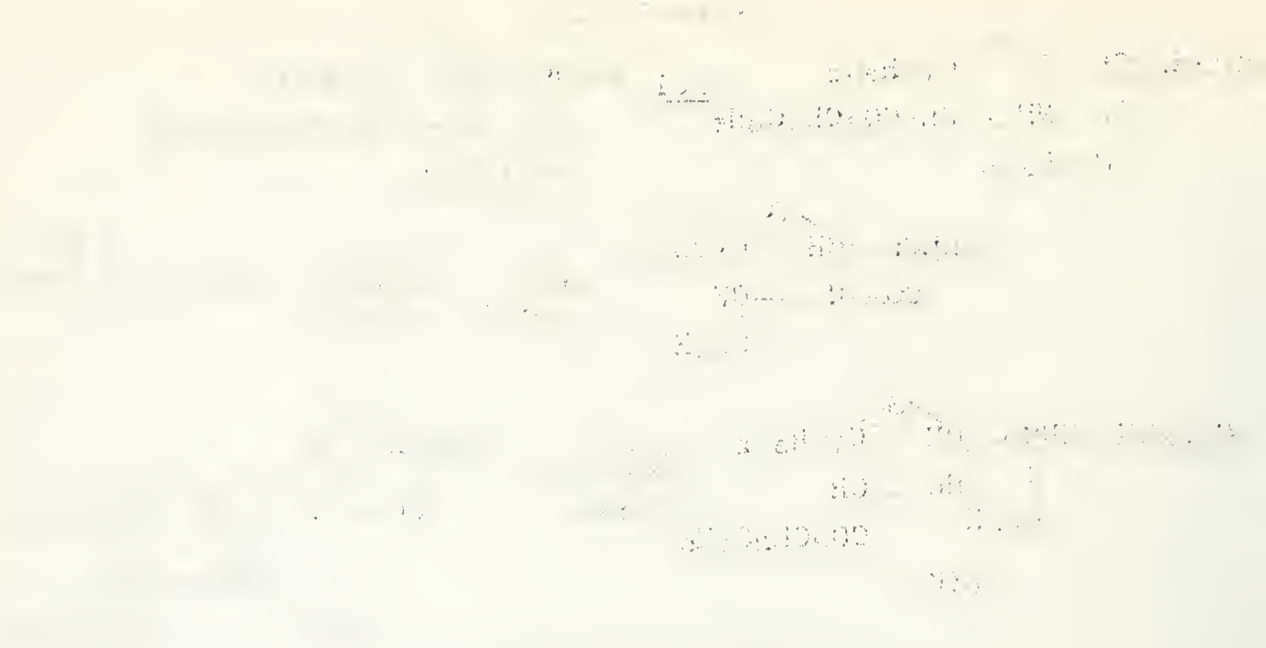

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CYCLOPENTENE-3,5-DIONE AND RELATED STRUCTURES

Reported by C. R. McArthur October 3, 1960

Molecular orbital calculations of three-, five-, and seven-membered conjugated unsaturated rings show that the cation of the three-, and seven-membered rings, and the anion of the five-membered ring should be stabilized by aromatic resonance, whereas the other possible ionic species should not be so stabilized, and should be triplets in the ground state (1). The theory also predicts similar stability for the cycloöctatetraenyl dianion which has recently been synthesized (2). This situation is expressed by the "4n + 2 rule" advanced in connection with such structures (3). No simple planar molecules which violate this rule have been prepared in stable form (4). One might recall the many attempts to prepare cyclobutadiene. Cycloöctatetraene, although synthesized, has a non planar structure (5), and consequently is not pertinent to the theory. The resonance energy of cyclopentadiene is only 3 kcal./mole as calculated from the heat of hydrogenation, which is no greater than that of 1,3-butadiene. The cyclopentadienyl anion, however, has a resonance energy of 50 kcal./mole (as calculated from the molecular orbital theory (6)), but is also very reactive chemically (7). The tendency of the cyclopentadiene system to accept an electron is illustrated by dimethylfulvene (I), the dipole moment of which is 1.44D (7).


$\underline{n} = 0$


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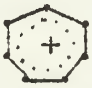
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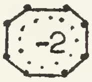
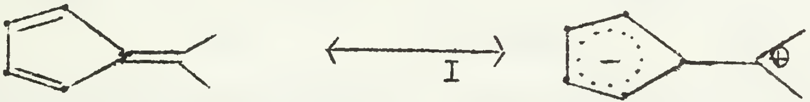
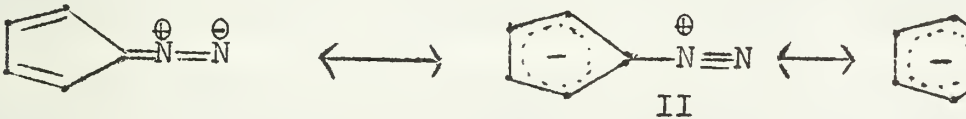
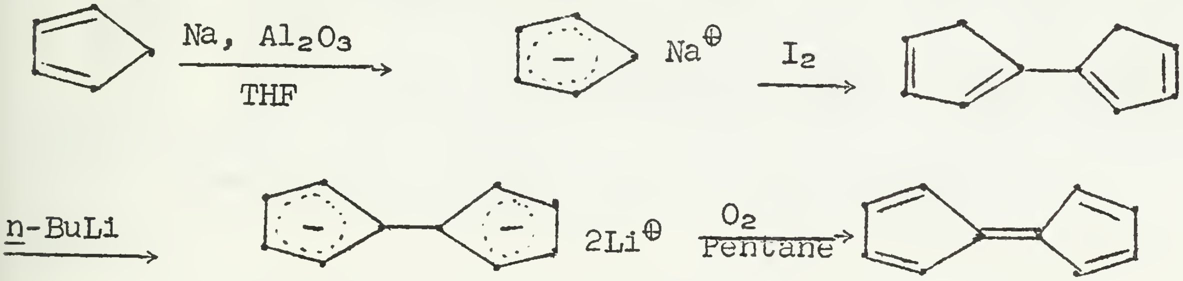

$\underline{n} = 2$


I

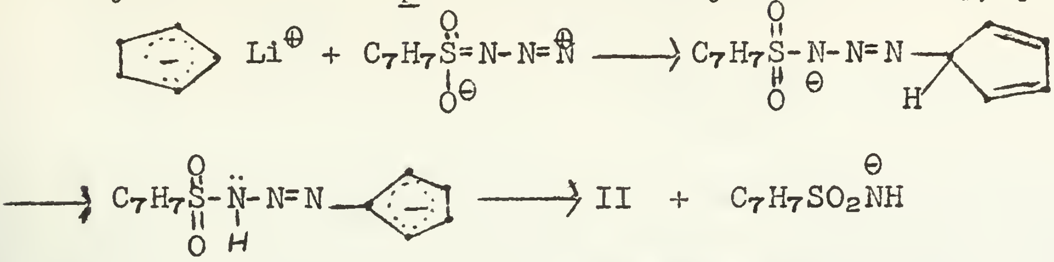
A remarkably stable cyclopentadiene derivative is diazocyclopentadiene (II) (8). In this compound, the positive charge is being accommodated by a nitrogen atom rather than a carbon atom as in the case of the fulvenes. An aromatic sextet is achieved in II by withdrawal of electrons from the diazo group. Fulvalene (III) has been detected as a product of the low temperature photolysis of diazocyclopentadiene (9). A significant amount of theoretical interest has been shown towards fulvalene (10), but the molecule has only recently been synthesized (11). The synthesis of dia-


II



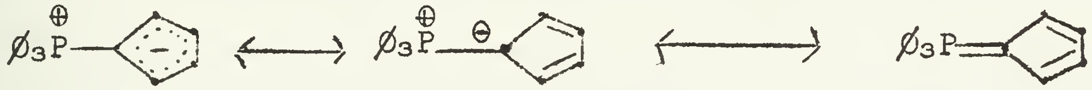
III

zocyclopentadiene was accomplished by a reaction of cyclopentadienyllithium with p-toluene-sulfonyl azide in 35% yield. An even



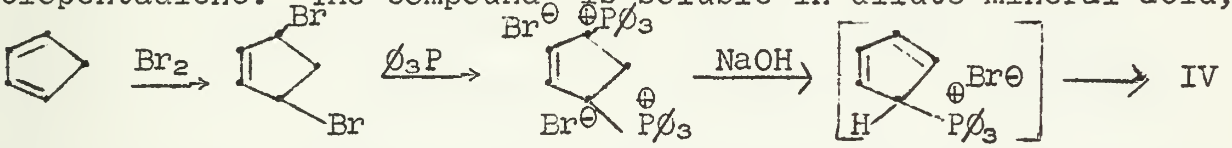
more striking illustration of aromatic character in a five-membered ring arose in an earlier attempt to prepare fulvalene. The action of ferric chloride on the Grignard reagent of cyclopentadiene constituted the first synthesis of dicyclopentadienyl iron (12).

Closely related to diazocyclopentadiene is the recently prepared (13) triphenylphosphoniumcyclopentadienylide (IV). It was synthesized for the purpose of studying a stable isolated phosphorus



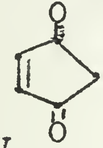
IV

"ylide". Many of these are not ordinarily isolated, and usually decompose under hydrolytic conditions. It was reasoned that the distribution of negative charge in IV should impart a high degree of stability. It was synthesized in an overall 41% yield from cyclopentadiene. The compound is soluble in dilute mineral acid,



and is regenerated unchanged by the addition of alkali. It is not affected by prolonged boiling with concentrated aqueous alcoholic potassium hydroxide. All attempts to effect a reaction of IV with ketones such as cyclohexanone, benzophenone, and fluorenone failed.

Compounds II and IV are examples of the relatively few completely unsaturated cyclopentane compounds which are known to be stable. The synthesis of many unsaturated, and substituted cyclopentane derivatives of theoretical and practical importance is hindered by the lack of readily available intermediates (14). This situation is in contrast to the seven-membered ring compounds, where a whole new chemistry has developed. The announcement of Depuy and Zaweski (15) of the synthesis of cyclopentene-3,5-dione (V) promises a new lead into five-membered unsaturated rings. Compound V is considered potentially useful in that it contains neither an intact cyclopentadiene ring nor a completely unsaturated ring. Monosubstituted cyclopentadienes are susceptible to dimerization and isomerization. Cyclopentene-3,5-dione is trifunctional, and all carbon atoms of the molecule are potentially reactive.

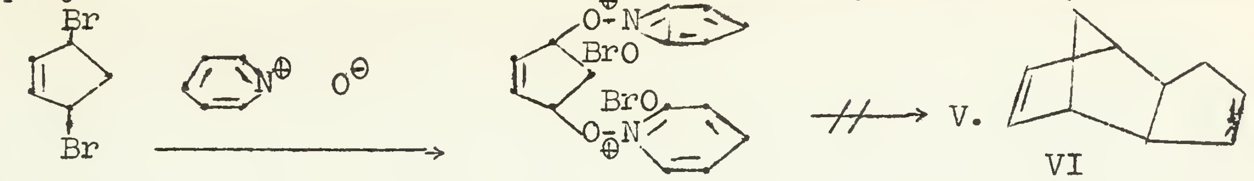


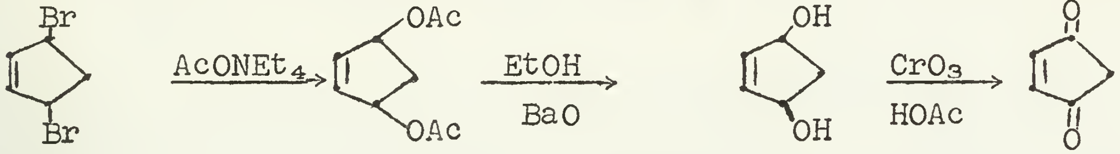
V

Synthesis

The decomposition of O-alkylpyridine-N-oxides to give ketones (16) was used in an attempted synthesis of cyclopentene-3,5-dione by the following sequence. Instead of the desired dione, a

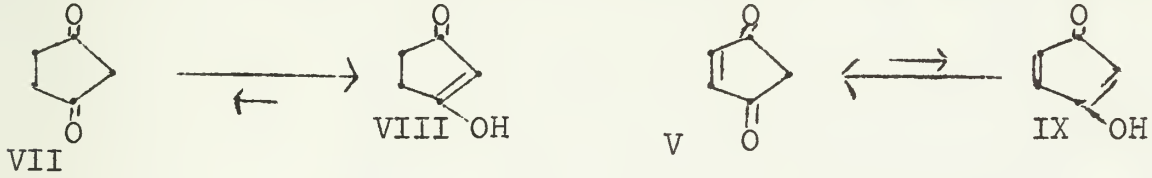
polymeric material was obtained from which 1,8-diketo-4,7-methano-3a,4,7,7a-tetrahydroindene (VI), the dimer of cyclopentadienone, could be extracted in 0-13% yield. A successful synthesis of the desired cyclopentene-3,5-dione was accomplished (14) by the oxidation of cyclopentene-3,5-diol. It has also been obtained in low yield by, the action of silver chromate on 3,5-dibromocyclopentene (17).





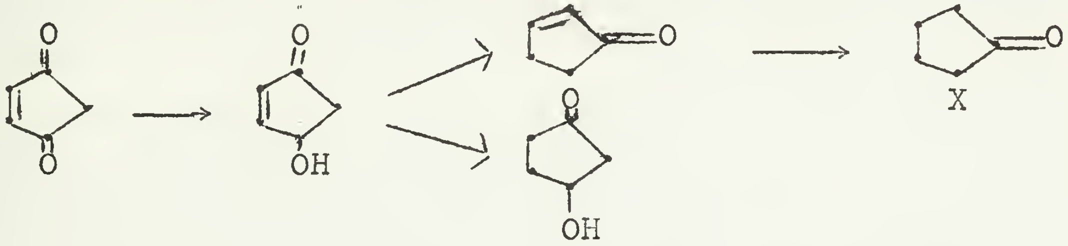
Properties

The dione V appears to be 100% ketonic as there is no -OH absorption in the infrared, and a ferric chloride test is negative (14). Reduction with zinc in acetic acid gave the known (18) cyclpentane-1,3-dione (VII) in 45% yield. This, on the other hand, appears to be completely enolic (VIII) under the same conditions.

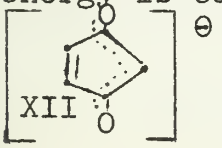


The preference for the dione V to remain ketonic must be a reflection of the instability of the cyclopentadienone system (IX). This situation has previously been recognized in the case of 1,2-cyclopentenediones. For example, it has been shown that 1,2-diphenyl-3,4-diketocyclopentene exists exclusively in the diketo form (19, 20). This has also been explained on the basis of the relationship of the enol to cyclopentadienone (6,21).

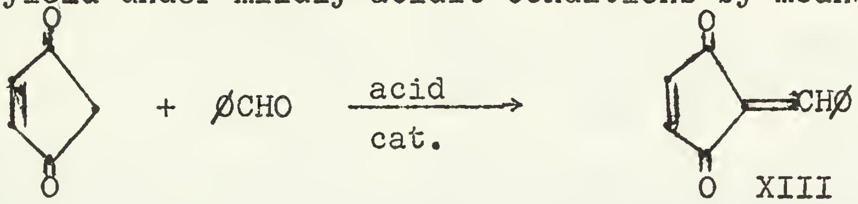
Hydrogenation of V with Adam's catalyst gave less than 2% of the dione VII, but instead, gave cyclopentanone (X), and β-hydroxycyclopentanone (XI) in practically equal amounts (14).



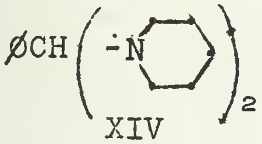
Cyclopentene-3,5-dione is quite acidic, neutralizing an aqueous bicarbonate solution (14). The anion (XII) being of low energy is easily formed. However, it is so reactive that one drop of piperidine added to a benzene solution of the dione causes a rapid precipitation of an enolic water soluble polymer. In fact, when an aqueous solution is allowed to stand, it gradually polymerizes, although it



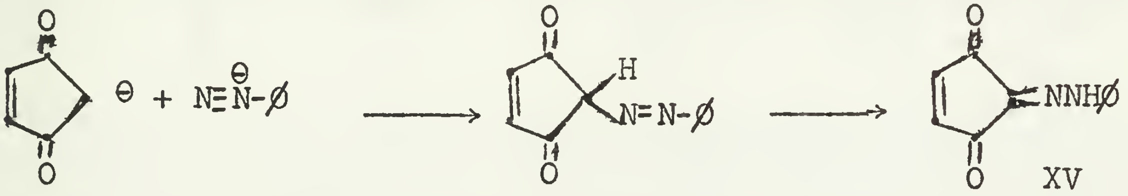
is stable in acidic solution. This makes alkylation and condensation reactions difficult. When benzaldehyde is added to V in aqueous or alcoholic base, only polymer is formed (22). Also, because of the apparent instability of the enol IX, acid catalyzed reactions would be expected to be correspondingly difficult. Surprisingly enough, however, the benzylidine compound (XIII) is formed in 50% yield under mildly acidic conditions by means of boron trifluoride as catalyst (22). This result prompted the use of catalytic amounts of sulfuric acid in an acetic acid medium where the enol itself is still a more likely intermediate. A 42% yield of the benzylidine compound (XIII) was formed. Apparently the hydroxycyclopentadienone (IX) is not stable enough to be observable, but it is in equilibrium with the dione. The best result in basic medium (20% yield) was obtained by means of a benzaldehyde-piperidine "complex". This had been used previously (23) to effect the condensation of benzaldehyde with cyclic 1,2-diketones. The technique consists in the mixing of benzaldehyde and piperidine in a 1:2 molar ratio in cyclohexane, removal of the water formed, stripping of the cyclohexane, and addition of the solvent (usually absolute ethanol) for the subsequent reaction. The structure of the "complex" is thought to be XIV. Because of the competing polymerization reaction in the base-catalyzed reactions, the acid-catalyzed reactions appear to be more promising from a synthetic standpoint. The enolate XII has been successfully trapped with benzenediazonium chloride. When an acidic solution of cyclopentene-3,5-dione and benzenediazonium chloride is neutralized with sodium acetate, the 4-phenylhydrazone (XV) of cyclopentene-3,4,5-trione is immediately precipitated (22).



XIII



XIV



XV

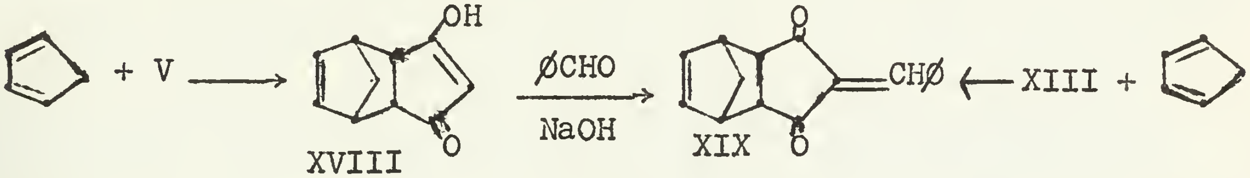
Attempted hydrolysis under mild conditions with formaldehyde (24), or with levulinic acid (25) led only to recovered hydrazone. Other approaches to cyclopentene-3,4,5-trione are promised (22).

The carbonyl groups of V are extremely reactive (14). Of course, reactions of these groups can be complicated by the polymerization in basic solution. Nevertheless, mon- and/or dioximes, phenylhydrazones, p-toluenesulfonylhydrazones, and O-methyl oximes are formed easily. An attempt to prepare the diazoketone (XVI) failed (14). This compound would have been of interest because of the possibility that it might enolize. The diketone reacted with p-toluenesulfonylhydrazine to form the hydrazone (XVII), but when XVII was treated with base at 100° it formed a salt from which the hydra-

XVII XVI

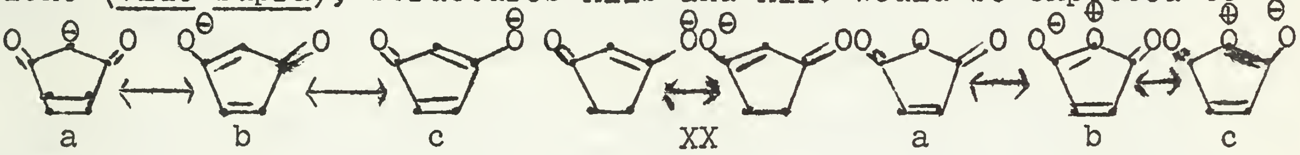
zone was recovered unchanged.

Cyclopentene-3,5-dione is a very reactive dienophile, undergoing an immediate and quantitative reaction with cyclopentadiene (14). The adduct (XVIII) is enolic. Reaction with anthracene is slower, however; a 90% yield of the adduct is obtained after four



days refluxing in benzene. Compound XVIII reacts with benzaldehyde in ethanolic sodium hydroxide to form the benzylidine compound (XIX), the same compound that is formed from the reaction of XIII with cyclopentadiene (22).

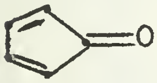
An interesting use of the enolic property of XVIII was to compare the reactivity of cyclopentene-3,5-dione with that of maleic anhydride (14). Equal amounts of the dione and the anhydride were allowed to compete for cyclopentadiene. The proportion of XVIII produced was determined colorimetrically with the use of ferric chloride. Maleic anhydride was found to be four times more reactive than cyclopentene-3,5-dione towards cyclopentadiene. This might seem surprising at first since the reactivity of a dienophile is increased by electron-withdrawing substituents (26). Maleic anhydride has the ring oxygen atom which would be expected to donate electrons to the carbonyl groups, and thereby decrease their electron-withdrawing power. However, the π-electron system of maleic anhydride is isoelectronic with that of the cyclopentene-3,5-dione anion (XII). Because of the apparent instability of the enol form of cyclopentene-3,5-dione relative to that of cyclopentane-1,3-dione (vide supra), structures XIIb and XIIc would be expected to



contribute only to a small extent to the endione anion relative to the analogous structures XX. Consequently, the structures XXIb and XXIc should not contribute as much to the stability of maleic anhydride as analogous structures would to a saturated anhydride. Therefore, in forming an adduct, maleic anhydride would be gaining some resonance energy, and this could be an additional driving force for the reaction.

Cyclopentadienone.

Cyclopentene-3,5-dione is of theoretical interest because of its relationship to cyclopentadienone (XXII). The dienone and its simply substituted derivatives are unknown. Until recently (27) XXII had not been nkown to have formed. Attempts to prepare the oxime of XXII by the action of ethyl nitrite of cyclopentadiene resulted only in the formation of the dimer (XXIII) (28). By examination of known substituted cyclopentadienones or the dimers of such, empirical rules



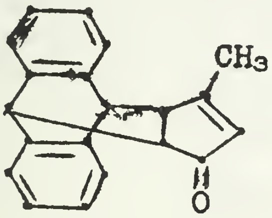
XXII

XXIII

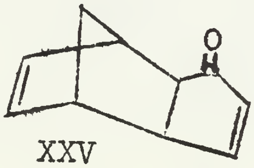
indicating in which form (dimer or monomer) the dienone will exist have been summarized (29). Any having fewer than three substituents will exist only as a non-dissociated dimer. If three substituents are present, only the non-dissociated dimer will exist except in the extreme case in which there are two aryl groups next to the carbonyl. When all four positions are substituted, a monomer results except if the substituents in the 2- and 5-positions are methyl and an alkyl in which case a dissociable dimer results.

This problem has been treated theoretically (30). The formation of an adduct involves the localization of two of the π-electrons of the conjugated system of the diene to form two new σC-C bonds (31). The fundamental assumption of the theory is that the ease of formation of an adduct at a pair of atoms *m* and *n* of the diene depends only on the energy required to localize two of the π-electrons upon atoms *m* and *n*, provided *m* and *n* are orientated favorably. Because in the case of a polycyclic hydrocarbon *m* and *n* are para to each other, the energy quantity has been termed the *para*-localization energy "P" of the pair of electrons *m* and *n*. The mobile bond orders and bond localization energies for cyclopentadienone indicate a high reactivity for the 2,3-bond. These bond orders are high enough to indicate that the most important resonance structure for this molecule is XXII. However, the charge densities require a certain polarization of the C=O bond. The value of "P" for the appropriate diene reaction centers for cyclopentadienone is relatively small indicating a large Diels-Alder reactivity. Substituents have been shown (32) to increase the localization energy. At the same time, Diels-Alder reactivity is also decreased because of steric hindrance of the substituents. In spite of this, tetraphenylcyclopentadienone reacts with maleic anhydride (33). This must confirm the high diene activity of cyclopentadienone itself.

Cyclopentadienone would be a valuable compound to study (4). The reactivity of the carbonyl group might be correlated with that of more normally situated ones; and it might be studied as a diene and/or as a dienophile. Spectral studies might enlighten our knowledge of the electronic interactions involved. The anthracene adduct (XXIV) of 3-methylcyclopentadienone was pyrolyzed, and the products reported (34) were anthracene and a compound that gave the correct analysis for 3-methylcyclopentadienone. The structure of the product is open to question (4), however, because of its high boiling point (218-220°). The material apparently polymerized and was not further characterized. When 3a,4,7,7a-tetrahydro-4,7-endomethylene-1-indene-3-one (XXV) was pyrolyzed, monomers apparently formed, but



XXIV

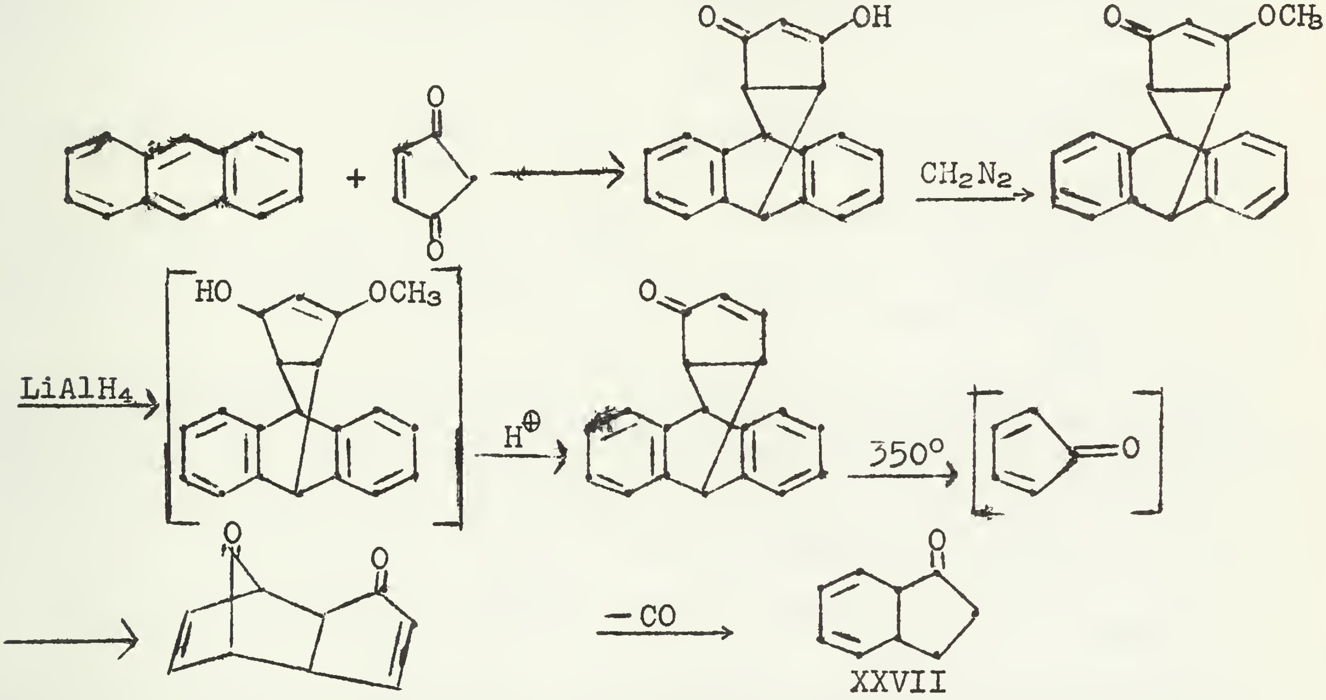


XXV

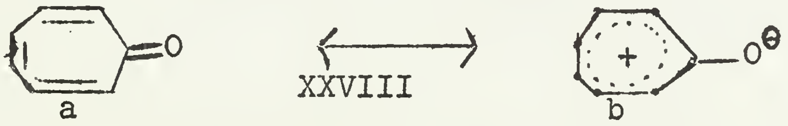
these dimerized in all expected ways (27). A recent attempt to produce cyclopentadienone by the pyrolysis of XXV failed (35).

However, 3-hydroxy-4,7-endomethylene-3a,4,7,7a-tetrahydroindene (XXVI), the alcohol from which XXV was obtained, gave a quantitative yield of cyclopentadiene and 2-cyclopentenone when pyrolyzed in the vapor phase.

In view of the availability of the new cyclopentene-3,5-dione, it was decided (4) that the generation of cyclopentadienone might best be accomplished by a reverse Diels-Alder reaction. The conversion was made by the following sequence of reactions (14) leading to 8,9-dihydroindene (XXVII) as the final product. An authentic sample of 1,8-diketo-4,7-methano-3a,4,7,7a-tetrahydroindene (VI), the dimer of cyclopentadienone, was subjected to the same conditions of pyrolysis. This gave the same product XXVII. Thus, cyclopentadienone can be formed through pyrolysis of its anthracene adduct, but the dione immediately dimerizes. The subsequent loss of the bridged carbonyl is not uncommon (36).



The instability of cyclopentadienone is in sharp contrast to cycloheptatrienone (tropone) (XXVIII) whose stability is related to the aromaticity of the cyloheptatrienyl cation. Until the cation had been prepared, it had been inferred from the failure of cyclopentadienone to exist contrasted with the stability and basicity of tropone that the theoretical predictions of a stable and aromatic cycloheptatrienyl cation should be correct. Its preparation (21)



verified these predictions. Whereas the carbonyl absorption frequency of cyclopentadienone is high (calculated to be 1703 cm.$^{-1}$

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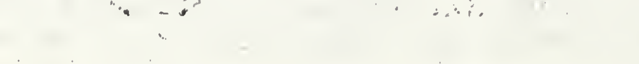

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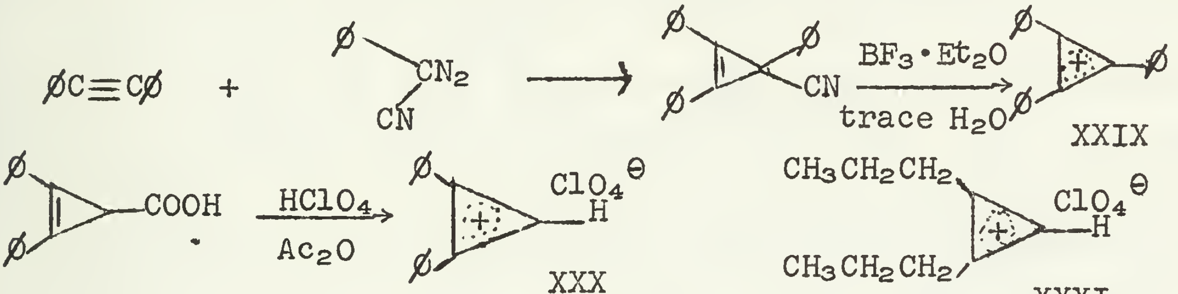
(37)), that of tropone is very much lower (1638 $cm.^{-1}$ (38)). Further illustration of the high contribution of XXVIIIb is the failure of the ketone to form a 2,4-dinitrophenylhydrazone. Oximes and phenylcarbazones are formed only under vigorous conditions (39). Also, the dipole moment is 4.3D as compared with 2.97D for benzophenone, and 2.8D for acetone (7).

For further comparison, molecular orbital calculations (1) have also predicted the cyclopropenyl cation (and not the anion) to be resonance stabilized and aromatic. It should be borne in mind, however, that these calculations involve "extra" stabilities due to conjugation and do not include angle strain (40). Nevertheless, the sym-triphenylcyclopropenyl cation (XXIX) (40,41), and the diphenylcyclopropenyl cation (XXX) (42) have been prepared. Further work was needed to help determine how much stability of these cations is due to increased conjugation with the phenyl groups, and how much is due to the cyclopropenyl aromatic system. Correspondingly, dipropylcyclopropenyl perchlorate (XXXI) was prepared (43), and appears to possess all of the stability of the diphenyl cation XXX.

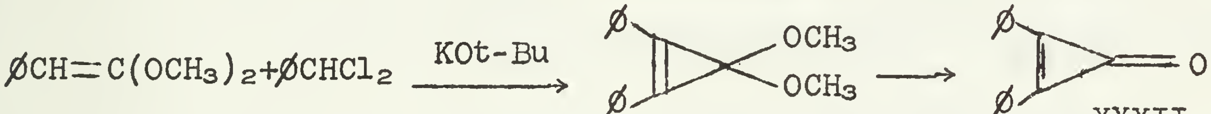


XXIX

XXX

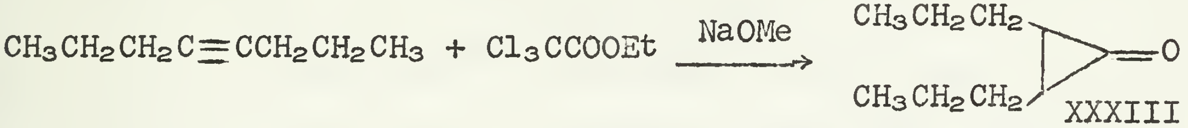
XXXI

The cyclopropenone system should likewise be expected to be resonance stabilized. Diphenylcyclopropenone (XXXII) has recently been synthesized (44) from phenylketene dimethyl acetal and phenylchlorocarbene. The facts that XXXII can be isolated from a hydroxylic



XXXII

medium, and that it requires a temperature of 130° to decompose it show that the cyclopropenone system must possess a strong resonance stabilization to compensate for its high angle strain. To show that the phenyl substituents do not stabilize an otherwise unstable ketone as they do in the cyclopentadienone series, dipropylcyclopropenone (XXXIII) was synthesized from dipropylacetylene and dichlorocarbene (45). Dipropylcyclopropenone is reportedly more stable



XXXIII

to heat and base than diphenylcyclopropenone (45). This does not necessarily signify a greater stabilizing effect for the n-propyl substituents in the ketone, but more likely reflects a greated stabilization by the phenyl groups of the transition states in the decompositions. The developing anion in the basic ring cleavage would be strongly stabilized by the phenyl groups. At any rate, the properties of dipropylcyclopropenone support the idea that the stability of these very strained compounds is due to a special aromatic conjugation (45).

Inasmuch as theory, which has enjoyed qualitative agreement with experimental results in these systems, predicts that the cyclopentadienyl cation should be a non-stabilized triplet in the ground state, it is not surprising that cyclopentadienone is not isolable. Furthermore, the normal carbonyl polarity should be strongly opposed in the structure XXII since all six unsaturation electrons are demanded for the utilization of three low energy molecular orbitals associated with the ring (46). In spite of this, the barrier to the formation of cyclopentadienone does not seem so great that this molecule cannot be formed at least transiently.

****

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THE CLEMMENSEN REDUCTION

Reported by B. H. Klanderman October 17, 1960

Introduction

The Clemmensen reduction has long been employed as a tool in organic synthesis as a means for converting the carbonyl group of aldehydes and ketones to a methylene group by the use of zinc amalgam and hydrochloric acid.

$$R\text{-}CO\text{-}R' \xrightarrow[HCl]{Zn(Hg)x} R\text{-}CH_2\text{-}R'$$

Aliphatic and aromatic aldehydes and ketones of various types are reduced by this method. A review was published by E. L. Martin in 1942 (1). This work includes a discussion of the types of compounds reduced, experimental procedures, and a table of the compounds reduced by the Clemmensen method; however, the mechanism of the reaction was not understood. In this seminar various types of evidence will be discussed and on the basis of these experimental results a possible mechanism will be proposed.

Reaction Products and Evidence for Intermediates

The Clemmensen reduction may be run under various reaction conditions and the yields and the types of products usually vary also. The hydrochloric acid concentration may be varied from 2% to 40%, the percentage of zinc in the amalgam may vary from 2% to 99%, and an organic solvent such as ethanol, acetic acid, dioxane, or toluene may be employed in addition to the hydrochloric acid. If the carbonyl compound is not sensitive to acid, the mixture is heated, usually to boiling, for four to ten hours.

Although saturated hydrocarbon constitutes the major product in most cases, various amounts of olefin, pinacol, pinacolone, and alcohol may also form. The fact that benzyl alcohol is reduced under Clemmensen conditions led Steinkopf and Wolfram to postulate the alcohol as an intermediate in the reaction (2). Likewise 1-phenylethanol (3) has also been reduced. However, in the vast majority of cases, reduction of the alcohol corresponding to the aldehyde or ketone does not take place; in fact, 1-phenylethanol and t-butylphenyl carbinol are not reduced with 2N HCl and 2% zinc amalgam (4). With 21% HCl, 1-phenylethanol is converted mostly to styrene after 5 min. and the styrene is gradually reduced to ethylbenzene; moreover, 1-phenylethanol is converted to styrene with zinc and HCl alone (3). In addition, ethanol is often used as solvent for the reaction. Therefore, the alcohol cannot be an intermediate in the reaction. Traces of alcohol have been found in the reductions of 2-octanone, 2-heptanone, 2-pentanone, and t-butylphenylketone; but again the corresponding alcohols could not be reduced (4,5,6), and therefore the alcohol can be considered as side product.

Olefin formation occurs occasionally, especially in the aromatic-aliphatic ketone series. It is to be noted that styrene is formed from acetophenone in large yield in 6% as well as in 21% HCl. (3,4,7). Although styrene is reduced in some cases, olefins cannot in general be reduced under Clemmensen conditions. Therefore, an olefin intermediate is very unlikely. However, the nature of the carbon skeleton for the olefinic products versus the saturated hydrocarbons is

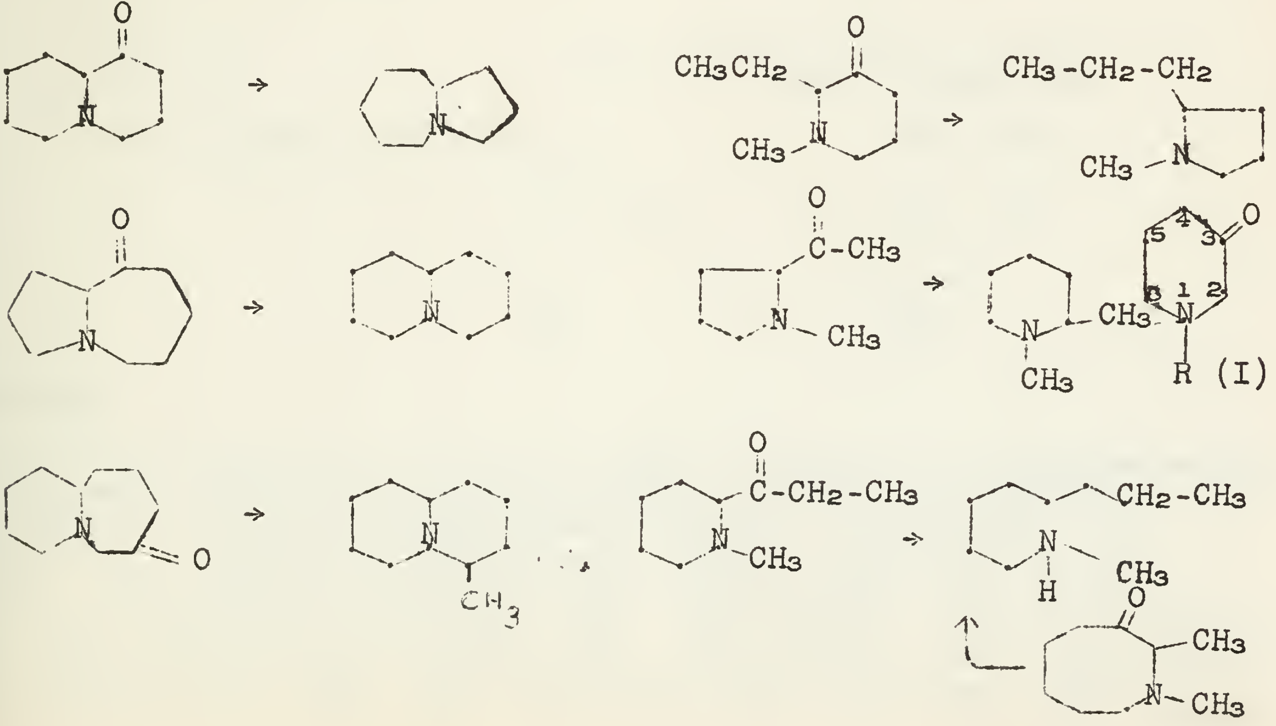
important. Reduction of t-butylphenylketone yields neopentylbenzene and 2-methyl-3-phenyl-2-butene, but no 2-methyl-3-phenylbutane; and pinacolone yields neohexane (4,8). Thus a rearranged olefin is formed, but no rearranged saturated hydrocarbon. Therefore, a free carbonium ion is most likely not an intermediate.

Pinacols and pinacolones are often found in the reduction of aromatic ketones. In some cases pinacol forms the major product. Depending on the substituent, substituted benzophenones yield dimeric product (pinacol) or saturated hydrocarbon: p-fluoro and p-chloro substituents favor dimeric products whereas p-methyl and p-hydroxyl substituents favor monomeric products. Ortho-substituents favor monomeric products; thus steric hindrance may be operative in this case (9). In general, pinacols form more readily with aromatic ketones which can give resonance stabilization to a radical intermediate. The rate of desorption from the metal surface and the rate of further reduction may also be important factors in comparing the pinacol formation of aliphatic and aromatic ketones.

Pinacols are formed to a greater extent if the concentration of reacting ketone is high in the aqueous phase (1,9). Benzophenone yields mostly diphenylmethane (monomer) if toluene is used as the additional solvent but only pinacol if ethanol is used as the additional solvent.(9). For this reason an immiscible solvent like toluene is often used in order to keep the concentration of the ketone small in the aqueous phase. This procedure helps to minimize radical dimerization. Pinacolones can arise from the pinacols by the pinacol-pinacolone rearrangement.

Rearrangements and Elimination Reactions

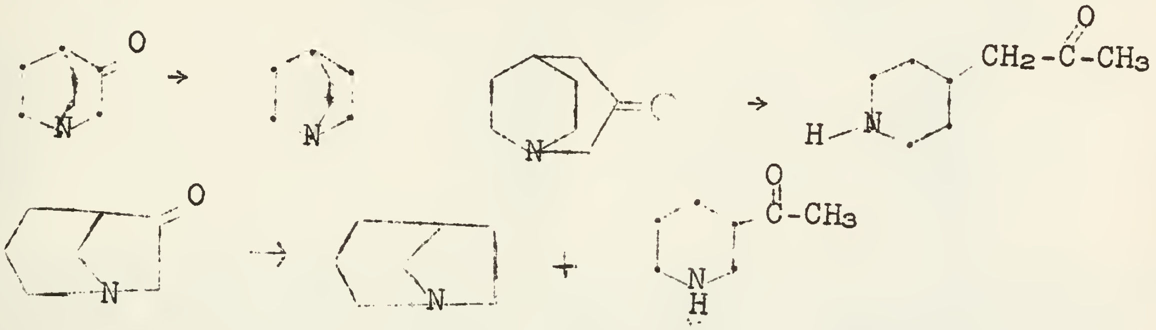
The rearrangement of α-amino ketones during the Clemmensen reduction has been studied extensively. (10-20). The C_α-N bond is broken, and a bond between nitrogen and the carbonyl carbon is formed if a five- or six-membered ring can be formed. The following reactions exemplify this:



Considering Compound I, a phenyl group at positions 1, 2, or 4 or two alkyl groups at position 2 of 1-substituted-3-piperidone does not affect the course of the reaction and the five-membered ring is formed. In the case of two alkyl substituents at position 2 racemization occurs. Because recamization could not occur with HCl alone, this reaction supports an initial C_α-N bond cleavage. Corresponding hydroxyl compounds such as 1-methyl-2-ethyl-3-hydroxypiperidine or 1-methyl-2(1-hydroxyethyl)-piperidine cannot be reduced by this method (11,20), thus giving further evidence that the alcohol is not an intermediate.

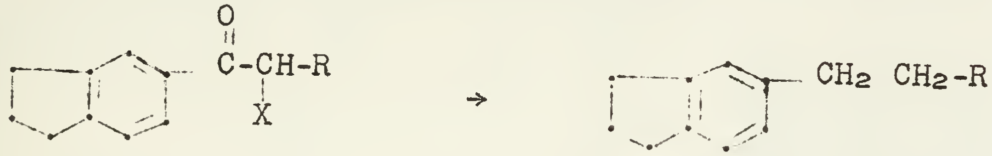
In the reaction of 1-methyl-2-acetylpiperidine to form 1-methylaminoheptane some 1-methylamino-6-heptanone forms, and this can be reduced to 1-methylaminoheptane (20). This again supports initial cleavage of the C_α-N bond.

In the case of certain bicyclics anomalous reactions occur: (21)



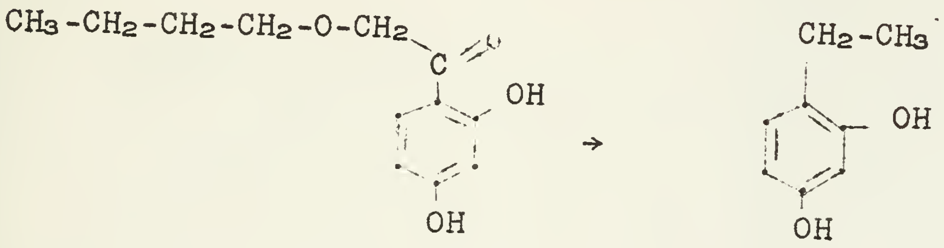
A similar type of reaction is represented by α-thioketones: (22)

Elimination reactions which involve reduction of the carbonyl group and elimination of α-substituents often occur (23,24).



R=H, CH_3

X=H, Cl, Br, $NHCH_3$, $N(C_2H_5)_2$, NH_2



Kinetics

Reaction kinetics for the Clemmensen reduction of p-hydroxyacetophenone were studied by Nakabayashi (25). Rates were determined by measuring the change in p-hydroxyacetophenone concentration with time at 60° using 13.3% ethanol and 2.03% zinc amalgam with 23 $cm.^2$ contact area between the amalgam and aqueous phase. The aqueous layer was stirred at a constant rate. The reaction velocity varies with acid concentration and with the type of acid: more concentrated acid increases the rate, the rate being about ten times faster in 2.72N HCl than in 0.452N HCl; and the rate is about ten times slower

in 2.72N H_2SO_4 than in 2.72N HCl. The first-order rate plot shows a decrease in the rate constant with time in the initial stages of reaction with an HCl concentration less than 1.81N; however, it is linear from the beginning of the reaction if the HCl concentration is greater than 2.15N or if polyvinyl alcohol (a polarographic maximum suppressor) is added to a smaller acid concentration. For smaller acid concentrations the rate constants calculated neglecting the first 5-10 min. of reaction agree with those calculated using the polyvinyl alcohol. The purpose of the polyvinyl alcohol is to prevent retardation in the rate due to adsorption on the amalgam surface of product competitive with hydrogen. (26). Table I shows that the first-order rate constant varies very little with the initial ketone concentration, c_o, thus showing that the reaction is first order with respect to the ketone.

Table I - Effect of c_o on the First-order Rate Constant k at 60°

Conc. of HCl, N.	$c_o \times 10^2$, moles/l.	$k \times 10^2$, min.$^{-1}$
2.15	1.99	3.26
2.15	1.19	3.36
2.26	3.98	3.40
2.26	2.05	3.57
2.72	1.99	4.03
2.72	0.80	4.21

Although the rate varies with acid concentration, either hydrogen and/or chloride ion could be causing this effect. Therefore KCl is added to make the total chloride and electrolyte concentration constant. The total electrolyte concentration is essentially constant throughout the reaction since the electrolyte concentration is high compared to p-hydroxyacetophenone concentration, and therefore, the effect of HCl concentration on the activity coefficient of hydrogen is comparatively small. Fig. 1 shows the results in 3.00N and 2.00N chloride ion concentration with 2.03% zinc amalgam at 60°. For acid concentration low compared to chloride ion concentration the apparent rate constant definitely is dependent on hydrogen ion concentration, but for higher acid concentration, the apparent rate constant is only slightly dependent on acid concentration. If the rate is assumed to be independent of hydrogen ion concentration, then chloride ion but not hydrogen ion may take part in the rate-determining step. It should be noted that most Clemmensen reductions are carried out with more concentrated acid and with a higher concentration of zinc in the amalgam.

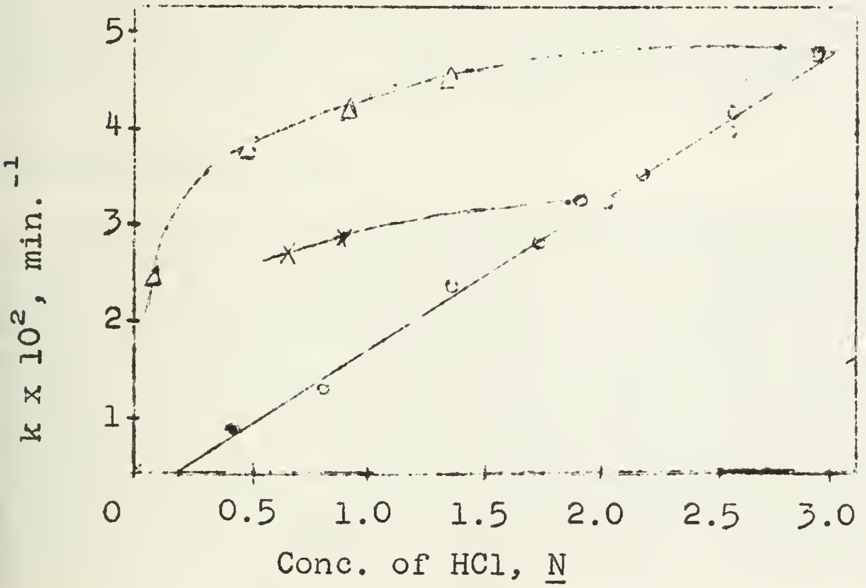


Fig. 1. o, HCl; Δ,[HCl]+[KCl]=3.00N; X,[HCl]+[KCl]=2.00N.

The energy of activation was determined to be 5.1 kcal./mole for 2.00N HCl, 2.00% zinc amalgam, 2.0×10^{-2} mole/l. initial p-hydroxyacetophenone concentration, in a temperature range of 30-70°.

The percentage of zinc in the amalgam affects the rate of reaction, the type of products formed, and the yield of products. Thus the zinc is most likely taking part before or during the rate-determining step.

From these data, two mechanistic aspects can be discussed. Consider:

$$A + H_3O^{\oplus} \underset{\text{fast}}{\overset{K}{\rightleftarrows}} AH^{\oplus} + H_2O \qquad A = \text{p-hydroxyacetophenone}$$

$$AH^{\oplus} + Cl^{\ominus} + (Zn)_x \xrightarrow[\text{slow}]{} \text{product}$$

If the equilibrium constant of the first step is so large that most of A is converted to $AH^{\oplus}$, the velocity of the reaction may become independent of hydrogen ion concentration. For the protonation of p-hydroxyacetophenone K is very small; so that this mechanism would require hydrogen ion dependence. Experimentally, this reaction is independent of hydrogen ion concentration for concentration of HCl above 1N where the ketone is not largely protonated. Therefore consider the alternate mechanism:

$$A + Cl^{\ominus} + (Zn)_x \underset{\text{slow}}{\rightleftarrows} \text{intermediate}$$

$$\text{intermediate} + H_3O^{\oplus} \xrightarrow[\text{fast}]{} \text{product}$$

In this case the rate is not dependent on hydrogen ion concentration and the rate-determining step is the formation of a complex involving ketone, chloride ion, and the metallic zinc. The difference in the rate for chloride ion and sulfate ion may be due to a steric factor.

Electrochemical Data

Electrolytic reduction of aldehydes and ketones produces products similar to those found in the Clemmensen reduction; the nature of the products depends on the electrolytic conditions and especially on the metal or alloy used for the cathode. Reviews have been made by Swann (27,28). An important factor in the electrolytic reduction is the overvoltage of the electrode. Studies of the electrolytic reduction of acetone and 2-pentanone show that the potential of an electrode is more reducing when no ketone is present than when the ketone is added; that is, a more negative voltage is necessary for hydrogen gas evolution than for ketone reduction (29,30). The high hydrogen overvoltage is explained by the following mechanism: (26,31-33).

1) $H_3O^{\oplus} + e^{\ominus} \xrightarrow{(Zn)_x} (Zn)_xH + H_2O$ fast

$(Zn)_xH$ = adsorbed hydrogen atoms

2) $(Zn)_xH + (Zn)_xH \longrightarrow H_2 + (Zn)_{2x}$

or $(Zn)_xH + H_3O^{\oplus} + e^{\ominus} \longrightarrow H_2 + (Zn)_x + H_2O$ slow

Because the rate of combination of hydrogen atoms $[(Zn)_xH]$ is slow, hydrogen gas evolution will be slow and the adsorbed hydrogen atoms can be considered a source of hydride for reaction with some form of the ketone adsorbed on the surface.

Polarographic reduction of para-substituted acetophenones gives reduction potentials which compare favorably to the amalgam potentials (measured versus a standard calomel electrode) observed in the Clemmensen reduction for acetophenone and p-hydroxyacetophenone (34). This suggests a similarity of the processes occurring in electrochemical reduction and the Clemmensen reduction. A mercury cathode produces pinacols exclusively. The mechanism for hydrogen evolution at the mercury electrode is different from that at amalgamated zinc: (26,33)

$$1)\quad H_3O^{\oplus} + e^{\ominus} \xrightarrow{(Hg)_x} (Hg)_xH \qquad \underline{\text{slow}}$$

$$2)\quad (Hg)_xH + (Hg)_xH \longrightarrow H_2 + (Hg)_{2x}$$

$$\text{or}\quad (Hg)_xH + H_3O^{\oplus} + e^{\ominus} \longrightarrow H_2 + (Hg)_x + H_2O \qquad \underline{\text{fast}}$$

In this case formation of "metal hydride" is slow and that which forms reacts immediately to form hydrogen gas; consequently, no "metal hydride" is available for ketone reduction and only one-electron products (pinacols) and alcohols will occur. The following mechanism is suggested for pinacol formation (34,35).

$$1)\quad R_2CO \xrightarrow{e^{\ominus}} R_2\dot{C}O^{\ominus} \xrightarrow{H_3O^{\oplus}} R_2\dot{C}OH$$

$$\text{or}\quad R_2CO \xrightarrow{H_3O^{\oplus}} R_2COH^{\oplus} \xrightarrow{e^{\ominus}} R_2\dot{C}OH$$

$$2)\quad 2R_2\dot{C}OH \longrightarrow R_2COHCOHR_2$$

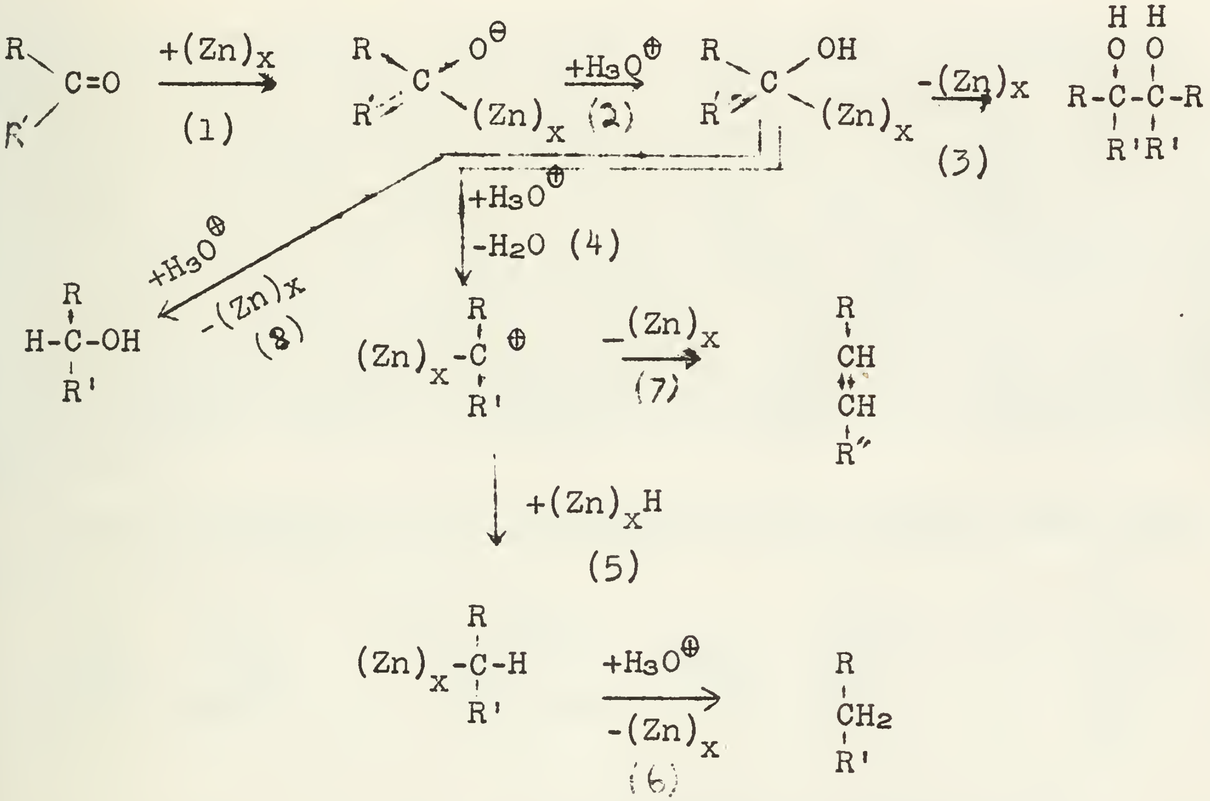
Another observed fact is that zinc is necessary for hydrocarbon formation. The accepted mechanisms for hydrogen molecule formation suggest that on zinc, hydrogen atom combination is slow enough so that reduction of the ketone can occur by means of the adsorbed atomic hydrogen ("metal hydride").

Nakabayashi has also studied the effect of the zinc amalgam potential on the products of the reaction for the Clemmensen reduction of acetophenone and p-hydroxyacetophenone (34). An increase in electrolysis current shifts the amalgam cathode potential to more negative (reducing) values with a concommitant increase in the ratio of pinacol to hydrocarbon in the product. Thus the rate of pinacol formation versus the rate of hydrocarbon formation increases as the potential becomes more negative. Considering a common intermediate RCOHR', it might be argued that, since pinacol formation from this intermediate involves no electron transfer whereas hydrocarbon formation would involve electron transfer, the rate of pinacol formation is not affected with potential change whereas hydrocarbon formation may increase or remain unchanged as the potential becomes more negative. Consequently, the pinacol to hydrocarbon ratio should not increase as is observed with the potential becoming more negative. However, increasing the current increases the rate of radical formation so that more dimer may form, and therefore the pinacol to hydrocarbon ratio will be larger due to the increased rate of radical formation and not the subsequent reactions of the radical. Moreover, the potential of the amalgam affects many factors such as rates of diffusion

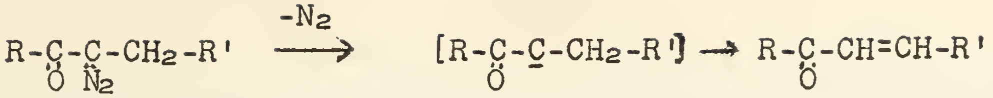
and adsorption, activity of the zinc electrode, and hydrogen atom recombination; so that an argument based on the potential change does not rule out a common radical intermediate (26).

Mechanism

In order to postulate a mechanism, the following facts must be taken into account: alcohol and olefin are not intermediates, a free carbonium ion is not an intermediate, the rate-determining step is independent of hydrogen ion concentration except for very small hydrogen ion concentration, the rate-determining step is influenced by chloride ion concentration, the zinc takes part before or during the rate-determining step, and a means for the formation of pinacol, saturated hydrocarbon, olefin, and alcohol should be possible. The following proposal meets these requirements. The point in the reaction sequence at which the organic compound becomes bound to the surface could involve only the ketone directly or an intermediate radical which has formed. (26,30,31).



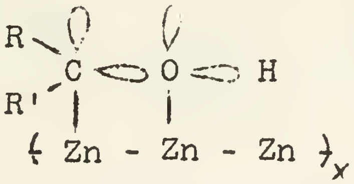
The step in which the metal-carbonyl complex forms, Step 1, is both the rate-determining step and the potential-determining step. The course of the reaction is determined by the free energy of activation for each step which can occur; thus pinacol formation will predominate if a stabilized radical can be formed or if the concentration of ketone molecules near the amalgam is very large. The chemisorbed organic molecule on the metal surface is stabilized in such a way that reaction with protons is retarded as in the case of adsorbed hydrogen, so that alcohol formation would require a high activation energy. Olefin formation can occur if the intermediate resulting from Step 4 leaves the metal and the resulting carbene-like intermediate rearranges to the olefin. A similar type of reaction takes place with the conversion of diazoketones to α,β-unsaturated carbonyl compounds. (36).



$$R-\underset{O}{C}-\underset{N_2}{C}-CH_2-R' \xrightarrow{-N_2} [R-\underset{O}{C}-\underline{C}-CH_2-R'] \rightarrow R-\underset{O}{C}-CH=CH-R'$$

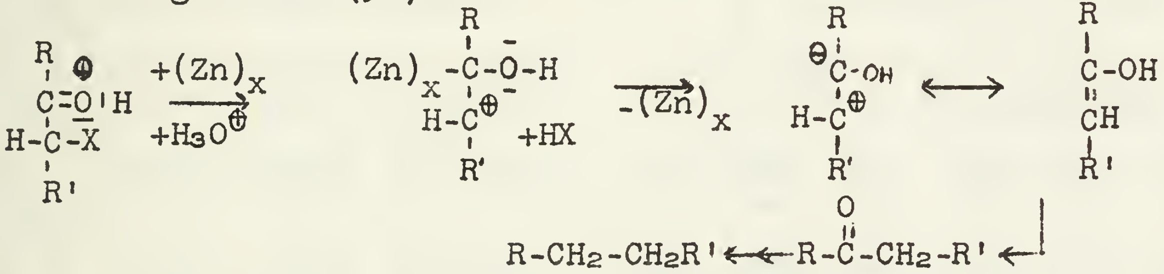
Therefore rearranged olefins may be formed, but not rearranged saturated hydrocarbons. Olefin formation may be favored if the complex resulting from Step 4 can be stabilized by resonance as in the aromatic series, so that the intramolecular hydrogen shift (Step 7) occurs more readily than the hydride reaction (Step 5).

The metal-organic bond may form with the carbonyl carbon alone or it could form with both the carbon and oxygen of the carbonyl group (30). Shared electron bonds could be formed between the π-bond of the ketone, a hydrogen ion, and the metal so as to give a species like:



So far the chloride ion effect has not been accounted for. In contrast with the above mechanism the chloride ion may enter the transition state, however, it could produce the observed effect on the rate by certain electrochemical phenomena. When chloride ion is present in electrolytic reactions it enters the double layer at the metal surface and forms a layer on the metal surface. If the concentration of chloride ion is large the phenomen of electrostriction is important (37). This process involves the "squeezing out" of solvent molecules from the surface of the metal so that the activity of the solvent molecules is lowered. Therefore when the organic molecule surrounded by solvent molecules approaches the electrode, the surrounding solvent molecules are stripped off the ketone more readily and the ketone can diffuse more rapidly to the electrode and react faster.

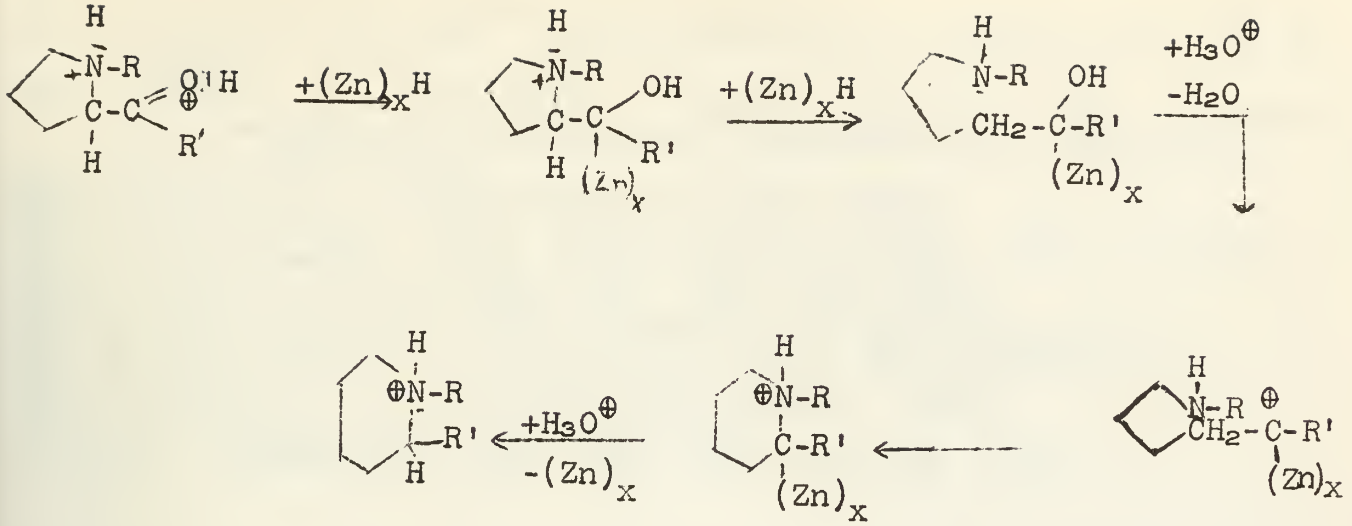
The elimination of α-electronegative substituents may occur in the following manner (31):



X= -OH, -OR, -SR, -NH$_2$, -NR$_2$, -Cl, -Br

The bond with the metal provides added electron atmosphere for the bonds in the neighborhood of the carbonyl carbon atom, and the α-electronegative substituent exerts an electron attracting effect. Thus elimination becomes possible. The resulting intermediate ketone may be isolated in some cases as previously noted.

The rearrangement of α-amino ketones may be explained as follows:



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FREE RADICAL REACTIONS OF ORGANOPHOSPHORUS COMPOUNDS

Reported by C. Heins October 24, 1960

Introduction

Although free radical reactions constitute only a small number of the reactions of organophosphorus compounds, they are interesting not only because of their synthetic possibilities, but also because a study of them helps shed light on the understanding of free radical mechanisms in general. For convenience, the reactions dealt with in this seminar have been classed into two groups: those in which phosphorus is attacked by an aryl or alkyl radical to yield products, and those in which products are formed by attack of a phosphorus radical on organic compounds.

Reactions of Phosphorus Radicals with Unsaturated Compounds

When phosphorus trichloride is refluxed with a terminal olefin in the presence of small amounts of diacetyl peroxide, addition across the double bond takes place to give the 2-chloroalkyldichlorophosphine in 15-20% yield. (1)

$$(1)\quad RCH{:}CH_2 + PCl_3 \longrightarrow RCHClCH_2PCl_2$$

As the reaction does not take place except in the presence of free radical initiators, the following radical chain mechanism has been proposed to account for the results:

$$(2)\quad Z. + PCl_3 \longrightarrow ZCl + .PCl_2$$

$$(3)\quad .PCl_2 + RCH{:}CH_2 \longrightarrow R\underset{\cdot}{C}HCH_2PCl_2 \quad (I)$$

$$(4)\quad (I) + PCl_3 \longrightarrow RCH(Cl)CH_2PCl_2\ (II) + .PCl_2$$

$$(5)\quad (I) + RCH{:}CH_2 \longrightarrow R\dot{C}HCH_2CH(R)CH_2PCl_2 \quad (III)$$

$$(6)\quad (III) + PCl_3 \longrightarrow RCH(Cl)CH_2CH(R)CH_2PCl_2 + .PCl_2$$

The formation of high-boiling materials which always constitute a portion of the product can be explained either by reactions such as (5) and (6), or by the formation of a $RCH(Cl)CH_2P.Cl$ radical from (II), which could then attack a second molecule of olefin.

Phenyldichlorophosphine reacts with olefins to form the corresponding 2-chloroalkylphenylchlorophosphine. (2) The reaction reportedly proceed more readily than with trichlorophosphine, perhaps because of the weakened C-Cl bond. The reaction with acrylonitrile, methyl methacrylate and styrene produce telomers in which the olefin:phosphorus trichloride ratio appears to be quite high. A 1:1 product can be obtained with allyl ether. (2) The mechanism seems to be analogous to that suggested for the addition of phosphorus trichloride to olefins, except that in this case the $C_6H_5P.Cl$ radical is the chain carrier, and telomerization, as demonstrated in (5) and (6), is the predominant reaction.

In the presence of radical initiators, phosphine itself reacts readily with olefins to form addition products. (3)

$$(7) \quad PH_3 + RCH{=}CH_2 \longrightarrow RCH_2CH_2PH_2,\ (RCH_2CH_2)_2PH,\ (RCH_2CH_2)_3P$$

When phosphine and butylene are combined in a 1:1 ratio, the yield of mono-, di-, and tributylphosphine amounts to 38, 10 and 2% respectively, with 36% phosphine recovered unchanged. A good yield of tributylphosphine can be obtained when a 3:1 ratio of butylene to phosphine is used. Table I lists products and yield for several of these reactions.

TABLE I

Unsaturated compound	moles	moles phosphine	product phosphine	yield %
1-butene	0.5	0.5	butyl	38
			dibutyl	10
			tributyl	2
1-butene	0.28	0.09	tributyl	68
cyclohexene	0.15	0.15	cyclohexyl	34
allyl alcohol	0.32	0.33	-- hydroxypropyl	26
			bis(")	5
			tris "	2

It has been proposed that the reaction proceeds through the radical species .PH₂, .PHR and .PR₂. (3) Although no mechanism has been formulated, the most straightforward would involve the formation of alkyl- and dialkylphosphines as intermediates. A possible mechanism is given below.

$$(8) \quad Z\cdot + PH_3 \longrightarrow \cdot PH_2 + ZH$$

$$(9) \quad \cdot PH_2 + RCH{=}CH_2 \longrightarrow R\underset{\cdot}{C}HCH_2PH_2 \quad (IV)$$

$$(10) \quad (LV) + PH_3 \longrightarrow RCH_2CH_2PH_2 \quad (V) \quad + \quad \cdot PH_2$$

Radical attack on (V) could then result in the formation of $RCH_2CH_2PH\cdot$, which could then undergo reactions (9) and (10) to generate dialkylphosphine. This, in the same fashion, could then form the trialkylphosphine.

Diethylphosphite in the presence of benzoyl peroxide also adds to double bonds. (4) Isopropenyl acetate and vinyl acetate form (VIIIa) and (VIIIb) respectively. The mechanism appears to be as follows:

$$(11) \quad Z\cdot + HP(O)(OEt)_2 \longrightarrow ZH + \cdot PO(OEt)_2 \quad (VI)$$

$$(12) \quad (VI) + CH_2{=}C(R)OAc \longrightarrow R\dot{C}(OAc)CH_2P(O)(OEt)_2 \quad (VII)$$

$$(13) \quad (VII) + HP(O)(OEt)_2 \longrightarrow RCH(OAc)CH_2PO(OEt) \quad (VIII)$$

$$\qquad\qquad\qquad\qquad\qquad\qquad (a)\ R{=}CH_3$$

$$\qquad\qquad\qquad + \cdot PO(OEt)_2 \quad (b)\ R{=}H$$

$$(4) \quad (VII) + n\ CH_2{=}C(R)OAc \longrightarrow \text{telomer}$$

Considerable telomerization is observed when isopropenyl acetate and diethylphosphite are used in a 1:1 ratio. With a 2.5 molar excess of the phosphite, a 72% yield of the 1:1 product is formed. The presence of the olefin itself appears to have an inhibitory effect on the reaction. This might be caused by hydrogen abstraction to yield rela-

tively unreactive allyl radicals, which would effectively interrupt chain addition. (5)

Recent work has shown that phosphorous acid itself will add to double bonds to form phosphonic acids. (6)

(15) $RCH{=}CH_2 + P(OH)_3 \longrightarrow RCH_2CH_2PO(OH)_2$

Here again, free radical initiators are necessary to bring about a reaction. The mechanism is probably analogous to that proposed for the addition of the diethyl ester, with $.PO(OH)_2$ as the chain carrier. Yields of about 20% of the monoaddition product were reported for a number of olefins. (6) Chromatography of the reaction mixtures resulted in the isolation of the 2:1 telomers. In the case of 1-hexene, the 2:1 telomer was shown to be 2-butyl octylphosphonic acid, indicating telomer formation occurs in a head to tail fashion. This compound was synthesized using 2-butyl-1-bromo-octane and triethylphosphite. (7)

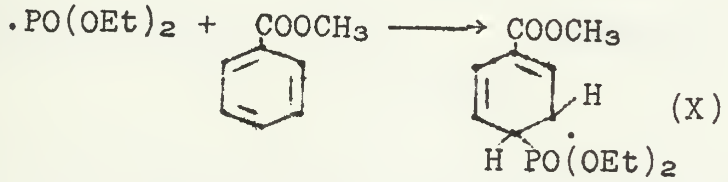
(16) $C_6H_{13}CH(C_4H_9)CH_2Br + P(OEt)_3 \rightarrow \underset{(IX)}{C_6H_{13}CH(C_4H_9)CH_2PO(OEt)_2}$

(17) $(IX) \xrightarrow{H_3O\,\oplus} C_6H_{13}CH(C_4H_9)CH_2PO(OH)_2$

A reaction that appears to have interesting synthetic possibilities is the free radical phosphonation of aromatic compounds using diethylphosphite. Methyl benzoate and diethylphosphite were refluxed several hours with a half-molar quantity of di-tertiarybutyl peroxide. Distillation of the reaction mixture removed unreacted starting material and a quantity of isobutylphosphonate, leaving behind a gummy mass which, upon hydrolysis, gave a 65% yield (based on methyl benzoate) of p-carboxyphenylphosphonic acid. (8) The following mechanism was suggested.

(18) $(t\text{-}C_4H_9O)_2 \longrightarrow 2\ t\text{-}C_4H_9O.$

(19) $t\text{-}C_4H_9O. + HPO(OEt)_2 \longrightarrow .PO(OEt)_2 + t\text{-}C_4H_9OH$

(20)


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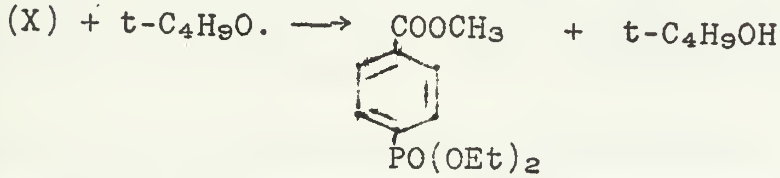


(22) $t\text{-}C_4H_9OH \xrightarrow{-H_2O} CH_3C(CH_3){=}CH_2$

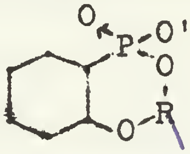
(23) $CH_3C(CH_3){=}CH_2 + .PO(OEt)_2 \longrightarrow (CH_3\dot{C}(CH_3)CH_2PO(OEt)_2 \quad (XI)$

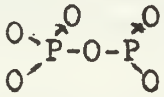
(24) $(XI) + HPO(OEt)_2 \longrightarrow CH_3CH(CH_3)CH_2PO(OEt)_2 + .PO(OEt)_2$

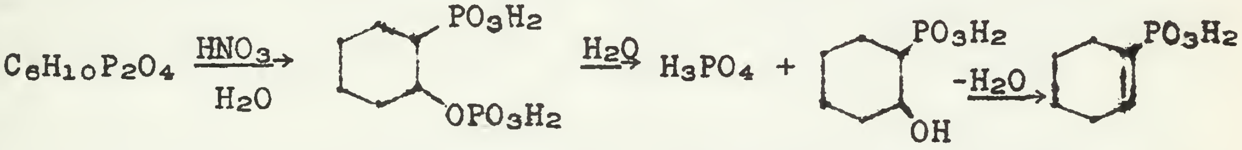
This mechanism is not completely satisfactory, however. One mole of di-tertiarybutyl peroxide is consumed for each mole of product formed. Hence, barring another source of radicals, a 50%

yield of carboxyphenylphosphonic acid would be the maximum employing only one half mole of the peroxide. The fact that the p isomer was formed almost exclusively has also not been explained.

In 1914, Willstatter observed that cyclohexene reacts with white phosphorus and oxygen to produce a white, hygroscopic solid with an empirical formula of $C_6H_{10}P_2O_4$. (9) When hydrolyzed under oxidizing conditions (40% HNO_3), 1-cyclohexene phosphonic acid (isolated as the Pb salt) and phosphoric acid were formed. Recent study has confirmed Willstatter's work, and has shown that the reaction appears to proceed by a radical chain process. When freshly distilled olefin was used (little peroxide present) the reaction proceeded very slowly; addition of azobisisobutyronitrile immediately initiated a rapid oxygen uptake. Addition of hydroquinone effectively inhibited the oxidation process. (10) The product formed, insoluble in benzene and decomposed by water and alcohols, appears to be a polymeric anhydride, possibly of the form:



Molecular weight determinations indicated there are roughly 5 units to the chain. The NMR spectrum showed a strong signal at +26.3 p.p.m. (17 megacycles, dimethylformamide solvent, phosphoric acid standard) which was attributed to  $O_2P(O)\text{-}O\text{-}P(O)O_2$. When the product was allowed to react with ethanol and the reaction mixture distilled, diethylphosphite was obtained in a 29% yield, indicating a non-carbon-bonded phosphorus in the phosphite state. When the oxygen-phosphorus adduct using isobutylene was subjected to oxidative hydrolysis, a lead salt was isolated of composition corresponding to a hydroxyphosphonate, presumably $HOCH_2C(CH_3)_2PO_3Pb$ since no elimination had occurred. This would lend support to the following hydrolysis mechanism of the cyclohexene adduct. (11)

(25)


The mechanism by which the "phosphorate", $C_6H_{10}P_2O_4$, is formed is not known. One possibility is that the olefin is attacked by a radical with the partial structure P-O. The radical generated might then attack a phosphorus molecule to form a carbon-phosphorus bond. (11)

Reactions Involving Radical Attack on Phosphorus

Carbon tetrachloride reacts with triethylphosphite to give trichloromethylphosphonate and ethyl chloride. (12)

$$(26)\quad CCl_4 + P(OEt)_3 \longrightarrow CCl_3PO(OEt)_2 + EtCl$$

It might appear that this reaction is simply another example of the Arbuzov synthesis of phosphonates, which involves nucleophilic displacement of the halide. This does not appear to be the case, however. Although at 80° without a radical initiator an excellent yield of trichloromethylphosphonate is obtained, traces of benzoyl peroxide in-

crease the rate at this temperature fourfold. Irradiation with ultraviolet light gives an 80% yield at room temperature; no reaction occurs at 25° after thirty days in the dark. The yield is significantly decreased by the addition of hydroquinone. (13)

The mechanism which has been suggested involves trichloromethyl as the chain carrier, and the formation of an intermediate phosphoranyl radical with an expanded valence shell. (14)

(27) $CCl_3\cdot + (EtO)_3P \longrightarrow CCl_3\dot{P}(OEt)_3$ (XII)

(28) $(XII) + CCl_4 \longrightarrow CCl_3\overset{+}{P}(OEt)_3Cl^-$ (XIII) $+ CCl_3\cdot$

(29) $(XIII) \longrightarrow CCl_3PO(OEt)_2 + EtCl$

An alternative mechanism would be one in which (XII) would collapse to give the product and an ethyl radical.

(30) $(XII) \longrightarrow CCl_3PO(OEt)_2 + Et\cdot$

(31) $Et\cdot + CCl_4 \longrightarrow EtCl + CCl_3\cdot$

Some workers have ruled out this second mechanism because no material resulting from ethyl coupling or disproportionation could be isolated. (13) Walling has pointed out, however, that this is not a valid objection because of the extreme reactivity of ethyl radicals with carbon tetrachloride. (15)

An ionic product similar to (XIII) is obtained in the reaction of bromoform with triphenylphosphine. (16)

(32) $CHBr_3 + (C_6H_5)_3P \longrightarrow (C_6H_5)_3\overset{\oplus}{P}CHBr_2Br^-$

Here also, irradiation will initiate a reaction at room temperature that would not otherwise occur. A possible mechanism is analogous to that depicted for the reaction of carbon tetrachloride with triethyl phosphite in equations (26) and (27). The product, which is fairly soluble in hot water, contains ionic bromine. Its infrared spectrum exhibits a band at 2780 cm^{-1}, which is characteristic of $R_3P\oplus CH$.

A few years ago it was discovered that at elevated temperatures or under irradiation at room temperature, mercaptans and triethylphosphite give the corresponding alkane and thiophosphonate (triethylphosphorothionate) (17).

(33) $RSH + P(OEt)_3 \longrightarrow RH + SP(OEt)_3$

Later work showed that disulfides could be used (giving thioethers rather than alkanes), and that free radical initiators other than light would cause the reaction to proceed at room temperature. (18) The suggested mechanism is as follows.

(34a) $RSH \longrightarrow RS\cdot + H\cdot$

(34b) $RSSR \longrightarrow 2\ RS\cdot$

(35) $RS\cdot + P(OEt)_3 \longrightarrow RS\dot{P}(OEt)_3$

(36) $RS\dot{P}(OEt)_3 \longrightarrow R\cdot + SP(OEt)_3$

(37a) $R. + RSH \longrightarrow RH + RS.$

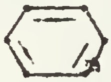
(37b) $R. + RSSR \longrightarrow RSR + RS.$

Here again the phosphorus radical must have an expanded valence shell to accomodate nine electrons. It has been suggested by Walling that reaction (35) derives considerable driving force from the contribution of a polar structure to the transition state. (15)

(38) $RS.\ P(OEt)_3 \longleftrightarrow R\overset{-}{S}.\overset{+}{P}(OEt)_3$

In the decomposition of the intermediate radical, cleavage of the R-S bond takes place almost to the exclusion of R-O cleavage. When benzyldiethylphosphite was reacted with butyl mercaptan only three percent of the product was toluene, even though the intermediate benzyl radical would be much more stable than the alkyl radical. (19)

It was found that this reaction could be extended to the synthesis of triethylphosphate, using alkoxide radicals and triethylphosphite. Here, however, the reaction does not appear to proceed via a chain mechanism, since a 45.5% of the dialkyl coupling product was isolated (15).

(39) $RO. + P(OEt)_3 \longrightarrow RO\dot{P}(OEt)_3$ R =  $-C(CH_3)_2-$

(40) $RO\dot{P}(OEt)_3 \longrightarrow OP(OEt)_3 + R. \longrightarrow 1/2\ R\text{-}R$

A rather unusual reaction is the oxidative chlorophosphonation of alkanes.

(41) $RH + 2\ PCl_3 + O_2 \longrightarrow RPOCl_2 + HCl + POCl_3$

The procedure simply consists in bubbling oxygen through a mixture of hydrocarbon and PCl_3. The dichlorophosphonate can then be isolated by distillation (20). The reaction appears to proceed instantaneously, the rate seeming to be dependent only on the speed at which oxygen is dissolved in the mixture. Moreover, the reaction does not appear to be temperature-dependent: using cyclohexane as the hydrocarbon, cyclohexyldichlorophosphonate is obtained in about a 30% yield between the temperatures of -40° and 70° (21). The mechanism of the reaction has not been completely elucidated. The trichlorophosphoperoxide diradical, $CCl_3\dot{P}OO.$, has been presumed to be an intermediate (22,23). It is questionable, however, whether this species actually plays a role. In a recent, unpublished report is was stated that hydroperoxides, formed in the hydrocarbon by short exposure to oxygen, appear to be excellent initiators. The rate of the reaction depends directly on the peroxide concentration and is first order in PCl_3 (24). An earlier unpublished paper presented evidence that relatively unreactive peroxide radicals could react with PCl_3 to form $POCl_3$ and the more reactive alkoxide radical. This species might displace a halide radical from PCl_3 to give the alkyl dichlorophosphonate. Atomic chlorine could then generate an alkyl radical by removal of a hydrogen atom from the hydrocarbon (25).

(42) $ROO. + PCl_3 \longrightarrow RO. + POCl_3$

(43) $RO. + PCl_3 \longrightarrow RPOCl_2 + Cl.$

(44) $RH + Cl. \longrightarrow HCl + R. \xrightarrow[O_2]{} ROO.$

In all of the reactions involving alkanes with non-equivalent hydrogens, mixtures of isomers are obtained (26). Recent work has shown that the isomers formed stand practically in the same ratio to one another as the corresponding isomers produced in the free radical chlorination and sulfochlorination of alkanes (27a). Table II lists the ratios of products obtained in the various reactions involving propane, butane and isobutane.

TABLE II (27)

Products	propane		n-butane		isobutane	
	1°	2°	1°	2°	1°	3°
alkylphosphonyldichloride a	50	50	32	68	70	30
	46	54	28	72	-	-
alkylsulfonyl chloride b	50	50	33	67	100	0
Alkyl chloride c	48	52	32	68	67	33

This suggest that an alkyl radical is generated in each case by removal of a hydrogen atom from the alkane with atomic chlorine.

The reaction has been extended to include the synthesis of dialkylphosphinylchlorides by using methyldichloro- and ethyldichlorophosphines, (28) and alkylphenylphosphinyl chlorides using phenyldichlorophosphine (29).

Under special conditions, diazonium salts can react with triarylphosphines to produce tetraarylphosphonium salts and nitrogen.

(45) $ArN{=}NX + (Ar)_3P \longrightarrow (Ar_4P)^+X^- + N_2$

The reaction must be carried out in a two-phase ethyl acetate-water system buffered with sodium acetate. Addition of triarylphosphine to this system containing the diazonium salt causes an immediate evolution of nitrogen (30). In the presence of acrylonitrile, the addition of phosphine causes polymer formation as well.

The course of the reaction appears to be quite involved, and although no mechanism has been definitely established, a rather interesting one has been proposed. What makes elucidation difficult is that other reactions take place in a single phase alcohol-water system, or in the unbuffered two-phase system (31). They are:

(46) $ArN{=}NCl + (C_6H_5)_3P \xrightarrow{H_2O} ArH + HCl + (C_6H_5)_3PO + N_2$

(47) $ArN{=}NCl + 2\ (C_6H_5)_3P \xrightarrow{H_2O} ArNHNH\overset{+}{P}(C_6H_5)_3Cl^- + (C_6H_5)_3PO$

Both reactions are assumed to proceed through the formation of the arylazophosphonium salt.

(48) $ArN{=}NCl + (C_6H_5)_3P \longrightarrow ArN{=}N\overset{+}{P}(C_6H_5)_3Cl^-$

It would appear that the unstable product of this last reaction might decompose into the tetraarylphosphonium salt, but this has not been observed in either alcohol solution or in the two-phase system in

which no acetate has been added. In the formation of the tetraaryl salt in buffered solution, it has been suggested that rather than proceeding through such an intermediate as this, the reaction involves a single electron transfer between the triarylphosphine and aryl diazonium acetate; the diazonium radical thus formed collapses to give acetate ion, nitrogen and a phenyl radical, which combines with the triarylphosphinium radical generated in the first step (30).

$$(49)\quad (C_6H_5)_3P: \qquad CH_3COON{=}NAr \longrightarrow (CH_3COON{=}NAr)^{\dot{-}} \longrightarrow CH_3COO^- + Ar\cdot + N_2$$

$$(50)\quad Ar\cdot + (C_6H_5)_3\dot{P}^{\oplus} \longrightarrow (C_6H_5)_3\overset{\oplus}{P}Ar$$

It might be noted that decomposition of aryldiazotriphenylphosphonium acetate has not really been ruled out as a means of producing the teraarylphosphonium ion. Also, the polymerization of acrylonitrile (presumably induced by free radicals) does not necessarily mean that formation of the phosphonium salt proceeds along a free radical pathway. In any case, it will be interesting to see whether this mechanism is confirmed by future work.

Tetraarylphosphonium salts can also be formed from aryl halides and triphenylphosphine in the presence of Grignard reagents and cobalt chloride (32).

$$(51)\quad (C_6H_5)_3P + ArX \xrightarrow[ArMgX]{COCl_2} (C_6H_5)_3PAr^{\oplus}X^-$$

Here the probable mechanism is a little more straight-forward, as the decomposition of aryl halides in the presence of Grignard reagents and cobalt chloride seems to proceed in the following manner (33).

$$(52)\quad 2C_6H_5MgX + CoCl_2 \longrightarrow (C_6H_5)_2Co + 2\ MgX_2$$

$$(53)\quad (C_6H_5)_2Co \longrightarrow Co + C_6H_5\text{-}C_6H_5$$

$$(54)\quad Co + 2\ C_6H_5X \longrightarrow 2\ C_6H_5\cdot + CoX_2$$

When this reaction is carried out in the presence of triphenylphosphine, biphenyl formation is not suppressed, but the phenyl radical generated in reaction (54) attacks the phosphine to yield a tetraarylphosphonium radical which is then oxidized to the cation; it is not definitely known what compound is the electron acceptor in this case.

$$(55)\quad C_6H_5\cdot + P(C_6H_5)_3 \longrightarrow (C_6H_5)_4\dot{P} \xrightarrow{-e^-} (C_6H_5)_4P^{\oplus}$$

The fact that the fourth aryl group is not donated by the Grignard reagent is clearly demonstrated by the use of a Grignard compound derived from a different halide. With ethyl magnesium bromide and bromobenzene, the tetraphenylphosphonium salt is formed; using phenyl magnesium bromide and bromotoluene, the p-tolyltriphenylphosphonium ion is formed. The Grignard compound appears to serve only as a reducing agent in the synthesis of metallic cobalt, necessary for aryl radical formation, and has been replaced by other reducing agents. Triphenylphosphine and bromobenzene have formed the tetraphenylphosphonium ion in the presence of cobalt chloride and lithium aluminum hydride.

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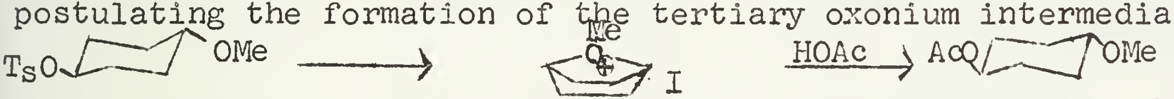
OXONIUM IONS

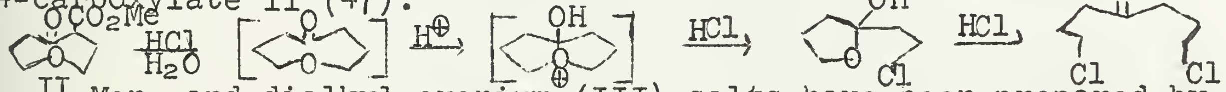
Reported by W. J. McMurray October 27, 1960

Oxonium ions have been postulated as reactive intermediates in reactions involving anchimeric assistance by methoxyl or hydroxyl groups (1-4). Neighboring group participation by an ester involves an intermediate which is designated as a carboxonium ion (5,6). Kreevoy and Taft have proposed both alkyl oxonium and alkylidene oxonium ions as intermediates in the mechanism of the acid catalyzed hydrolyses of ketals (7). Stable oxonium salts were first prepared by Meerwein in 1937 and since then other derivatives containing positively charged oxygen have been synthesized and some of their properties determined. In addition to their role as mechanistic intermediates, stable oxonium ions can also function synthetically as alkylating agents. Pyrylium salts, oxonium ions containing an aromatic system, are valuable starting materials for the preparation of unusual aromatic hydrocarbons or heterocycles (8). Since the addition products of alkyl cations are more stable than the corresponding proton addition products and can be isolated, oxonium salts offer a potentially valuable method to elucidate the mechanism of acid catalyzed reactions (9).

Tertiary oxonium-like transition states have been proposed to explain enhanced rates and as intermediates to explain products in a solvolysis reaction. To illustrate: trans-4-methoxy-cyclohexyl-p-tosylate undergoes solvolysis in acetic acid with both a rate enhancement (compared to the cis isomer) and with retention of configuration (1). Noyce and Thomas explain this result by postulating the formation of the tertiary oxonium intermediate (I).



Examination of the relative rates of solvolysis of 2-,3-,4-, 5-, and 6-methoxy-1-alkyl brosylates in a common solvolyzing medium shows that the rate of 4- and 5- methoxy-1-alkyl brosylates is rapid and dominated by anchimerically assisted ionization. To explain this anchimerically assisted ionization, Winstein proposed a cyclic oxonium ion in the transition state (3). Streitweiser has observed that the acetolysis of optically active 1-butyl-1-d p-nitro benzenesulfonate in a mixed solvent (55% dibutyl ether-45% acetic acid) produced 29% undeuterated butyl acetate. To explain this loss of deuterium the intervention of a tributyl oxonium ion as a discrete but unstable intermediate was suggested (10). Applequist and McGreer have formulated an oxonium ion intermediate to explain the incorporation of ether fragments in the products derived from the reaction of acid on diazocyclobutane in ether-ethanol or tetrahydrofuran-methanol solvents (41). Leonard and co-workers have proposed a transannular oxonium salt to explain the formation of 1,7-dichloro-4-heptanone from the aqueous hydrochloric acid hydrolysis-decarboxylation of methyl 1-oxacycloocta-5-one-4-carboxylate II (47).



II Mon- and dialkyl oxonium (III) salts have been prepared by reaction of anhydrous hydrogen chloride at -70° with the antimony pentachloride adduct of alcohols or ethers in carbon tetrachloride, methylene chloride, or liquid sulfur dioxide (20). If the solvent

is removed and an ether added, hydrogen bonded adducts are formed giving increased stabilization to the oxonium salt. All the salts investigated showed at room temperature an observable hydrogen chloride pressure. From the temperature dependence of this pressure, the heat of decomposition could be calculated. The primary alkyl or aryl oxonium ions show higher heats of decomposition than the

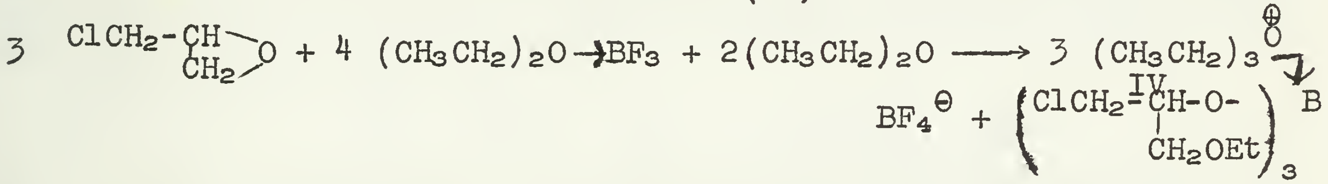
$$CH_3CH_2OCH_2CH_3 + SbCl_6^{\ominus} \xrightarrow{-70^\circ} (CH_3CH_2)_2O \rightarrow SbCl_6 \underset{}{\overset{HCl}{\rightleftharpoons}} \underset{III}{(CH_3CH_2)_2\overset{\oplus}{O}H} \quad SbCl_6^{\ominus}$$

dialkyl or aryl oxonium ions as shown in Table I by comparison of mono- and diphenyloxonium hexachloroantimonate. Further, a comparison of the heats of decomposition of the diethyl-oxonium tetrachloroferrate and tetrachloroaluminate, assuming small entropy differences, indicates the stability of the salts depend upon the anion. In a series of salts which include the same oxonium ion, the stability decreases in the order $SbCl^{\ominus}_6 > FeCl_4^{\ominus} > AlCl_4^{\ominus} > Bf_4^{\ominus} > SnCl_6^{\ominus} > ZnCl_3^{\ominus}$ (20).

Table I
Heats of Decomposition of Alkyl Oxonium Ions

Salt	H(kcal/mole)
$(\phi OH_2)^{\oplus}SbCl_6^{\ominus}$	7.0
$(\phi_2OH)^{\oplus}SbCl_6^{\ominus}$	6.4
$(Et_2OH)^{\oplus}FeCl_4^{\ominus}$	3.84
$(Et_2OH)^{\oplus}AlCl_4^{\ominus}$	8.5
$(EtOH)_2^{\oplus}SbCl_6^{\ominus}$	6,2

Meerwein and co-workers discovered that the reaction of boron trifluoride etherate in excess ether with epichlorohydrin at 20-25° yielded triethyloxonium tetrafluoroborate (IV). The oxonium salt precipitates from solution. The boronic ester (V) which is ether soluble was isolated and characterized (11). It should be mentioned



$$3\ ClCH_2-CH(CH_2)O + 4\ (CH_3CH_2)_2O \rightarrow BF_3 + 2(CH_3CH_2)_2O \longrightarrow 3\ \underset{IV}{(CH_3CH_2)_3\overset{\oplus}{O}}\ BF_4^{\ominus} + \left(ClCH_2-\underset{CH_2OEt}{CH}-O-\right)_3B$$

that ethylene oxide can be used instead of epichlorohydrin and that the etherates of antimony pentachloride, ferric chloride and aluminum chloride exhibit the same behavior as boron trifluoride etherate. The remaining Lewis acid ether complexes investigated but found to be unsuccessful were $BeCl_2$, $ZnCl_2$, $BiCl_3$, BCl_3, $AlBr_3$, $SbCl_3$, SiF_4, $SnCl_4$, and $TiCl_4$. Meerwein and his co-workers have studied the mechanism of this reaction and have isolated all the proposed intermediates (12, 13,40). Unfortunately this method of preparation of trialkyl oxonium ions does not work for higher molecular weight ethers, n-propyl ether being the highest molecular weight ether which reacts (12).

Meerwein found that triethyloxonium tetrafluoroborate melted at 92° and was deliquescent. It was further observed that dry distillation yielded boron trifluoride etherate and ethyl fluoride. This reaction was shown to be reversible when it was found that these

$$(CH_3CH_2)_3O^{\oplus}\ BF_4^{\ominus} \xrightarrow{\Delta} CH_3CH_2F + (CH_3CH_2)_2O \rightarrow BF_3$$

$$CH_3OCH_3 \cdot BF_3 + CH_3CH_2F \xrightarrow[\text{room temp.}]{\text{14 days}} \underset{VI}{(CH_3)_2\overset{\oplus}{O}C_2H_5}\ BF_4^{\ominus}$$

two components when mixed in a bomb at room temperature for five months gave 73% yield of triethyloxonium tetrafluoroborate. Therefore, with regard to an unambiguous structure proof, it was then possible to prepare ethyldimethyloxonium tetrafluoroborate (VI) by the reaction of boron trifluoride dimethyl etherate and ethyl fluoride.

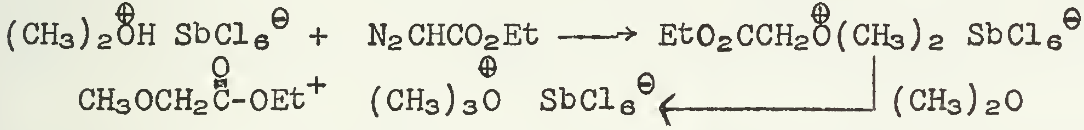
Thermal decomposition of ethyldimethyloxonium tetrafluoroborate produced a gaseous mixture of methyl fluoride and ethyl fluoride

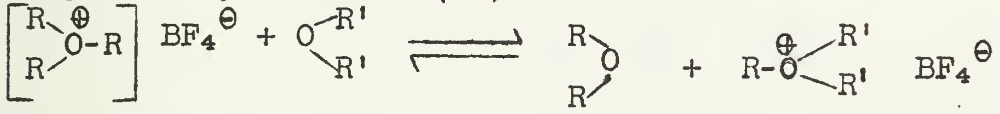
$$(CH_3)_2\overset{\oplus}{O}C_2H_5\ \ BF_4^{\ominus} \xrightarrow{\Delta} CH_3F + C_2H_5F + MeOEt\cdot BF_3 + Me_2OBF_3$$

and the boron trifluoride etherates of methyl ethyl ether (73%) and dimethyl ether (27%). In addition, the reaction of ethyldimethyloxonium tetrafluoroborate with 3,5-dinitro-benzoic acid gave 70% methyl ester and 30% ethyl ester (11).

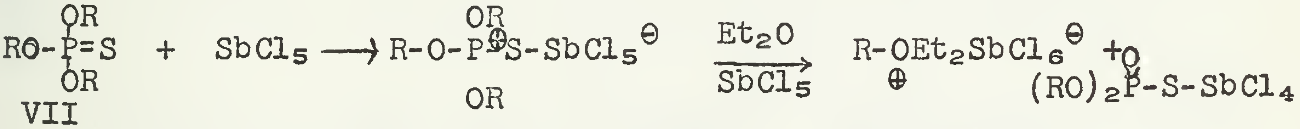
Klages and Meuresch have prepared trialkyl oxonium salts by treatment of the dialkyl oxonium hexachloroantimonate with a diazo paraffin, e.g., diethyl oxonium hexachloroantimonate reacts with diazomethane to give diethylmethyl oxonium hexachloroantimonate in 83% yield (14). The scope of this reaction was not reported. They prepared only the triethyl-, trimethyl-, and methyl diethyl oxonium salts by this method. By a somewhat analogous reaction, Klages and Meuresch prepared trialkyl oxonium ions by reaction of diazoacetic ester with the dialkyl oxonium ion (15). The dialkyl oxonium hexachloroantimonate is treated with diazoacetic ester at -30° in liquid sulfur dioxide. The crystalline residue remaining after evaporation of the sulfur dioxide is treated with the appropriate ether to yield the trialkyl-oxonium ion and the α-alkoxy ester. The latter was isolated when methyl ether was used. By this method tributyloxonium ion could be prepared. This reaction involves an exchange reaction between a tertiary oxonium ion and an ether which was reported by Meerwein (13).

$$(CH_3CH_2)_2\overset{\oplus}{O}H\ \ SbCl_6^{\ominus} \xrightarrow{CH_2N_2} (CH_3CH_2)_2\overset{\oplus}{O}\ CH_3\ \ SbCl_6^{\ominus} + N_2$$





A newer preparation of trialkyl oxonium ions involving the use of trialkylthionophosphate (VII) appears to be applicable to the synthesis of the higher molecular weight trialkyl oxonium ions previously unobtainable by the usual methods (16). The method involves the addition with cooling of antimony pentachloride (2 moles) to a solution of the ester in an excess of the appropriate ether. The precipitated crystals can be isolated after a short period. By this method tributyloxonium hexachloroantimonate was prepared in 63% yield compared to the 33% yield obtained in the diazoacetic ester synthesis.



VII

$$RO-\overset{OR}{\underset{OR}{P}}=S + SbCl_5 \longrightarrow R-O-\overset{OR}{\underset{OR}{P}}{}^{\oplus}S-SbCl_5^{\ominus} \xrightarrow[SbCl_5]{Et_2O} R-\underset{\oplus}{O}Et_2SbCl_6^{\ominus} + (RO)_2\overset{O}{P}-S-SbCl_4$$

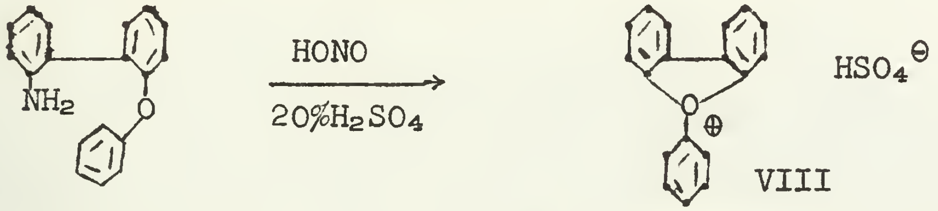
Meerwein has found that alkyl bromide or fluoride in the presence of anhydrous silver tetrafluoroborate are effective alkylating agents for compounds which do not react with alkyl halides alone or with dialkyl sulfate. Triethyloxonium tetrafluoroborate can be prepared at room temperature in 89.5% yield by this method (17,18).

$$(CH_3CH_2)_2O + CH_3CH_2Br + AgBF_4 \longrightarrow (CH_3CH_2)_3\overset{\oplus}{O}\ \ BF_4^{\ominus} + AgBr$$

Triaryl oxonium ions have been synthesized by decomposition of

aryldiazonium tetrafluoroborates in the presence of the appropriate diaryl ether at 80°. In this way, triphenyloxonium tetrafluoroborate was prepared in 2% yield in one hour (19,24). By the same method, O,O'-diphenylenephenyloxonium (VIII) bisulfate was prepared (22).

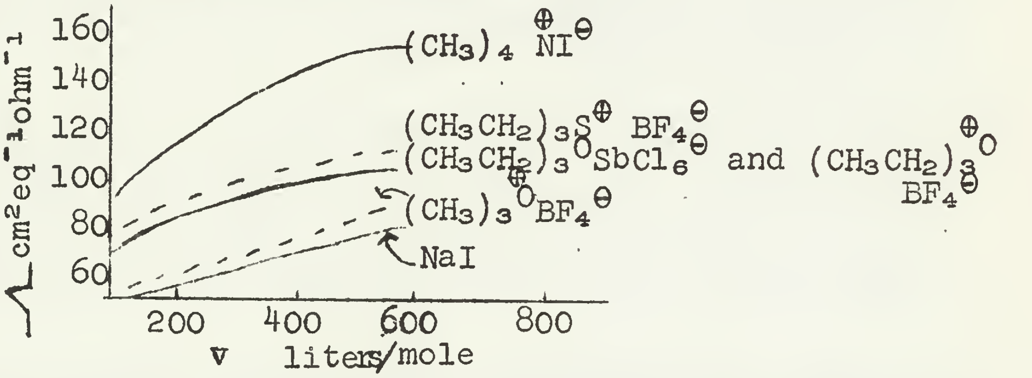
$$\phi_2O + \phi N_2^{\oplus}\ BF_4^{\ominus} \xrightarrow{80^\circ} \phi_3\overset{\oplus}{O}\ BF_4^{\ominus} + n_2$$



VIII

It should be noted that trialkyl oxonium salts containing secondary and tertiary alkyl groups have not been prepared as yet. The failure is ascribed to a steric effect (12).

The trialkyl oxonium compounds behave like salts. They are soluble in liquid sulfur dioxide, nitromethane, less soluble in nitrobenzene and insoluble in ether. The equivalent conductances were measured at 0° in liquid sulfur dioxide to allow comparison with sodium iodide and tetramethyl ammonium iodide. The conductivity measurements show the oxonium salts are dissociated into ions which can carry electric current. The authors ascribed the difference in conductivity between the trimethyl-and triethyl oxonium tetrafluoroborate to a solvation difference (12).

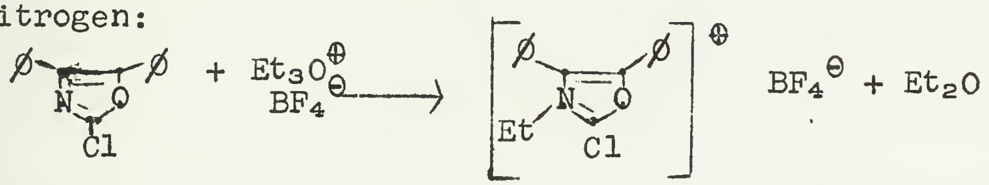


Trialkyl oxonium tetrafluorobroate are immediately hydrolyzed by water to ether, alcohol and tetrafluoroboric acid. In addition

$$R_3O^{\oplus}\ \overset{\ominus}{B}F_4 + H_2O \longrightarrow R_2O + ROH + HBF_4$$

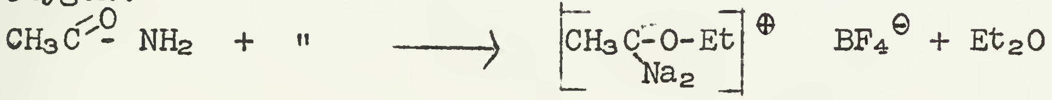
they are powerful alkylating agents reacting with organic nucleophiles containing nitrogen, oxygen or sulfur. To illustrate:

On Nitrogen: ref.



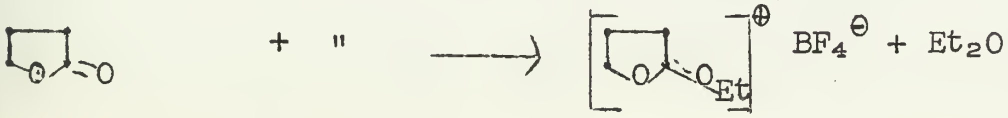
(28)

On Oxygen:



$$CH_3\overset{O}{C}-NH_2 + '' \longrightarrow \left[CH_3\underset{NH_2}{C}-O-Et\right]^{\oplus} BF_4^{\ominus} + Et_2O$$

(12)



(9)

ref. (9)

On Sulfur:

$$Et_2S + \text{"} \longrightarrow Et_3\overset{\oplus}{S}\ BF_4^{\ominus} + Et_2O \qquad (9)$$

On Halogen:

$$NaI + Et_3\overset{\oplus}{O}\ BF_4^{\ominus} \longrightarrow EtI + NaBF_4 + Et_2O \qquad (11)$$

Triphenyl oxonium tetrafluoroborate is colorless and is soluble in acetone, less soluble in alcohol and insoluble in cold water and ether (19). The ultraviolet spectrum of triphenyl oxonium tetrafluoroborate shows peaks at approximately 213 mμ(ϵ=1600), 253mμ(ϵ=1000) and 267mμ(ϵ=600) (solvent, ethanol).

In contrast to the trialkyl oxonium salts the triaryl oxonium compounds are unusually stable. They can be heated at the boiling point in water for 25 hours and still leave 50% of the oxonium ion unchanged (19). Triphenyl oxonium salts are poor phenylating agents and in fact their reactivity toward nucleophiles does not appear to take place in the expected order. For example, refluxing triphenyloxonium tetrafluoroborate (1g.) with 30 ml. of a 7% aqueous solution of sodium azide for fourteen hours yielded only 27% phenyl azide (19). Treatment of triphenyloxonium tetrafluoroborate with aqueous sodium nitrite for 25 hours gave 25% nitrobenzene. No mention is made of the presence of phenol or phenyl nitrtie in the product.

However, 51% of unreacted triphenyloxonium tetrafluoroborate was isolated at the conclusion. In contrast, refluxing triphenyloxonium tetrafluoroborate with pyridine for four hours gave in 89% yield of N-phenylpyridinium tetrafluoroborate. Diethylamine reacts with the triaryloxonium salt to give after eight and one half hours a 59% yield of diethylaniline. This reaction occurs only in the presence of water (19).

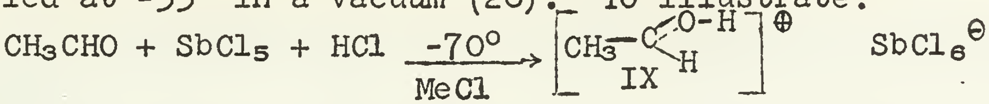
Nesmeyanov has reported recently that nitration of triphenyloxonium salt by either nitronium tetrafluoroborate (NO_2BF_4) at room temperature or nitric acid and sulfuric acid (1:1,5) for 60 hours at 100° gives an 80% yield of tri-nitrophenyloxonium salt of which at least 95% is the para isomer (23). Nitration of triphenyl sulfonium, phenyl trimethyl ammonium, triphenyl carbonium, diphenyl chloronium and bromonium salts give exclusively the meta isomer. Diphenyl iodonium salt yields 72% meta and 28% para isomer.

CARBOXONIUM SALTS:

With the properties and reactions of alkyl and aryl oxonium ions well investigated, attention was turned towards the preparation and examination of oxonium ion derivatives. The tertiary oxonium ions derived by alkylation of carbonyl compounds are designated by Meerwein by the general term carboxonium ions since they show simultaneously the properties of carbonium and oxonium ions (25).

Oxonium salts of aldehydes and ketones, termed by Klages alkylidene oxonium salts, have been prepared (26). The cation of the alkylidene oxonium salts (IX) are of special interest since they are proposed as intermediates in the acid catalyzed condensation of aldehydes and ketones (27). The alkylidene oxonium ions are prepared in the same way as the mono- and dialkyloxonium ions and similarly are stable only with complex anions. The antimony pentachloride

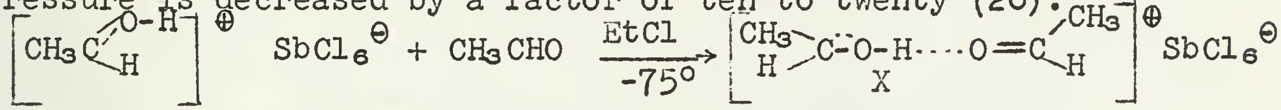
adduct of the carbonyl compound is treated at -70° in methyl chloride with dry hydrogen chloride. After a half hour, the solution is warmed to -20°, cooled again to -70°, filtered, and dried at -55° in a vacuum (26). To illustrate:



IX

The yield when acetaldehyde is used is 80-90%.

The alkylidene oxonium salts have an appreciable hydrogen chloride pressure and as a result fume in the air. They must be stored below 0°. Similar to the mono- and dialkyloxonium salts, the alkylidene oxonium salts form hydrogen bonded adducts (X). By formation of these hydrogen bonds the hydrogen chloride pressure is decreased by a factor of ten to twenty (26).

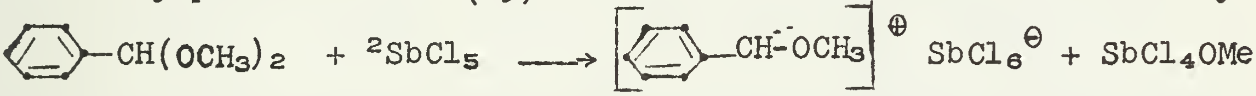


X

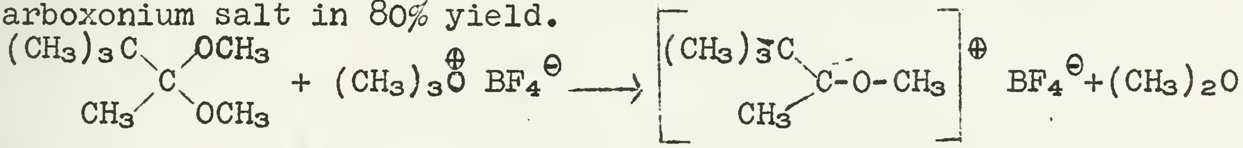
Alkyl alkylidene oxonium salts (unsaturated tertiary oxonium salts) have not been prepared by alkylation of the alkylidene oxonium salts by diazo paraffins (26). However, these can be prepared in a number of other ways. The reaction of methyl [2-halo alkyl] ethers with antimony pentachloride yields methyl alkylidene hexachloroantimonate. The yield is 75% when methyl-α-chloroethyl ether is used (26). It should be noted that the alkyl alkylidene oxonium ion possesses the structure of the intermediate proposed by Kreevoy and Taft in the acid catalyzed hydrolysis of ketals (7).

$$CH_3O\underset{Cl}{C}HCH_3 + SbCl_5 \longrightarrow \left[CH_3CH\overset{..}{=}O\text{-}CH_3\right]^{\oplus} SbCl_6^{\ominus}$$

Alkyl alkylidene salts may also be prepared from the acetal of the appropriate carbonyl compound in two ways. The first method involves the reaction of the acetal with boron trifluoride or antimony pentachloride (29). This method is limited however by a side reaction in which the elements of alcohol are eliminated to form a vinyl ether which is polymerized by the acid present. Acetals which do not possess an α-hydrogen e.g., the dimethyl acetal of benzaldehyde, can be successfully converted by antimony pentachloride to the tertiary unsaturated carboxonium ion. The yield in this case is 73%.

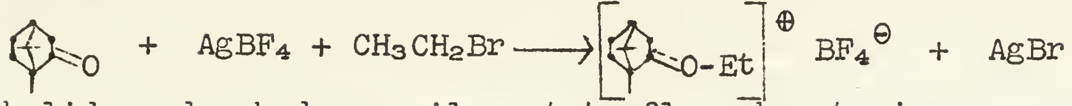


The second method is the reaction of an acetal with trialkyloxonium tetrafluoroborate to produce the alkyl alkylidene oxonium ion (9). The dimethyl acetal of pinacolone reacts with trimethyloxonium tetrafluoroborate in one hour at 43° to give the unsaturated carboxonium salt in 80% yield.



The carbonyl oxygen can be alkylated by reaction with trialkyl oxonium ion or with anhydrous silver tetrafluoroborate and alkyl bromide. However, both these alkylation methods are of limited value since they have been successfully performed only on aldehydes or ketones which possess a tertiary alkyl group next to the carbonyl group e.g., trimethyl acetaldehyde, pinacolone, or

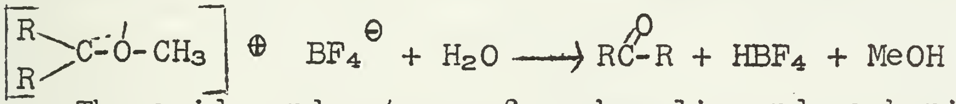
camphor. The ease of alkylation of carbonyl compounds by alkyl



halide and anhydrous silver tetrafluoroborate increases in the order aldehyde < ketone < carboxylic ester < lactone < amide < lactam (25).

The tertiary unsaturated carboxonium ions are more stable than the alkylidene oxonium ions but to avoid decomposition they must be stored below -20° (26), are hygroscopic (9), soluble in acetonitrile, insoluble in ether and can be recrystallized from ethylene chloride (9). The alkyl alkylidene oxonium ions spontaneously react at -30 to -50° with ether to give a resinous macromolecule. This resinous mass is believed to be polymerized vinyl ether arising from abstraction of a proton from the salt to give the vinyl ether which is then polymerized by the strong acid present (26). The tertiary oxonium salts are immediately cleaved by water to yield the original carbonyl compound (9).

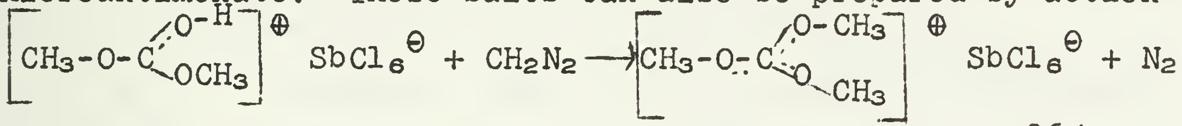
$$[H\text{--}CH_2CH\overset{\cdots}{-}OCH_3]^{\oplus}\ SbCl_6^{\ominus} + Et_2O \longrightarrow [CH_2{=}CHOCH_2] + [Et_2OH]^{\oplus}SbCl_6^{\ominus}$$



The acids and esters of carboxylic and carbonic acids have been converted with antimony pentachloride and hydrogen chloride into acid salts (XI) bearing a hydrogen atom on the oxonium oxygen atom (30,31). These could not be further methylated with diazomethane with the exception of the salt derived from dimethyl carbonate

XI

which formed the symmetrical trimethyl carbonatoacidium hexachloroantimonate. These salts can also be prepared by action of



trialkyl oxonium salts on the ortho carbonic ester in 86% yield (9) or boron trifluoride alone reacts on the orthoester to produce

$$(EtO)_4C + Et_3O^{\oplus}\ BF_4^{\ominus} \longrightarrow [(EtO)_3C]^{\oplus}\ BF_4^{\ominus} + 2\ Et_2O$$

the alkylated acidium salt (29). Esters can be alkylated by alkyl bromide and anhydrous silver tetrafluoroborate. The yield in the case of the dimethyl carbonate is 94% (25).

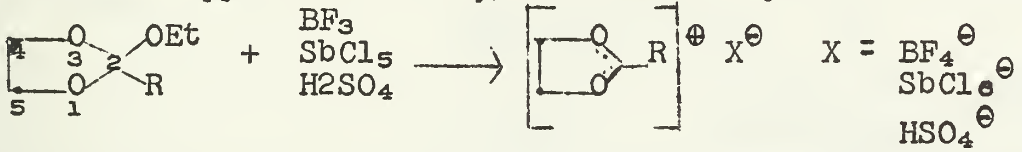
The acidium salts containing hydrogen on the carbonyl are unstable. They have an observable hydrogen chloride pressure, which is lowered when the acidium salt forms hydrogen bonds with a second molecule of unprotonated acid or ester. From the temperature dependence of the hydrogen chloride pressure, the heat of formation can be calculated which for the unalkylated acid salt is 10-11 kcal/mole and 13-14 kcal/mole for the unalkylated ester salts.

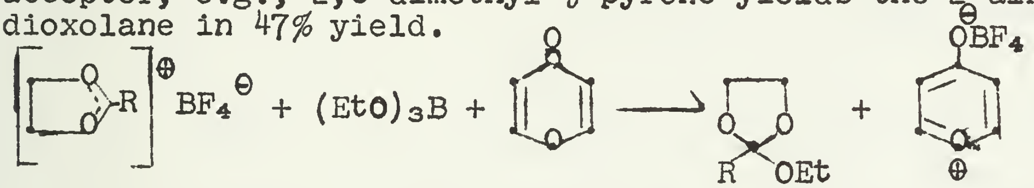
The non-tertiary acidium salts are decomposed by water immeasureably fast. The completely methylated carbonatoacidium salt decomposes with water more slowly and is scarecely hygroscopic when exposed to the air. It decomposes when heated at 70° in a high

vacuum to yield a gaseous mixture consisting of 70% methyl chloride and 30% hydrogen chloride. The decomposition appears to be non-uniform with the chief reaction being the decomposition to methyl chloride and antimony pentachloride adduct of dimethyl carbonate.

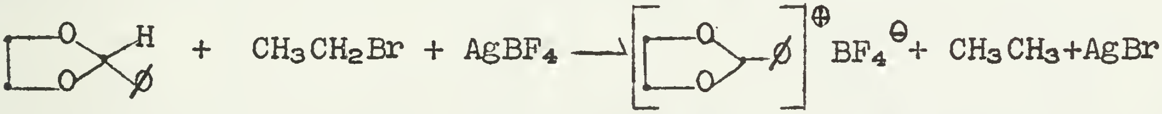
(A publication pertinent to the ensuing section on 1,3-dioxolenium salts has appeared since preparation of this abstract, H. Meerwein et al, Ann., 635, 1 (1960)).

The tertiary carboxonium ions derived from 1,3-dioxolane are of particular interest. It is easily prepared from 2-alkoxy-1,3-dioxolane by any reaction applicable to the ortho esters. The reaction is applicable to 1,3-dioxane but yields are lower. Attempts to prepare carboxonium salts of 1,3-dioxacycloheptane by this method were unsuccessful. In addition, carboxonium ions could not be prepared using boron trifluoride if a chloromethyl group was situated at C-2 (29). The reaction by which 1,3-dioxolenium salts are formed is reversible. Treatment of 1,3-dioxolenium tetrafluoroborate and boronic ester with a strong boron trifluoride acceptor, e.g., 2,6-dimethyl-γ-pyrone yields the 2-alkoxy-1,3-dioxolane in 47% yield.



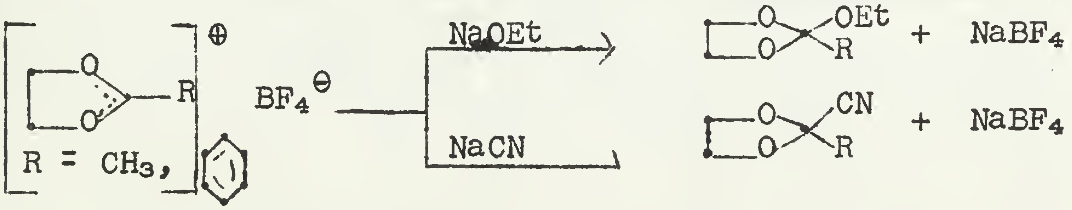


The 1,3-dioxolenium salt can be prepared from dioxolanes which contain one hydrogen in the 2-position by reaction with anhydrous silver tetrafluoroborate and ethyl bromide.

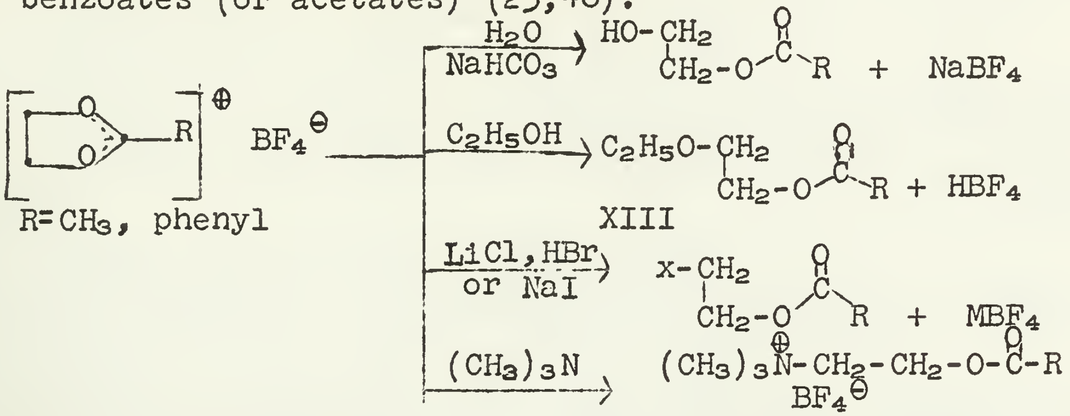


The 1,3-dioxolenium tetrafluoroborate has the same properties as the trialkyl oxonium salts. These oxonium salts are of major interest since they possess the same structure as the intermediates proposed in ionization anchimerically assisted by ester groups.

The 1,3-dioxolenium salts react with nucleophiles to form dioxolanes substituted in the 2-position or β-substituted alkyl esters. To illustrate, the reaction of 2-phenyl(or methyl)-1,3-dioxolenium tetrafluoroborate with sodium ethoxide in ethanol for a short time or with sodium cyanide in methylene chloride-acetonitrile (1:1) for forty-eight hours gave 2-phenyl-2-ethoxy-1,3-dioxolane (30% yield) and 2-phenyl-2-cyano-1,3-dioxolane (44% yield) respectively. The yields are nearly the same for the 2-methyl



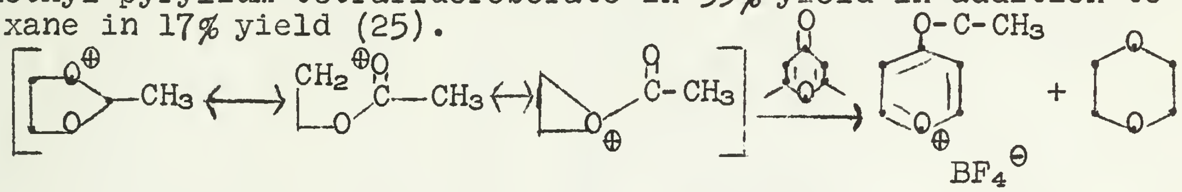
derivative. In both cases, no attempt was made to isolate other products from the reaction or to determine how much unreacted dioxolenium salt remained. In contrast, 2-phenyl(or methyl)-1,3-dioxolenium tetrafluoroborate reacts with water, or ethanol, lithium chloride, hydrogen bromide, sodium iodide, or triethylamine with splitting of the dioxolane ring and formation of β-substituted alkyl benzoates (or acetates) (25,46).



XIII

Meerwein states that the 1,3-dioxolenium ion behaves as a carbonium ion with strong nucleophiles to give the 2-substituted dioxolanes and as an oxonium with weak nucleophiles to give the β-substituted alkyl esters. However, sodium iodide is not a weak nucleophile and further, Winstein (42) has evidence that attack by water occurs at C-2. With 2-phenyl-1,3-dioxolenium tetrafluoroborate, attack by water at C-2 or C-4 would give the same product. However, in the case of ethanol, attack at C-2 gives rise to the orthoester obtained by ethoxide treatment whereas reaction at C-4 gives the observed product. One would expect ethanol and water to react in the same way. This can be accomodated by assuming that ethanol attacks reversibly at C-2 because of the acid present whereas attack at C-4 is not reversible under the reaction conditions i.e., attack at C-2 is kinetically controlled and attack at C-4 is thermodynamically controlled. The same argument of kinetic control verses thermodynamic control can explain the reaction of the dioxolenium salt with halide and amine. It should be mentioned that the ethylene glycol monoethyl ether acetate XIII($R=CH_3$) can be converted to 2-methyl-1,3-dioxolenium tetrafluoroborate by heating to 60° for one hour with trimethyloxonium tetrafluoroborate or by boron trifluoride in six months at room temperature.

In concluding the discussion of the conversions of 2-methyl-1,3-dioxolenium tetrafluoroborate mention should be made of its reaction with 2,6-dimethyl-γ-pyrone. The product obtained is 4-acetoxy-2,6-dimethyl-pyrylium tetrafluoroborate in 53% yield in addition to dioxane in 17% yield (25).



Dioxane is also formed in the reaction of ethylene oxide with triethyl oxonium tetrafluoroborate (13).

In conclusion mention should be made of the other onium salts prepared by Klages, Meerwein and co-workers. Onium salts of nitro compounds and sulfones have been prepared by the reaction with antimony pentachloride and hydrogen chloride (32). Non-tertiary sulfonium salts have been prepared in the same way from mercaptans, sulfides and disulfides (33,34). In the nitrogen family, hydrazinium (+2) salts (35,36), nitrilium salts (37,38), and carbonamidium salts

(39) have been prepared. The preparative value of the pyrylium salts has been recently reviewed (8). Kutzelnigg and Mecke indicate an infrared investigation of oxonium salts will be published in the future (44).

****

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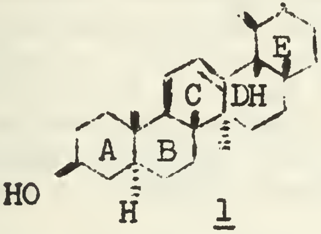
SYNTHESES IN THE TETRA- AND PENTACYCLIC TRITERPENE SERIES

Reported by R. J. Sauer October 31, 1960

The elucidation of gross structures for many tetra- and pentacyclic triterpenes has progressed rapidly since about 1930.[1] This, coupled with the use of the methods of molecular rotation differences[2] and optical rotatory dispersion[3] in assigning stereochemistry, has brought knowledge in this field to a point where synthetic approaches have been attempted. The earliest of these syntheses, the conversion of cholesterol to lanosterol, lanostenol, γ-lanosterol and agnosterol, has been previously reviewed.[4,5] Although the preparations of a number of interesting decalin derivatives of potential utility in triterpene syntheses have been reported, these will not be discussed because of spatial limitations. This discussion will be concerned, therefore, with the more recent routes to the tetra- and pentacyclic triterpenes of the ursane, onocerane and oleanane series.

Expression 1 for α-amyrin was proposed in 1956[6] after the molecule had been degraded and the E-ring fragment characterized as a 2,3,6-trimethylcyclohexanone. The following conversion[7] of glycyrrhetic acid (2) to α-amyrin confirms structure 1 and unambiguously establishes its stereochemistry.



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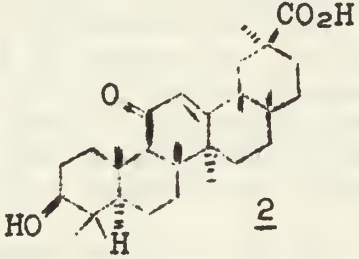

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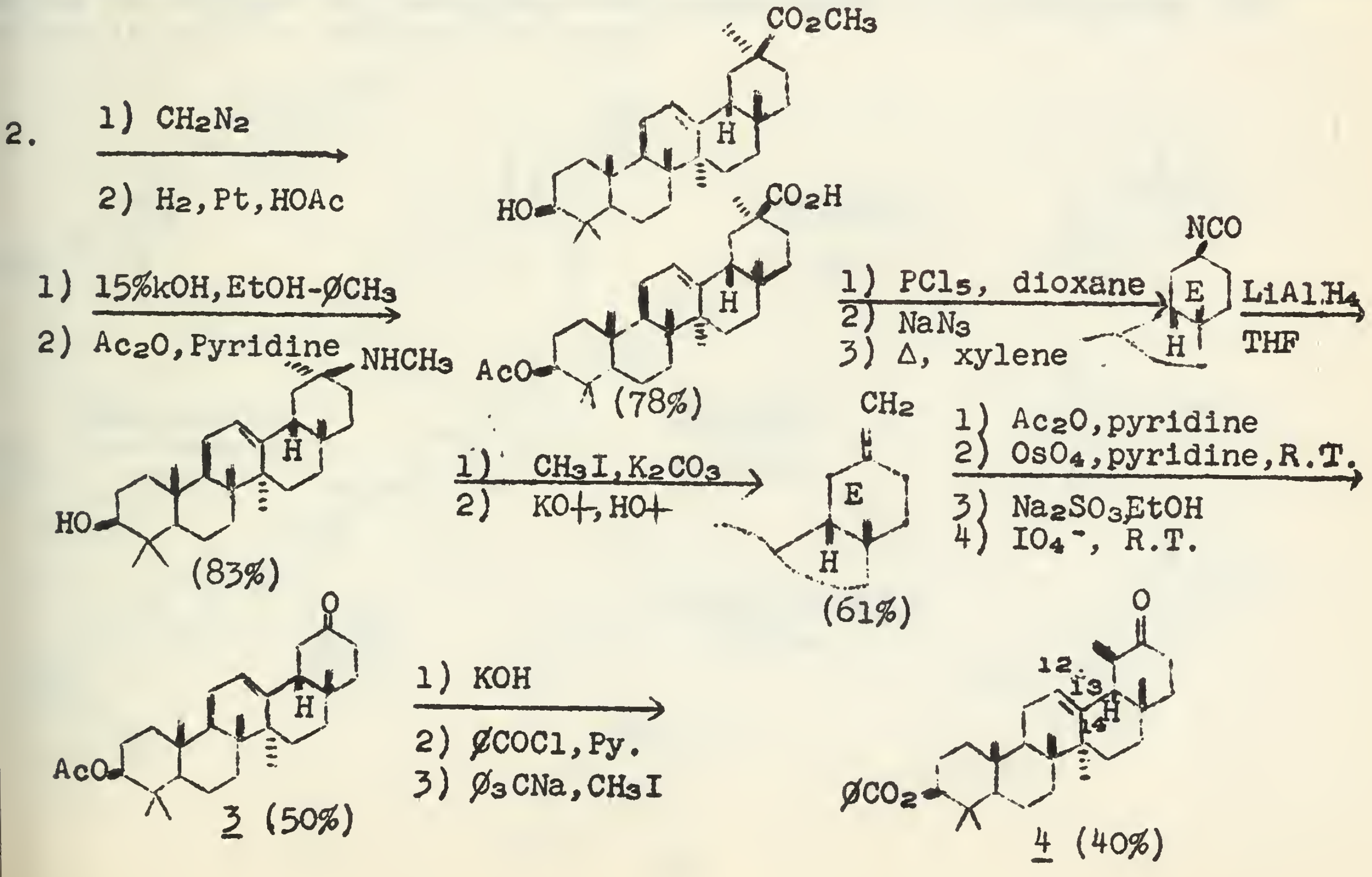
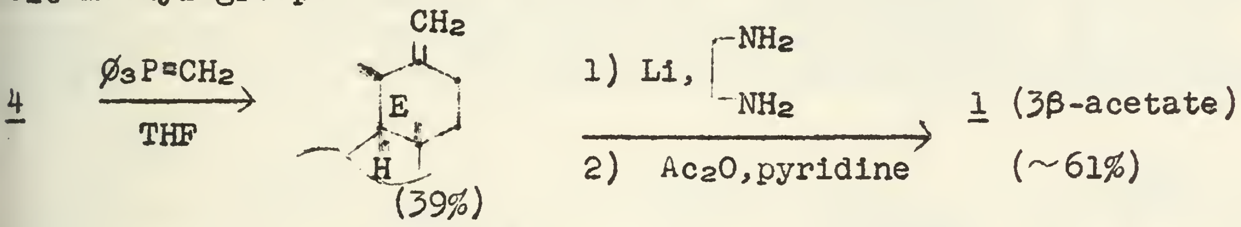


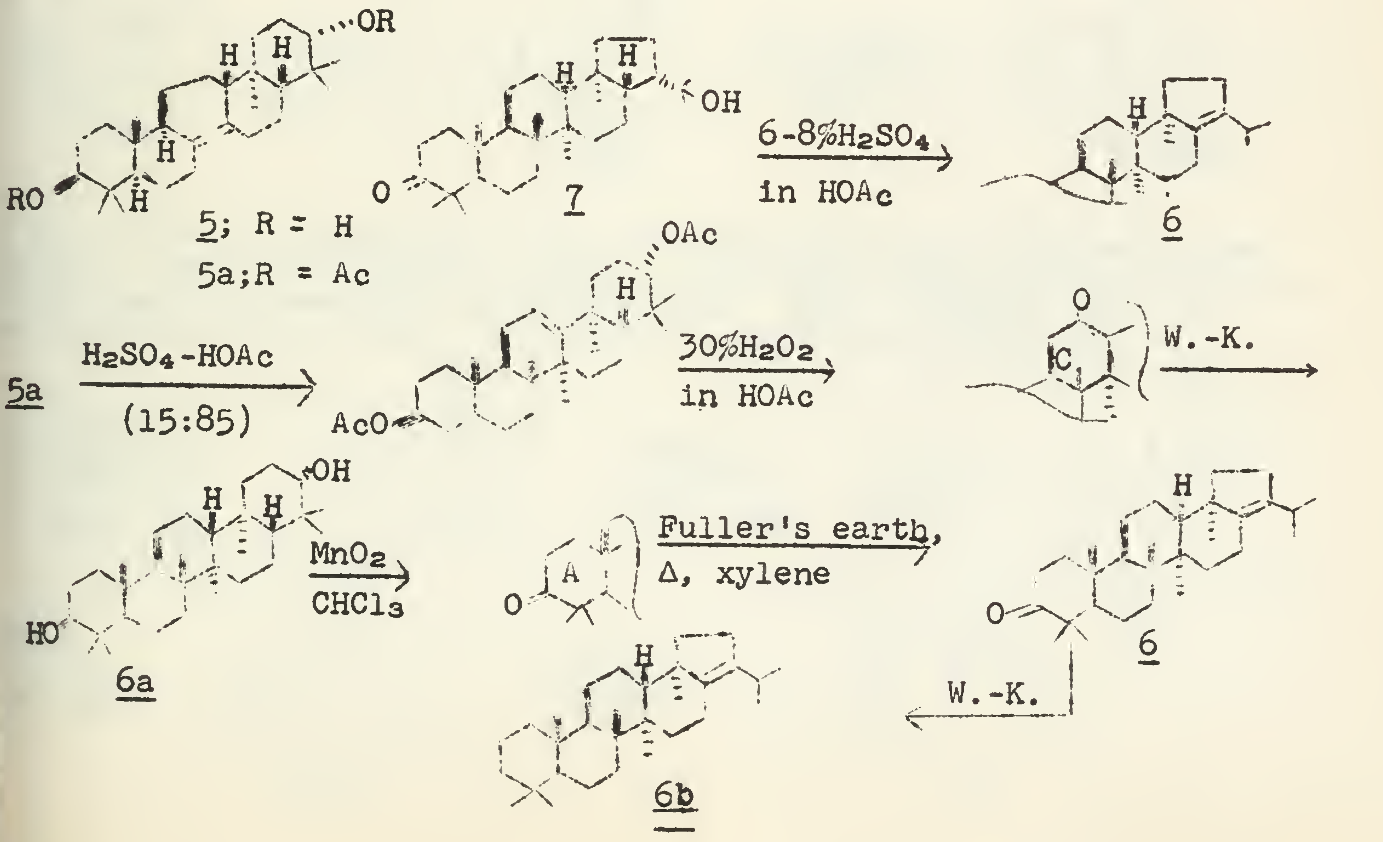
That the preceding reaction sequence had not affected the DE-cis ring fusion was shown by comparison of the rotatory dispersion curves of 3 and 4 with those for coprostan-3-one and its 2β- and 4β-methyl derivatives.^{8} The similarity in the shape (negative Cotton effect) for all of these compounds argues for both the cis-ring fusion and the β-orientation of the methyl group in 4. The location (C_{19} or C_{21}) of this same methyl group, however, does not follow^{3a} from the ORD data, but is to be expected at C_{19} because of steric acceleration of enolization, which results from rather severe non-bonded interactions among the 19α-hydrogen, 16α-hydrogen and 14α-methyl group, toward C_{19}.

The terminal steps of the conversion entail introduction of the C_{20} methyl group:



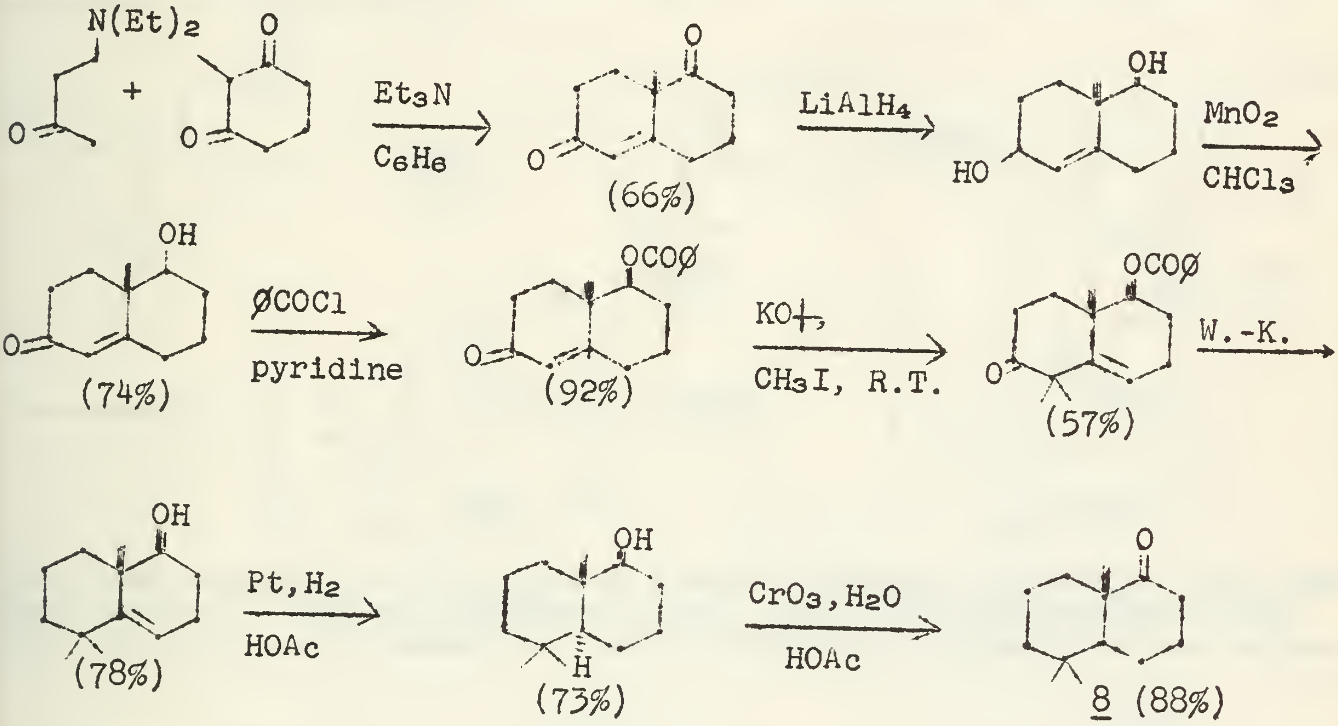
Lithium-amine reducing systems are known in several cases to give the thermodynamically more stable product on reduction of olefins. The orientation of the C_{20} methyl group would be expected, on this basis, to be equatorial to ring E and on the α side of the molecule. Comparison of melting points, mixed melting point, infrared spectra, x-ray powder patterns and ORD curves of the final product with those of authentic α-amyrin acetate proved the two substances identical.

A second conversion, that of α-onoceradiendiol (5) to hopenone-I (6),^{9} a degradation product of hydroxyhopanone (7),^{10,10a} is of interest since it relates the onocerane and hopane series of triterpenes and since it will be referred to later.

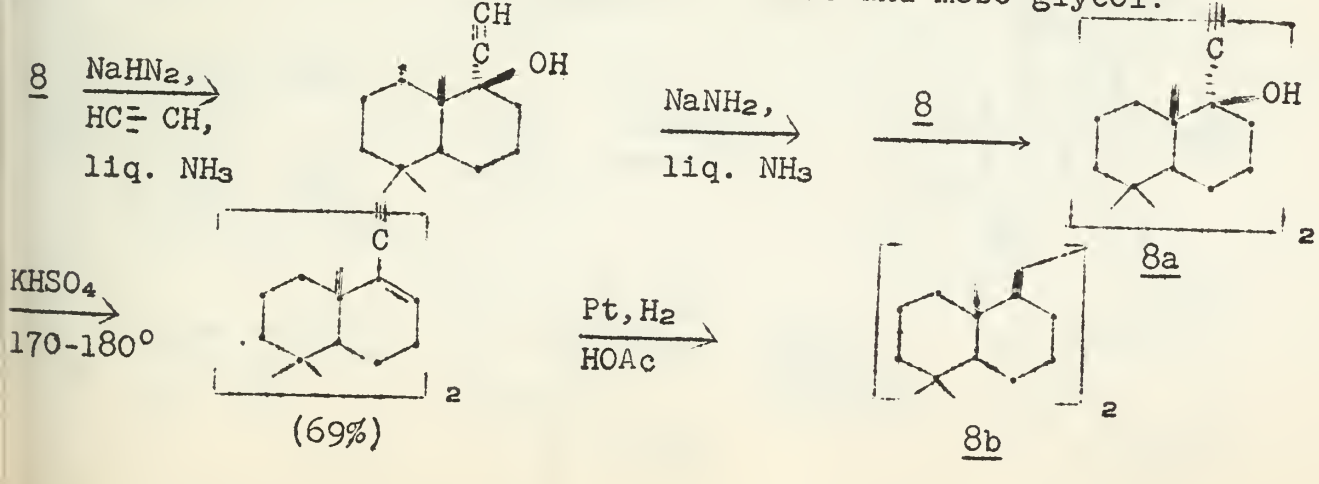


The apparent selectivity in the oxidation of 6a may result simply from control of the reaction time. Analogous semioxidation of 5 has also been accomplished in 60% yield.[24] Location of the double bond in 6 at 17:21 in preference to the 21-isopropylidene isomer would seem to arise from the relief of non-bonded C_{16} hydrogen-isopropylidene methyl interactions which are evident in models. Both 6 and the corresponding hydrocarbon 6b were identical with authentic material initially obtained from hydroxyhopanone (7).

Considering the symmetry of the onocerane carbon skeleton,[11] it is apparent that this series of triterpenes should be readily accessible by the coupling of either a) two identical 13- or 14-carbon units with a third two-carbon unit or b) two identical 14- or 15-carbon units. A route with interesting possibilities, following scheme (a), starts with the synthesis of the AB and DE ring systems, 8:[12,13]



By this method of synthesis, the intermediate 8 must necessarily be racemic. The sterochemical notation used here indicates the relative, rather than the absolute, configuration. Thus, 8 should lead, in the subsequent coupling,[14] to both a racemic and meso glycol:



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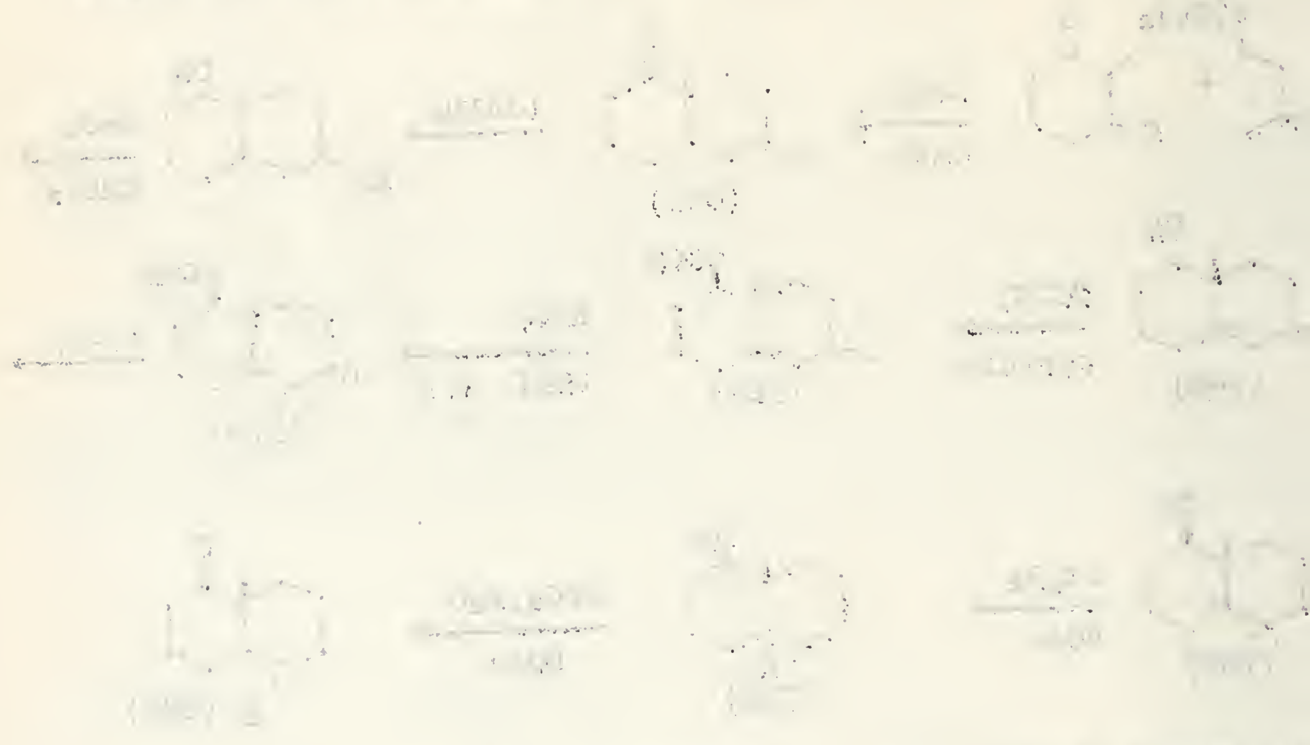

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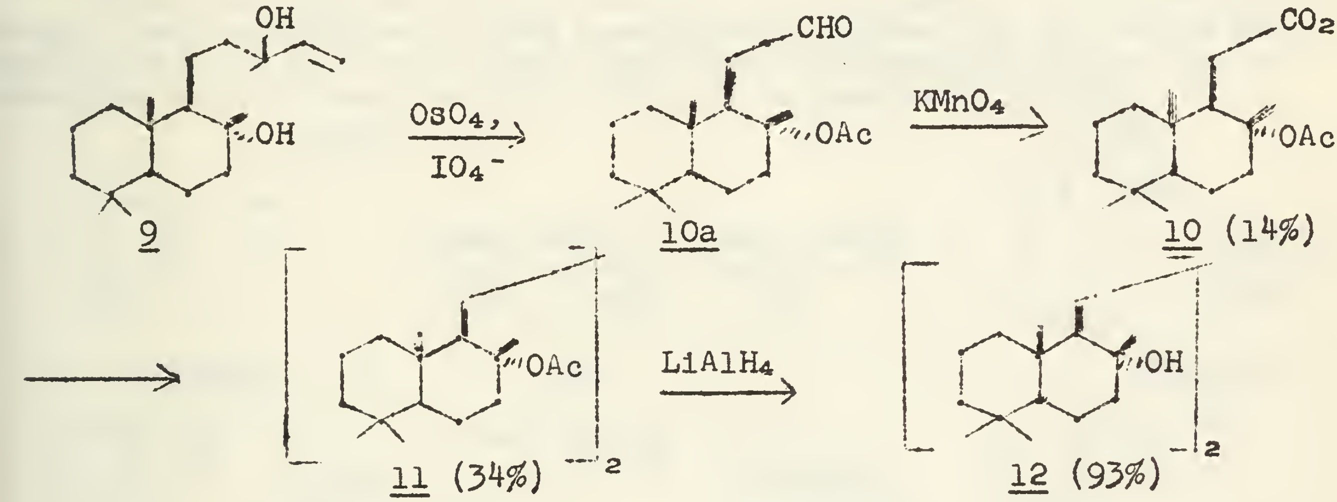
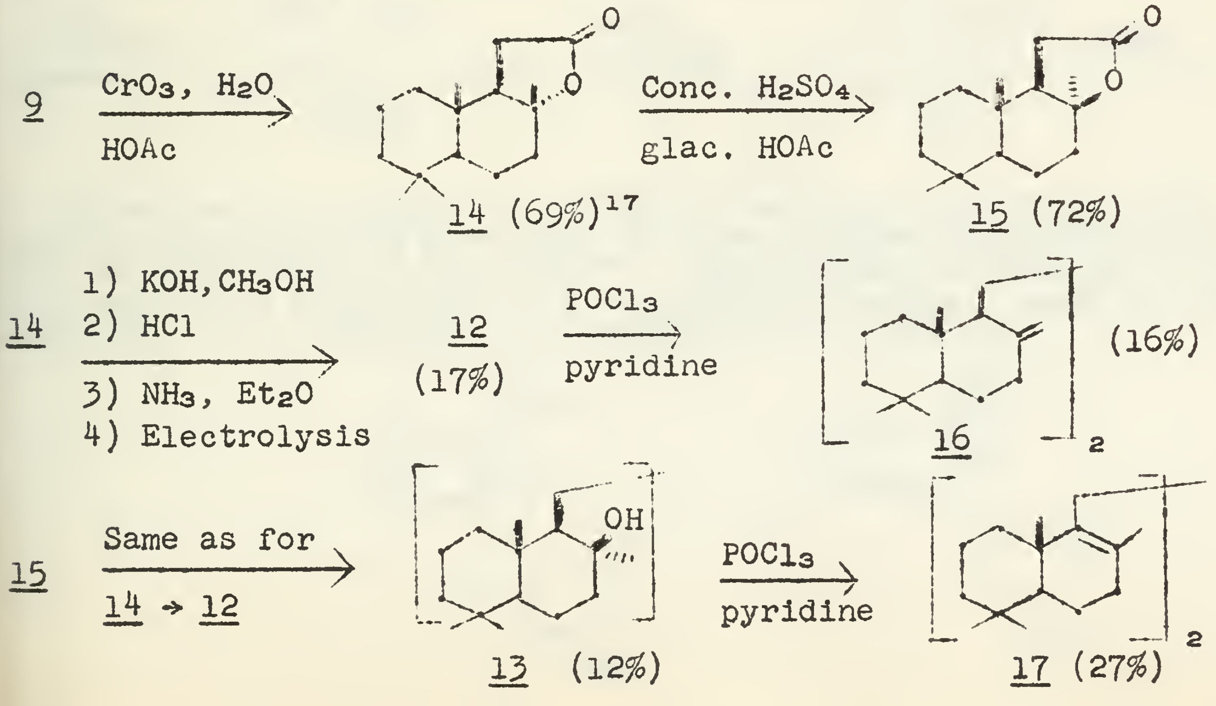
Accordingly, two glycols of melting points 190° and 210° were isolated; the structure 8a was assigned to the lower melting isomer since it is known[15] that there are very few exceptions to the rule that a centrosymmetric *meso* compound melts higher than the corresponding racemate. Although 8b is racemic, its infrared spectrum ($CHCl_3$, CS_2) is identical to that of the optically active bisnoronocerane[11] obtained from α-onoceradiendiol.

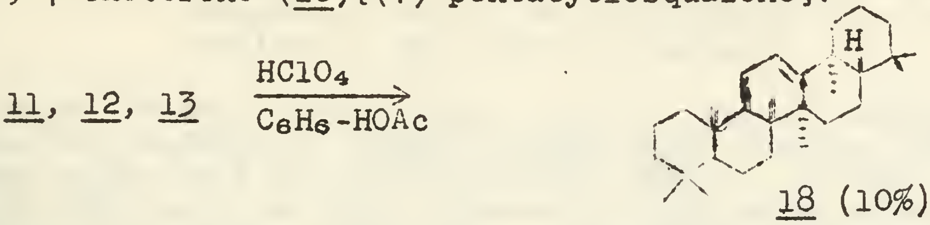
Following approach (b) above, two syntheses which utilize novel attacks on the AB-DE coupling problem have been reported. In the first of these,[16] the key step entails Kolbe electrolysis of a 16-carbon hydroxy acid or its acetate. The acetate 10 is obtained from sclareol (9) by a sequence which can be visualized as proceeding *via* hydroxylation, cleavage to the methyl ketone, formation of a cyclic ketol, dehydration and a final hydroxylation followed by cleavage to 10a. Electrolysis of 10 in methanol at reflux gives the tetracyclic diacetate 11:



This same tetracyclic diol 12 and its 8,8'-epimer 13 are also obtained from sclareol, through norambreinolide (14)[17] and isonorambreinolide (15) respectively in somewhat poorer yield than in the previous scheme.



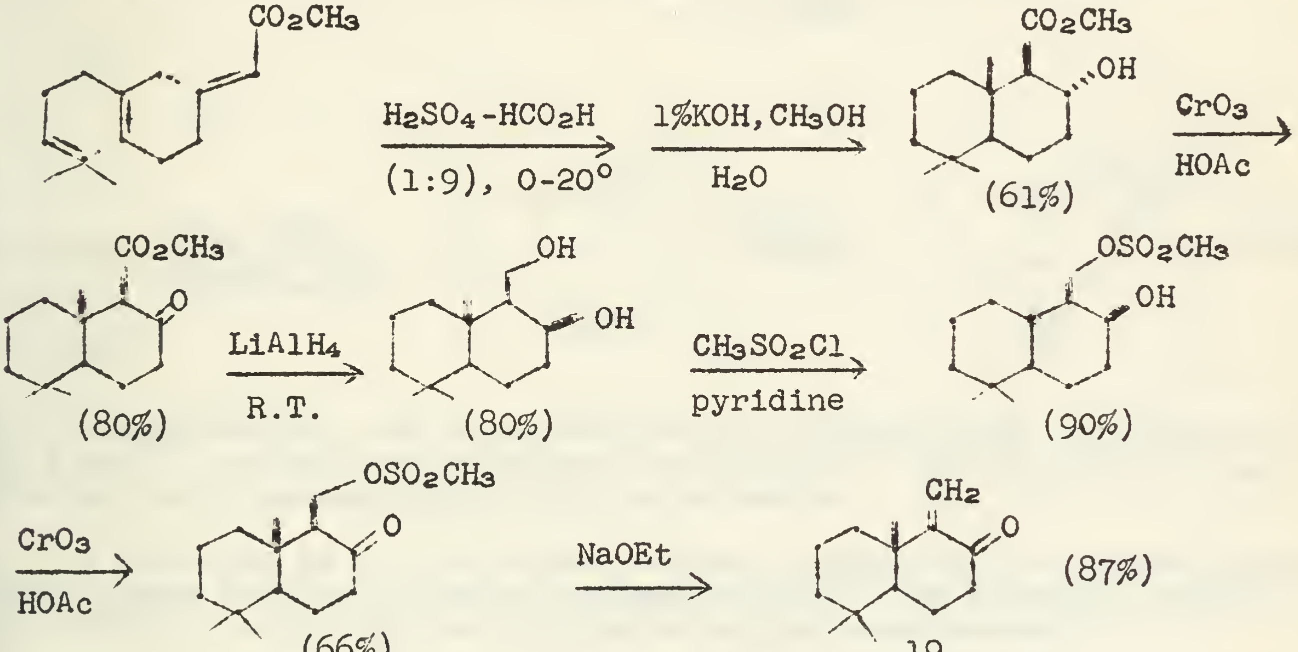
Comparison of the dehydration products 16 and 17 with authentic samples of α- and β-onoceradiene showed the compounds to be identical. Further treatment of the diacetate 11 and the diols 12 and 13 with strong acid leads to another member of the onocerane series of terpenes, γ-onocerene (18)[(+)-pentacyclosqualene]:



18 (10%)

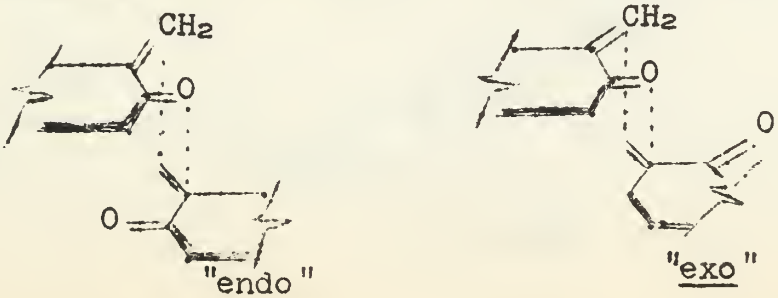
The foregoing total synthesis of α-onoceradiene is stereochemically significant in that it unequivocally substantiates the configurational assignments made by Barton[11] for this compound and α-onoceradiendiol at all asymmetric centers except 3 and 3'.

A second route to the tetracyclic diol 13 uses, in the coupling step, the dimerization of the α-methylenic ketone 19, for which the synthesis[19] is outlined below; the stereochemistry shown is, again, relative rather than absolute since 19 is necessarily racemic.



19

Dimerization of 19 is effected by heating in xylene at 110° (reduced pressure) and gives two different dimers of melting points 172° (46-47%) and 130° (21-24%).[18] Consideration of possible transition states for dimerization of α-methylenic ketones leads to several predictions as to favorable structures for the dimers:

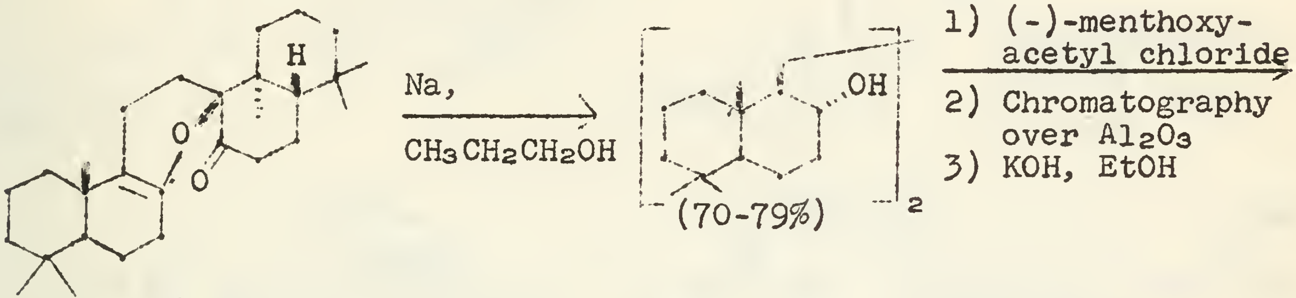


"endo" "exo"

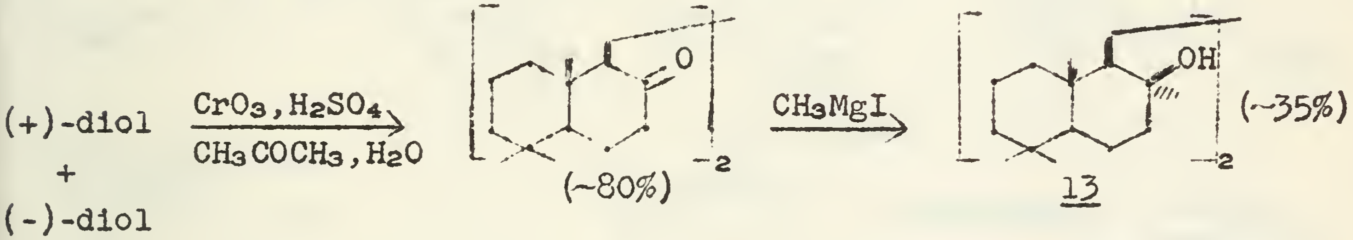
1) The "endo" configuration should be more favorable than the "exo" on the basis of the "maximum accumulation of double bonds."

2) Hindrance α to the methylene group in the "dienophilic" component should be more severe than the same interaction in the "diene" component.

The most favorable orientations for the angular methyl groups in 19 should be, therefore, trans, trans (each directed away from the plane of the other unit in the transition state). On this basis, then, 20 should represent the most favorable dimer which should consequently be formed in greater quantity; since 19 is racemic, 20 will also be racemic. Reduction, resolution of the diols and introduction of the 8 and 8' methyl groups then leads to 13:

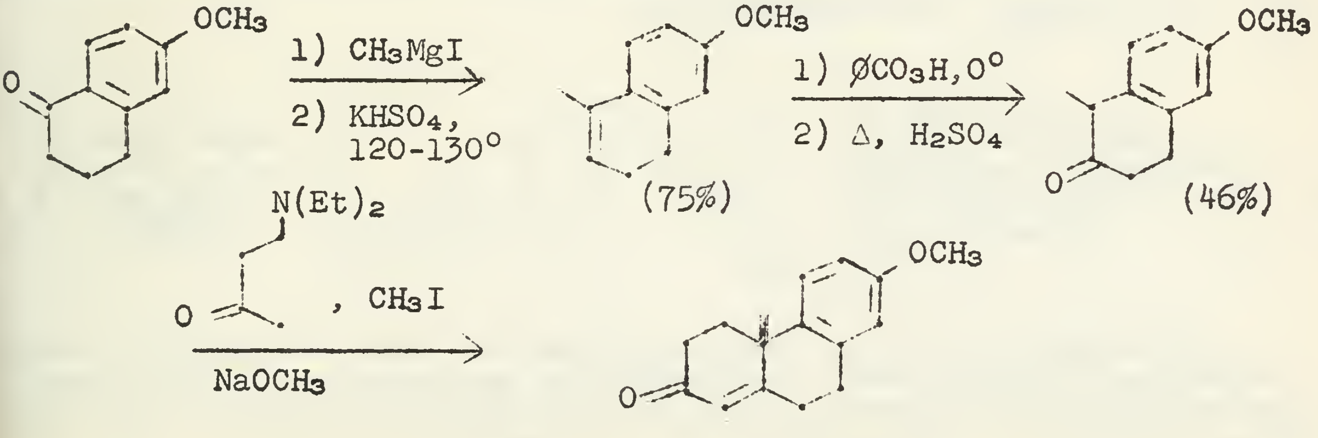


20



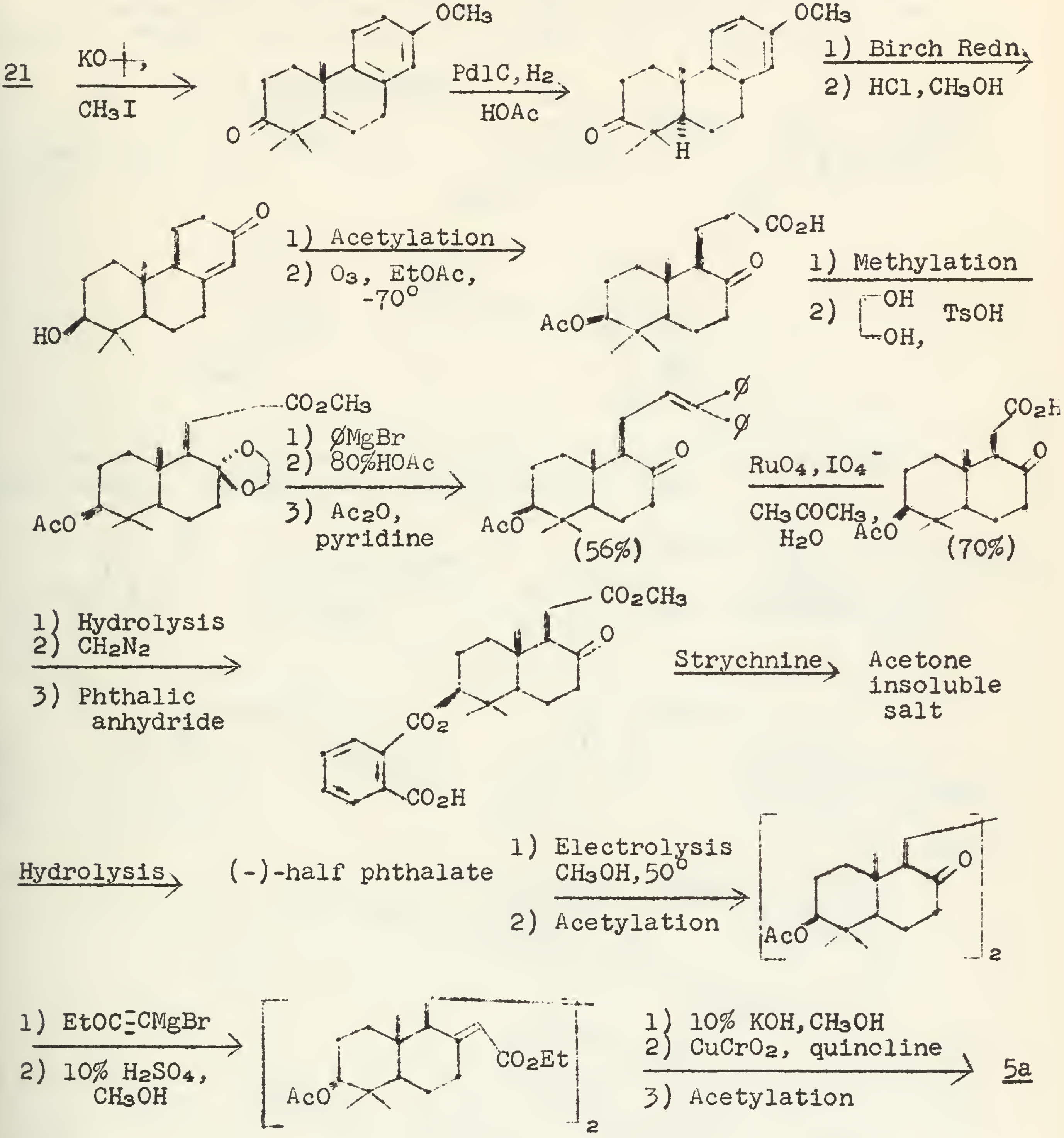
It is suggested that the stereoselectivity accompanying introduction of the 8 and 8' methyl groups arises from attack of the Grignard reagent from the less hindered α-side of the molecule.

In addition to the onocerane skeletal syntheses, α-onoceradiendiol (5) has been obtained totally synthetically.[20] The starting material, the tricyclic ketone 21, is available by the route shown:[21]



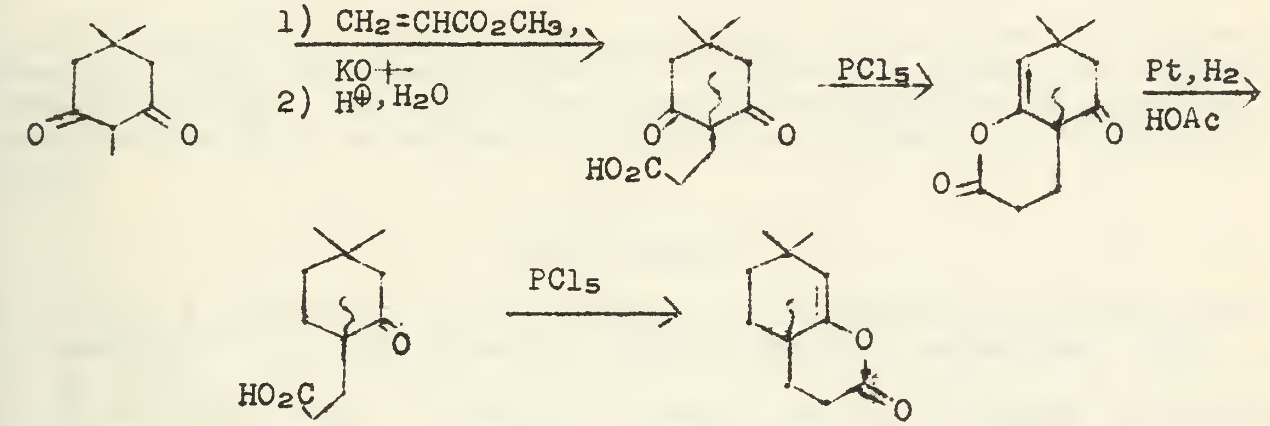
21 (25%)

The key step to the stereospecific synthesis is again Kolbe coupling accomplished here on the (-)-half phthalate 22:



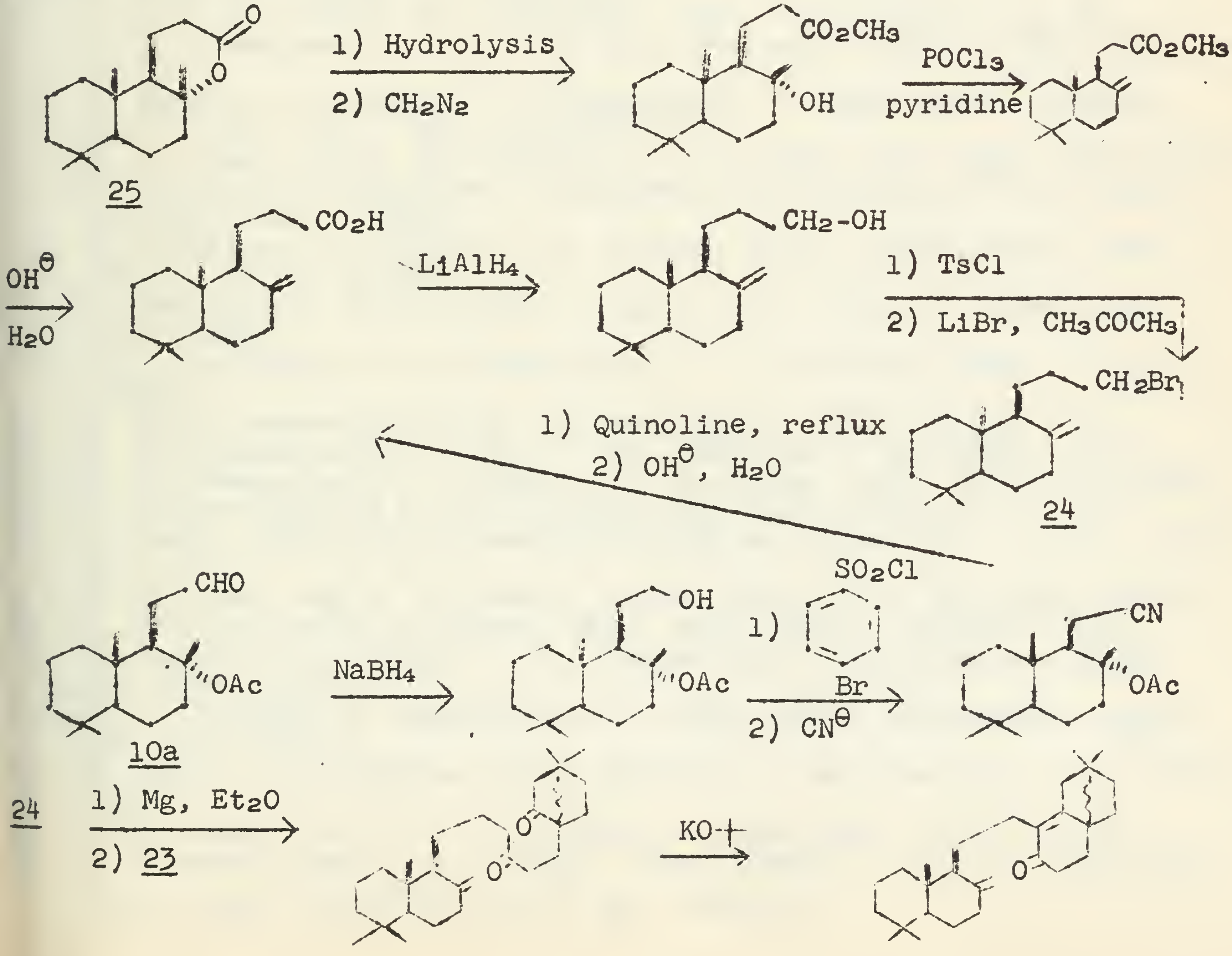
Since α-onoceradiendiol has been converted to β-onoceradiendiol, γ-onocerendiol, γ-onocerene and hopenone-I, the preceding synthesis also consititutes total syntheses of these compounds; however, the only naturally occurring triterpene in this group is the α-onoceradiendiol.

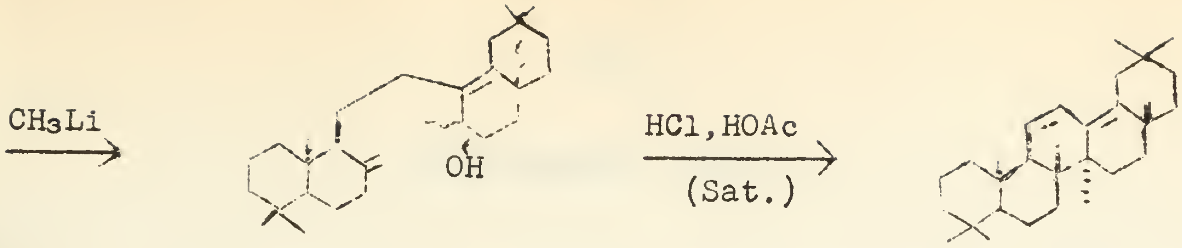
Degradation of β-amyrin by several routes[22] leads to an interesting compound, olean-11,12;13,18-diene (26). The recently reported synthesis of this compound constitutes the first successful attempt at total synthesis in the β-amyrin (oleanane) series of triterpenes.[23] In this series of reactions the key step is AB-E coupling of the Grignard reagent from 24 with the racemic enol lactone 23.



23

The AB unit (24) is available from (+)-ambreinolide (25), or, from sclareol, through the acetoxy aldehyde 10a.





26

The last step involving acid-catalyzed ring closure gives a mixture of pentacyclic diens which are epimeric at carbon 17; these are separable on chromatography. The synthetic material was shown to be identical with authentic 26 by mixed melting point and infrared and ultraviolet spectra.

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Elimination Reactions Involving Ylids

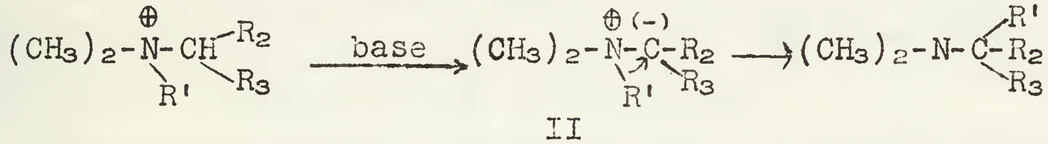
Reported by A. E. Yethon November 3, 1960

The term "ylid" is used to describe a zwitterion like compounds I, in which Y is usually an ammonium or sulphonium group.

$Y\text{-}{}^{\ominus}CH_2\text{-}R'$ I $Y=R_3\overset{\oplus}{N}$ or $R_2S^{\oplus}$

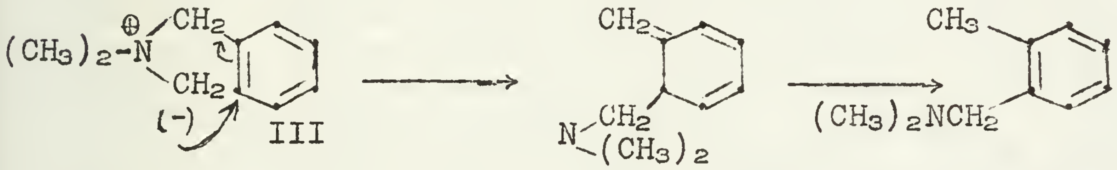
These compounds are obtained by the reaction of a base, e.g. phenyl lithium or an alkali amide, upon suitable ammonium or sulphonium salts.

The two most common reactions involving the ylid intermediate are the Stevens and Sommelet rearrangements. The Stevens rearrangement involves the intramolecular migration of a group from the nitrogen to the negatively charged carbon of the ylid II.



II

The Sommelet rearrangement again is intramolecular in nature, but migration is into the benzene ring via the ylid intermediate III.

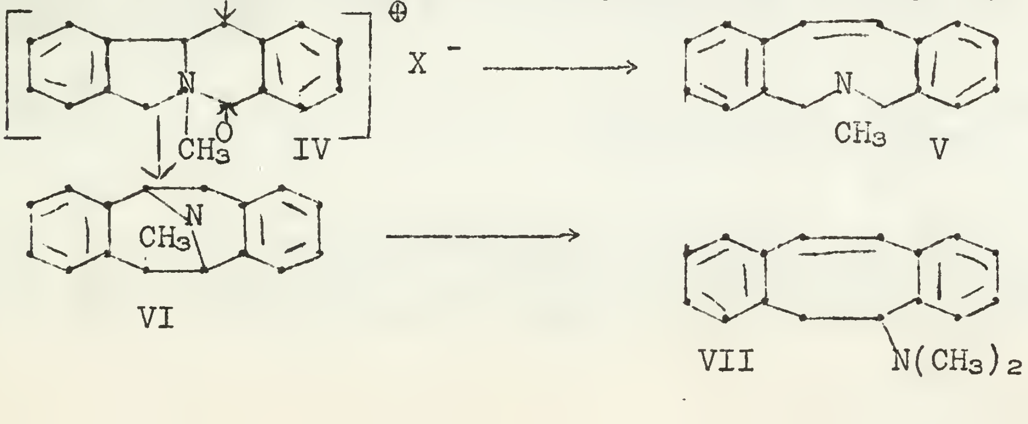


Both reactions have been thoroughly reviewed both from a mechanistic and a synthetic viewpoint (1,2,3).

This seminar will deal with some elimination reactions of quaternary ammonium and sulphonium salts which are believed to go through the ylid intermediate.

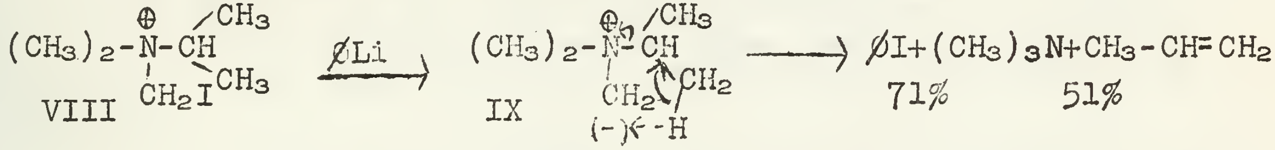
α',β-Elimination:

During their course of study on nitrogen-ylids Wittig and coworkers (4) observed that when the salt IV (X=OH) is subjected to Hofmann degradation conditions the tertiary amine V is formed, presumably arising by proton abstraction from the marked carbon (β-elimination). However in the presence of phenyl lithium the quaternary salt (X-Br ⁻) reacts to give VI. The formation of VI can be explained in terms of a proton abstraction from the marked carbon to give an ylid which then undergoes the Stevens rearrangement to the observed VI. Compound VI could then be converted to VII under Hofmann conditions or by reaction with phenyl lithium.



The question thus arose in the phenyl lithium case as to whether or not the proton was removed from the β-position by the phenyl anion (β-elimination) or from the α-position to give an ylid which then decomposed by a proton shift from the β to the α position to give the observed amine VII (α'β-elimination).

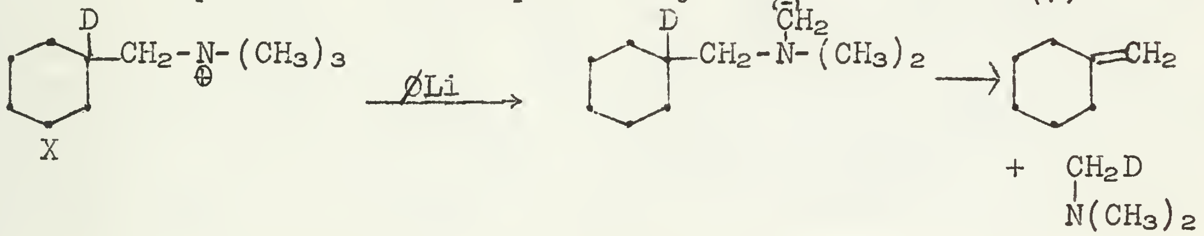
As a simple test for the α',β-elimination, dimethyl-iodomethyl-isopropyl ammonium iodide VIII was treated with phenyl lithium, with the expectation that a rapid halogen-metal interchange would give rise to the ylid IX, which could then decompose via a cyclic transition state to give trimethylamine and propene (5).



The isolation of iodobenzene in a 71% yield suggests that the exchange reaction does indeed take place and since trimethylamine and propene are also isolated it is felt that the decomposition is correctly represented by the above scheme.

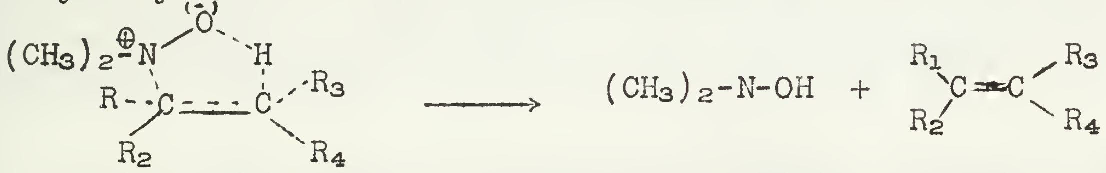
Dimethyl-iodomethyl-n-propylammonium iodide, trimethylisopropylammonium iodide and trimethyl-n-propylammonium iodide also react with phenyl lithium to give trimethylamine and propene. It is also found that when the reactions are carried out using the corresponding bromo salts, higher yields and faster rates of decomposition are obtained. This is in agreement with the finding that the reactivity of trimethylammonium methylid toward benzophenone is greatly diminished upon addition of lithium iodide (6). It is believed that the lithium iodide forms a stable complex with the ylid.

Additional evidence that the methylene group of the ylid, rather than the phenyl anion, is the eliminating base was obtained in the decomposition of the quaternary ammonium salt X (7).

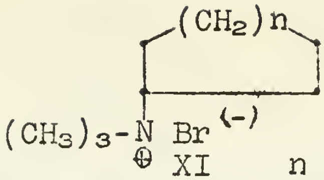


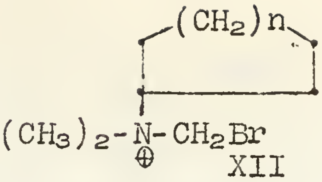
It was found that the β-deuterium atom appears in the trimethylamine rather than the benzene after elimination.

A mechanistically analogous reaction to that suggested for the α',β-elimination is the pyrolysis of amine oxides (8). An intramolecular cyclic mechanism has been proposed in which the oxygen of the amine oxide abstracts a hydrogen from the β-carbon to give olefin and hydroxylamine.



In order to obtain information concerning the steric course of the α',β-elimination, the trialkyl cycloalkylammonium salts XI and XII have been subjected to degradation conditions.


XI n = 1,2,3,4


XII

These compounds are cuased to react with phenyl lithium in ether and potassium amide in liquid ammonia. The reaction of alkali amides in liquid ammonia with quaternary ammonium salts to produce ylids, well known in the Sommelet rearrangement (9), was tried with the above mentioned salts with the expectation that the intermediate ylid would form and then undergo elimination in a manner analogous to the phenyl lithium reaction. Table I compares the results with the normal Hofmann degradation and the amine oxide pyrolysis.

Table I

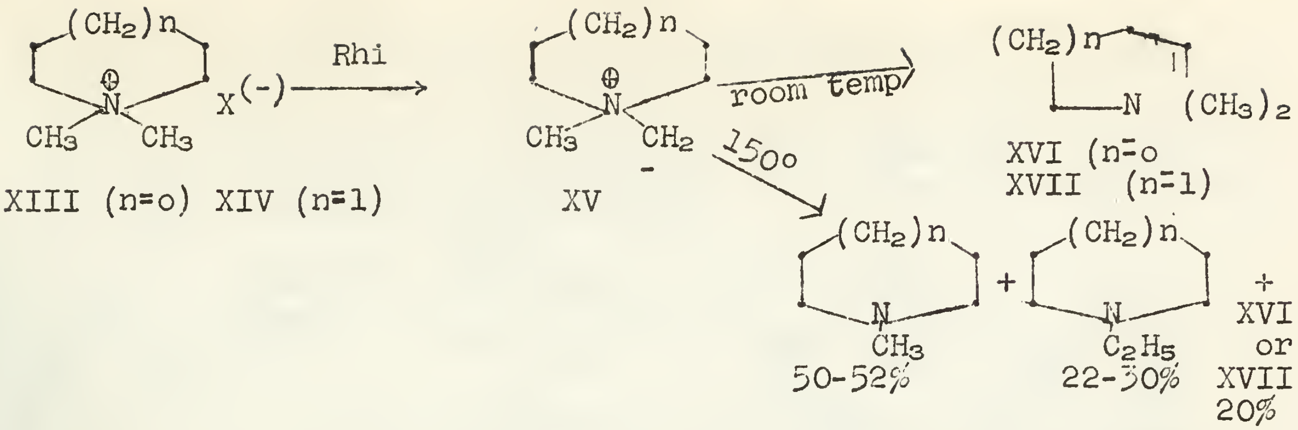
Cycloolefin Yields

Reagent	Cyclopentene (11)	Cyclohexene (12)	Cycloheptene (11)	Cyclooctene (10)
	from $(CH_3)_3\overset{\oplus}{N}$-cycloalkyl ion XI			
$OH^{(-)}$	41%	70%	45%	89%
$NH_2^{(-)}$	53	15	70	68% c:t 15:85
ØLi or BuLi	86	81	80	64% c:t 81:19
	from $(CH_3)_2-\underset{\oplus}{\overset{CH_2Br}{N}}$-cycloalkyl ion XII			
ØLi or BuLi	70%	76%	79%	74% c:t 90:10
	from $(CH_3)_2-\underset{O}{\underset{\downarrow}{N}}$-cycloalkyl			
	92%	93%	-	90% c:t 100:0

As can be seen from the table the olefin yields from the reaction of the dimethyl-bromomethyl- and trimethylcycloalkylammonium salts very closely parallel those from the decomposition of the corresponding amine oxides. The formation of more <u>cis</u>- than <u>trans</u>-cyclooctene provides evidence for the <u>cis</u> steric course of the α',β-elimination. Models show that the atoms eliminated can be in the preferred planar configuration in the transition state only if the hydrogen that is eliminated is <u>cis</u> to the methylene group of the intermediate ylid.

Similarily the predominant formation of <u>trans</u>- cyclooctene in the thermal hydroxide and potassium amide degradations suggests a similarity in mechanism, aβ-elimination. However a competing α',β-elimination cannot be ruled out, since the <u>cis</u> isomer was formed in appreciable amounts. In the case of the cyclopentyl and cyclohexyl quaternary salts, a coplanar relationship between the eliminating centers can be more easily attained for the α',β-elimination than for β-elimination, thus explaining the increased yields of cyclohexene and cycloheptene in going from potassium amide to phenyl lithium.

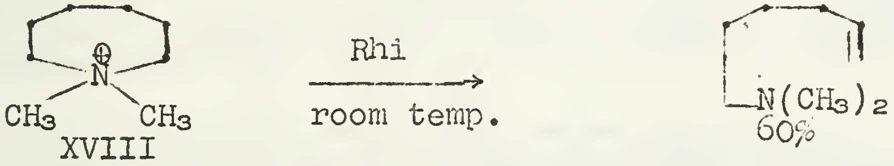
Additional support for the planar <u>quasi</u> five-membered ring transition state for the α',β-elimination reaction has been obtained in a study of the degradiation of the cyclic ammonium halides XIII and XIV (11).



When the N,N-dimethylpyrollidinium XIII and N,N-dimethylpiperidinium XIV halides are treated with phenyl lithium the reaction stops at the intermediate ylid XV stage. No 4-dimethylaminobutene-1 XVI or 5-dimethylaminopentene -1 XVII is formed. The ylid XV is stable and can be hydrolyzed back to starting material. On heating to 150° the ylids can be converted to the respective N-methyl (50%) and N-ethyl (22-30%) pyrollidine and piperidine in addition to small amounts of XVI (20%) and XVII (19%). On the other hand when XIII and XIV react with potassium amide or are subjected to thermal degradation ($X=OH^-$) conditions good yields of XVI (60%) and XVII (77%) are obtained.

In the above two examples α',β-elimination is ruled out on steric grounds. Although molecular models show that the carbanionoid methylene of the ylid XV is not at too unfavorable a distance from the β-hydrogens the preferred planar transition state, because of the steric requirements of the five- and six-membered rings, cannot be attained. Again these results agree very well with the amine oxide decomposition. N-Methylpiperidine oxide is very resistant to thermal decomposition and does not undergo ring cleavage (13).

In contrast to the resistance shown by the five- and six-membered ring cyclic ammonium halides to α',β-elimination, the homologous seven-membered ring compound, N,N-dimethylhexamethylene imonium bromide XVIII undergoes a smooth elimination with phenyl or butyl lithium to give 6-dimethylaminohexene-1 XIX in a 60% yield (11).

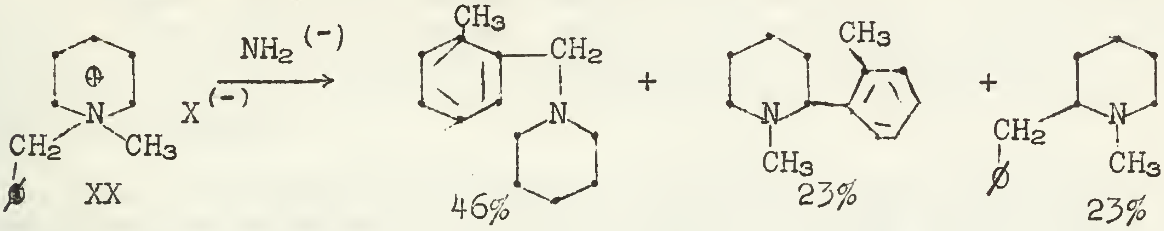


XIX

Similarily thermal decomposition of the corresponding seven-membered ring amine oxide results in ring cleavage with the formation of the hydroxyl amine olefin in a 53% yield (13). Models show that the cis-β-hydrogen can assume the proximity and coplanarity necessary for reaction in the seven-membered ring case.

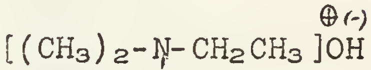
All the preceding evidence indicates that by the action of organo-lithium reagents on quaternary ammonium salts the α',β-elimination dominates if a proton shift via a planar five-membered ring transition state is possible. The same evidence points to a similarity in mechanism between the normal Hofmann degradation and

the potassium amide degradation, a β-elimination. However it should be pointed out that when the quaternary ammonium halide XX is caused to react with potassium amide in liquid ammonia no elimination products were detected (14). The only products isolated are those resulting from intermediate ylid formation, followed by a Stevens or Sommelet rearrangement. The thermal Hofmann degradation gives elimination products only.



The work on the α',β-elimination of quaternary ammonium salts using phenyl lithium prompted an investigation into the thermal Hofmann degradation to see if it also might proceed in part through an ylid intermediate (15). The technique used was the thermal degradation of the tritium-labeled quaternary bases XXI, XXII and XXIII, followed by radioactive analysis of the products.

$[(CH_3)_3\text{-N-CHT-}CH_3]^{\oplus}OH^-$ XXI $[(CH_3)_3\text{-N-}CH_2\text{-}CH_2T]^{\oplus}OH^-$ XXII



$[(CH_3)_2\text{-}\overset{\oplus}{\underset{CH_2T}{N}}\text{-}CH_2CH_3]OH^{(-)}$

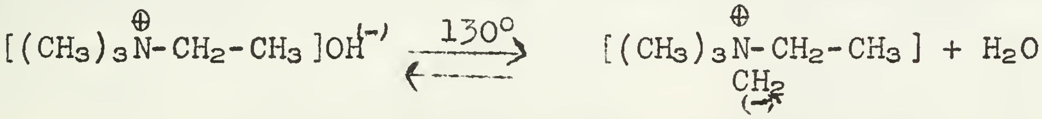
XXIII

Estimation of the radioactivity of the degradation products of XXI showed that practically all the tritium was present in the ethylene (98.7%). Thus α-elimination takes place to a negligible extent.

Thermal degradation at 150° of the quaternary ammonium hydroxide XXII resulted in three degradation products, all of which were radioactive. The trimethylamine contained 12% of the total tritium, ethylene 73% and the water 17%. A pure α',β-elimination would require a non-radioactive water, a pure β-elimination on the other hand a non-radioactive trimethylamine. These results suggest that two concurrent mechanisms are operating, namely the α',β-elimination and the β-elimination.

Analysis of the degradation products of XXIII showed that 82% of the original tritium was in the trimethylamine, 18% in the water and none in the ethylene. A purely statistical hydrogen abstraction of the α'-hydrogens would result in only 11% tritium in the water. The high value observed (18%) probably is due to an exchange reaction.

To determine whether the above results were invalidated by an exchange reaction the degradation of non-radioactive trimethylethylammonium hydroxide was carried out in the presence of tritiated water. Analysis of the degradation product shows that an exchange does take place above 130° and that it occurred only with the α'-hydrogens. Thus the following equilibrium takes place.



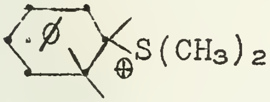
$$[(CH_3)_3\overset{\oplus}{N}\text{-}CH_2\text{-}CH_3]OH^{(-)} \underset{\longleftarrow}{\xrightarrow{130^{\circ}}} [(CH_3)_3\overset{\oplus}{\underset{CH_2^{(-)}}{N}}\text{-}CH_2\text{-}CH_3] + H_2O$$

However it can be demonstrated that an intramolecular proton shift does actually take place. Compound XXII is degraded at 150° and steam at 150° passed in so that the weight ratio of led in steam to that usually present in the Hofmann degradation is 1000:1.

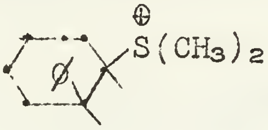
Nevertheless the specific molar activity of the resulting trimethylamine amounted to 8%, a value not much lower than that obtained in the absence of excess water (12%).

Compound XXII has also been studied at 40°C. under vacuum to determine the magnitude of the isotope effect in the Hofmann degradation. The intramolecular molecular isotope effect was found to be remarkably small (<2). The secondary isotope effect on the other hand is large (0.2 ± 0.02). An explanation for the anomalous kinetic behavior of this tritiated methyl group is not too apparent.

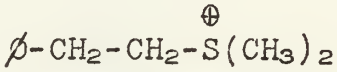
The α',β-elimination mechanism has also been offered as one possible explanation for the relatively high reactivity of trans-2-phenylcyclohexyldimethylsulfonium iodide XXIV towards ethanolic potassium hydroxide (16).



XXIV



XXV



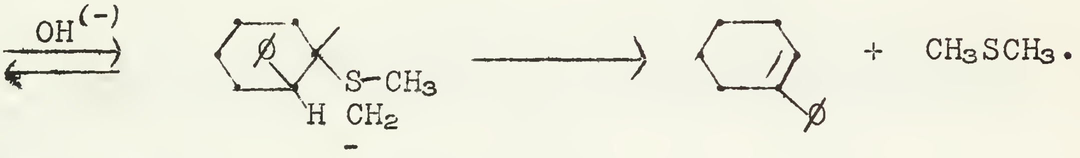
$$Ø\text{-}CH_2\text{-}CH_2\text{-}\overset{\oplus}{S}(CH_3)_2$$

XXVI

$k_{XXV}/k_{XXIV} = 383$ $k_{XXVI}/k_{XXV} = 1.28$ $k_{XXVI}/k_{XXIV} = 491$

The difference in reactivity between XXV (trans elimination) and XXIV (cis elimination) is 383, a small difference when compared to the benzene hexachlorides (k_{trans} elim./k_{cis} elim.$\simeq 10^4$) (17). The similarity in ratio (1.28) between XXV and the acyclic analog XXVI shows that the difference in reactivity between XXIV and XXV is not due to an anomalous trans-elimination in XXV. The following mechanism has been proposed to account for the rapid cis-elimination of XXIV

XXIV



α-Eliminations

Several reports have appeared in the literature which might indicate that certain quaternary ammonium or sulphonium salts, under the influence of a suitable base, may decompose via an α-elimination mechanism to give carbenes.

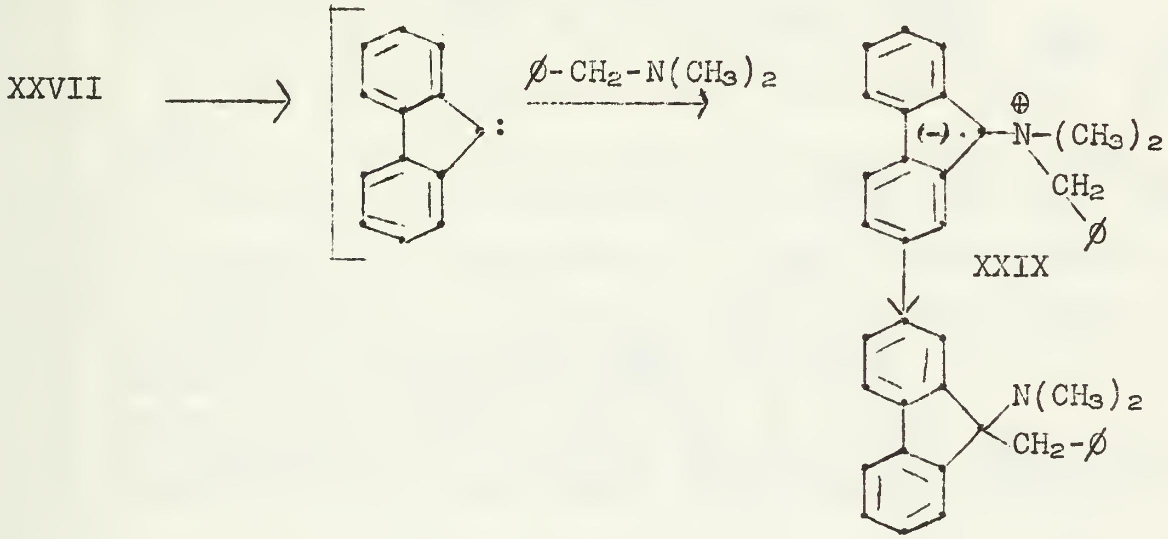
Ylid XXVII obtained by the reaction of base on the corresponding 9-fluorenyltrimethylammonium salts decomposes in part to yield 9,9'-bis-fluoroenylidene XXVIII (18).

XXVII

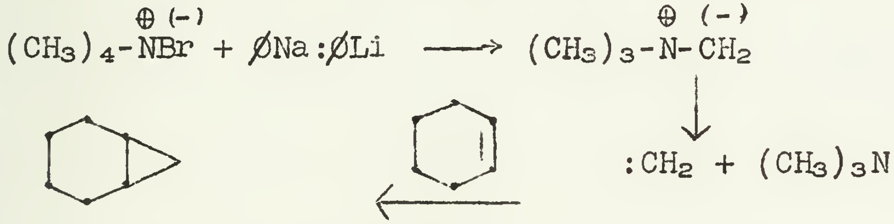
XXVIII

Similarily when trimethylsulphonium bromide (19) and tetramethylammonium bromide (6) are caused to react with phenyl lithium, polymethylene is formed in a 46% yield. One possible interpretation of these results is that the ylid decomposes to form a carbene, which can then react to give the observed products.

In order to determine whether ylid XXVII does decompose to a carbene, it was thermally decomposed in dimethylbenzylamine (20). Dimethylbenzylamine was used as the trapping agent since it had previously been shown that carbenes react quite readily with tertiary amines (31). In addition to polymeric material, 9-dimethylamino-9-benzylfluorene is isolated. This is explained by postulating that the intermediate fluorencarbene reacts with dimethylbenzylamine to give ylid XXIX, which then undergoes a Stevens rearrangement to the observed product. The product was identical to that obtained from the irradiation of diazofluorene with dimethylbenzylamine (22).



Similarily when tetramethylammonium bromide is reacted with ØLi:ØNa 1:10 in the presence of excess cyclohexene norcarane is obtained in yields of 5-18% (23).

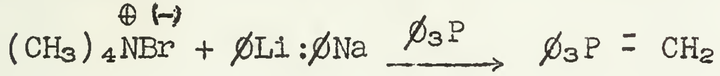


$$(CH_3)_4\text{-}\overset{\oplus\,(-)}{NBr} + \text{ØNa:ØLi} \longrightarrow (CH_3)_3\text{-}\overset{\oplus}{N}\text{-}\overset{(-)}{CH_2}$$

$$\downarrow$$

$$:CH_2 + (CH_3)_3N$$

The trimethylammonium methylid can also transfer methylene to triphenyl phosphine (23).



$$(CH_3)_4\overset{\oplus\,(-)}{NBr} + \text{ØLi:ØNa} \xrightarrow{\text{Ø}_3P} \text{Ø}_3P = CH_2$$

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RELATIVE STABILITIES OF EXOCYCLIC AND ENDOCYCLIC DOUBLE BONDS

Reported by J. A. Landgrebe November 10, 1960

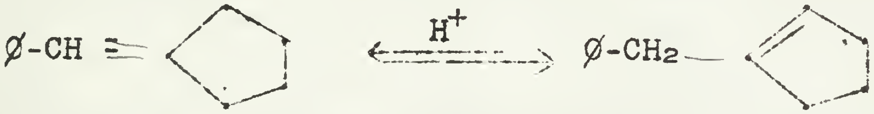
INTRODUCTION

In spite of certain controversial aspects concerning the relative thermodynamic stability of double bonds placed exocyclic or endocyclic in middle sized ring systems, useful generalizations have been made (3,7), and will be discussed in detail. Although this review is concerned primarily with carbon-carbon double bonds, some of the original theoretical work relating the relative stabilities of exocyclic double bonds in five and six membered rings (5,6,7) was based upon observations in the cycloalkanone series, and the results then generalized to include carbon-carbon double bands. Three types of thermodynamic relations will be considered: the relative stability of two exocyclic double bonds each in a different sized ring, two endocyclic double bonds each in a different sized ring, and an exocyclic versus an endocyclic double bond in the same sized ring.

ENDO VERSUS EXO-----SAME SIZE RING

This case is perhaps the most definitive in that Roth (45) as early as 1915, utilizing heats of combustion, determined the enthalpy of isomerization of methylenecyclohexane to 1-methylcyclohexene as -3.1 kcal/mole. Since that time numerous empirical observations (3,7) have added support to these data, and recently more refined measurements of equilibria (1,2) and heats of hydrogenation (3,4) have provided detailed quantitative information in five- to ten-membered ring systems (2).

One can perhaps better appreciate the magnitude of this relative difference in energy by noting that Δ^1-cyclohexenacetone in acid catalyzed equilibrium with its exocyclic isomer consists of approximately 70% of the endocyclic form in spite of the conjugation of the exocyclic double bond with the carbonyl group (23). The geometry of the exocyclic isomer is such that steric interference of the α-ring hydrogens with the carbonyl oxygen might be lessening the conjugative stabilization of this species by forcing the carbonyl group out of planarity with the double bond (34). The acid catalyzed isomerization of benzalcyclopentane to Δ^1-benzylcyclopentene (22) provides an example of the stability of the endocyclic double bond in the 5-ring system.



Additional examples of acid catalyzed isomerizations of allylic alcohols in the terpene series have been observed (31), but the need for more quantitative unambiguous data is obvious. Much of the validity of observations such as those made above is lost if one is uncertain of whether equilibrium has been fully attained. One must also be aware of mechanistic ambiguities, inadequate characterization of the products, and relative yields.

In view of these factors, Turner (3,4,15) has provided accurate heats of hydrogenation on a number of simple 1-alkylcycloalkenes and alkylidenecycloalkanes, thus furnishing a measure of the relative stability of the endocyclic to the exocyclic double bond, if the entropy

effects are assumed to be small (to be discussed). The data are indicated in the following table.

	$\Delta H_{Hydro.}$ (kcal/mole)[a]	$\Delta\Delta H_{Hydro.}$[b]
(1) methylenecyclobutane	-29.4	-0.9
(2) 1-methylcyclobutene	-28.5	
(3) methylenecyclopentane	-26.9	-3.9
(4) 1-methylcyclopentene	-23.0	
(5) methylenecyclohexane	-27.8	-2.4
(6) 1-methylcyclohexene	-25.4	
(7) methylenecycloheptane	-26.3	-2.3
(8) 1-methylcycloheptene	-24.0	
(9) ethylidenecyclopentane	-24.9	-1.3
(10) 1-ethylcyclopentene	-23.6	
(11) ethylidenecyclohexane	-26.3	-1.2
(12) 1-ethylcyclohexene	-25.1	

a. ± 0.1 kcal/mole
b. Enthalpy of the exo to endo isomerization.

Note that in every instance the endo isomer produced the lower heat of hydrogenation. The value of the isomerization enthalpy in the 6-ring system, -2.4 kcal/mole, is in good agreement with the data of Roth (45), -3.1 kcal/mole. The isomerization value for the 5-ring system is somewhat larger than that of the 6- or 7-ring systems, an observation which contradicts the prediction made previously by Brown (6,7). As one would expect, the small heat of isomerization of methylenecyclobutane to 1-methylcyclobutene is consistent with the large increase in strain produced by the addition of a second trigonal carbon atom into the endocyclic isomer. This strain is still not sufficient to make the endocyclic isomer unfavorable.

One must consider that in the first eight compounds of the table a comparison is being made between the heat of hydrogenation of a disubstituted double bond of the methylenecycloalkane and the trisubstituted double bond of the corresponding endo isomer. Kistiakowsky (32) has found that because of either polar effects, hyperconjugative effects, adjacent bond interactions, or a combination of these, the heat of hydrogenation of a trisubstituted double bond is some 1.5 kcal/mole lower than that of the corresponding disubstituted double bond. If this value is consistent it should only affect the heats of hydrogenation and not the heats of isomerization. The difference in heat of hydrogenation between methylenecyclohexane and ethylidenecyclohexane is 1.5 kcal/mole as expected, but the difference is slightly larger, 2.0 kcal/mole, for the corresponding 5-ring compounds. In addition, although there is no change in degree of substitution in comparing 1-methylcyclopentene to 1-ethylcyclopentene, a difference in heats of hydrogenation of +0.6 kcal/mole exists; the difference in heats of hydrogenation of 1-methylcyclohexene and 1-ethylcyclohexene is -0.3 kcal/mole. Since Kistiakowsky (14) has indicated that changes in the nature of the alkyl substituent have little effect on the heat of hydrogenation, steric effects are probably involved in these instances. The resulting values of the isomerization enthalpy (exo to endo) for the 5- and 6-ring systems (9-12 in the table) were -1.3 and -1.2 kcal/mole respectively, almost identical within experimental error.

One must emphasize at this point that Turner's work does not take into account changes in entropy. Cope (2) has used free energy data from acid catalyzed equilibration studies (to be discussed), in con-

jugation with Turner's enthalpy values to calculate entropy of isomerization, and has found an unusually large value, ΔS (exo to endo) = +2.8 e.u., for the methylenecyclohexane, 1-methylcyclohexene system. If this value is as large in the case of the ethylidenecyclohexane isomerization, the prediction of Brown (6,7) would be valid (vide supra).

Cope (1) has recently carried out a series of acid catalyzed equilibrations at 25° using 10% solutions of olefin in oxygen free acetic acid containing 0.25% p-toluenesulfonic acid. The use of this system prevents extensive polymerization (3). All equilibria were approached from both sides allowing each mixture to stand for at least one day (longer in the case of the six-membered ring) after the apparent equilibrium had been reached before determining the endo-exo olefin composition by gas chromatographic analysis. Pertinent information is indicated in the following table. A more detailed table can be found in the reference (2). Equilibrium compositions are those resulting from equilibration starting with the exo isomer; the values obtained starting with the endo isomers are nearly identical in every case.

methylene-cycloalkane isomerized RING SIZE	equilibrium composition %ENDO	%EXO	K endo/exo	$\Delta F^\circ_{isom.}$[a] kcal/mole	$\Delta H^\circ_{isom.}$[a,b] kcal/mole	$\Delta S^\circ_{isom.}$[b] e.u.
5	99.91	0.09	1144 ∓ 51	-4.17	-3.9	+0.9
6	99.56	0.44	240 ∓ 13	-3.24	-2.4	+2.8
7	98.67	1.33	74.4 ∓ 0.8	-2.55	-2.3	+0.8
8	99.81	0.19	598 ∓ 68	-3.79		
9	100.0 cis	0.0	> 1000[c]	< -4.0[c]		
10	99.5 cis	0.0	> 1000[c]	< -4.0[c]		
	0.5 trans	0.0				

a. Exo to endo.
b. Data from Turner's heats of hydrogenation; $\Delta S^\circ_{isom.}$ is calculated from, ΔF = ΔH-TΔS.
c. The values of K endo/exo and $\Delta F^\circ_{isom.}$ (exo to endo) for the 9- and 10-rings were estimated by determining the approximate limits of detectability of the exo compound by v.p.c. analysis.

The data clearly indicate the significantly greater stability of the endo isomer in all the ring systems studied; however, it should be noted that the relative amount of the exocyclic isomer at equilibrium increases as we go from the 5-ring to the 7-ring and then becomes less important in the 8-, 9-, and 10-ring systems. The very small amount of exo isomer present in the medium ring equilibrations has been attributed to the relief of ring strain, due to conformational eclipsing, by the introduction of an additional trigonal center in the structure upon its conversion to the endocyclic isomer.

In calculating molecular geometry by vector analysis, Corey (11) has indicated that cyclohexene is slightly less stable (12,47) than cyclohexane due to the introduction of a small amount of eclipsing and

[illegible]

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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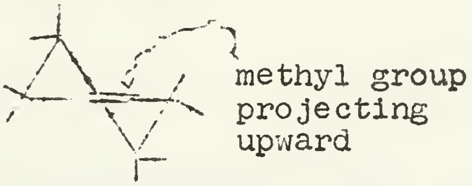
ring strain which is not present in the saturated analog. These effects are minimized by allowing cyclohexene to have the chair conformation (9,10) which is some 2.7 kcal/mole lower in energy than the corresponding boat form (10). In methylenecyclohexane the ring carbon atoms are essentially like those of cyclohexane, but there appear to be significant steric interactions between the methylene hydrogens and the equitorial hydrogens of the adjacent carbon atoms of the ring, making the exocyclic isomer somewhat less stable than the corresponding 1-methylcyclohexene (7,11). These interactions would be even more pronounced with ethylidenecyclohexane.



1-methylcyclohexene
(chair conformer)

methylenecyclohexane
(interactions indicated)

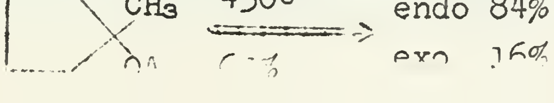
Although no calculations were made on methylenecyclopentane, models indicate that the methylene hydrogen interactions with the α-ring hydrogens should not be as important as in the methylenecyclohexane case. Although the introduction of an endocyclic double bond produces some strain (36), 6 of the 10 bond oppositions normally present in cyclopentane have been removed while in methylenecyclopentane only 4 of these oppositions have been removed. This is undoubtedly an important factor in determining the greater stability of 1-methylcyclopentene relative to methylenecyclopentane regardless of the additional steric factor imposed by the introduction of the methyl group on to the cyclopentene ring of the former compound.

Turning now to the entropy values calculated by Cope (2), it is interesting to note that the values for the 5-, 6-, and 7-ring systems are positive indicating more conformational restriction in the exocyclic isomers, which is due in part to the loss of C-methyl rotational freedom.

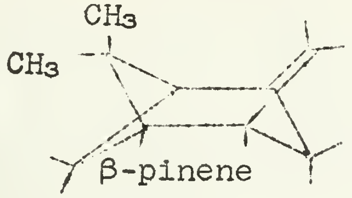
Recent chemical evidence consistent with the greater stability of the endocyclic bond (relative to exo) has been provided by a study of the Chugaev reaction (40). The xanthate esters of a series of 1-alkylcyclohexylcarbinols after pyrolysis at relatively low temperatures have produced alkenes which appear to have resulted neither from a preferential attack on tertiary or primary hydrogens nor by a statistical attack on hydrogen as has been observed in the high temperature pyrolysis of esters (16,42). The results are consistent if one assumes that the

methyl xanthate ester of	olefin yield(%)	pyrolysis temp.	% exo isomer in mixture
1-methylcyclohexanol	49	200°	21
1-ethylcyclohexanol	52	200°	12
1-isopropylcyclohexanol	46	100°	22
methylcyclohexylcarbinol	52	250°	38
dimethylcyclohexylcarbinol	51	150°	21

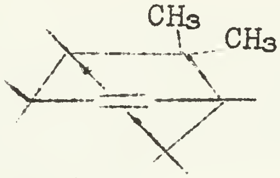
transition state resembles the product. One would then expect the relative thermodynamic stability of the products to determine the composition of the olefin mixture obtained. Bailey (41) has found that acetate pyrolsis carried out at temperatures below 250° frequently leads to the most stable alkene, and that with certain cyclic systems even higher temperatures can be used without producing a statistical distribution of isomers.



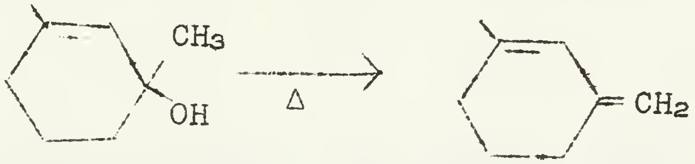
It is possible to increase the relative stability of the exocyclic isomer by introducing strain into the molecular either by formation of a bicyclic structure (38), or by introduction of an additional double bond endocyclic to the ring (21). As an illustration of the former, Hawkins (39) has measured the heat of combustion of β-pinene as 1483.0 kcal./mole while that of α-pinene, the endocyclic isomer, is 1485.1 kcal./mole, the exocyclic compound being some 2.1 kcal./mole more stable. Wheeler (21) has indicated that the thermal dehydration of the 1,3-dimethyl-2-cyclohexene-1-ol leads to the exocyclic product rather than the cyclohexadiene structure; in the latter structure the four trigonal carbon atoms have flattened the ring causing significant eclipsing strain. In this and many other examples predominantly exocyclic products have been observed, (17,18,19120,43), but in many instances the nature of the mechanism is not well understood.



β-pinene



α-pinene



ADDITIONAL STABILITY RELATIONS AMONG EXO AND ENDO DOUBLE BONDS

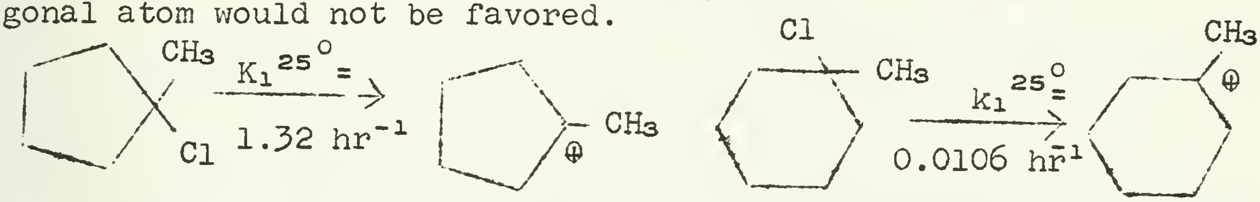
Since the strain in the saturated 5-ring system has been attributed primarily to unfavorable eclipsing effects (12,44), one might expect that by altering the hybridization at a ring carbon to sp², a relief of strain would result, while in the normally staggered 6-ring conformation introduction of an sp² hybridized ring atom would produce unfavorable non-bonded interactions. Equilibrium data on cyclopentylidene methyl ketone and cyclohexylidene methyl ketone (as well as the corresponding acids and esters shown in the following table) indicate that in the 5-ring system, the exocyclic double bond is more favored with respect to the endocyclic double bond than in the 6-ring system (7). Note that the comparison is being made on two exocyclic bonds on different sized ring systems. In each of these compounds a comparatively bulky group, -COMe, -COEt, -COOEt, was present, which because of the equitorial hydrogen interactions previously discussed in the methylenecyclohexane case, would tend to make the 6-ring exocyclic double bond particularly unstable, perhaps accounting for the anomalously high stability of the 5-ring exocyclic double bond.

R-	% EXO	% EXO
COCH₃	84	30
COEt	85-90	30
COOEt	60	38
COOH	14	12

in equilibrium with the endocyclic isomer.

The keto-enol equilibrium of cyclohexanone (20×10^{-3}% enol, 20°, aqueous soln.) (24) and cyclopentanone (4.8×10^{-3}% enol, 20°, aqueous soln.) (24) cannot be used as a definite argument that the 6-ring exocyclic double bond is less stable than the 5-ring exocyclic double bond (relative to the saturated compounds), since the 5-ring enol is more stra than the 6-ring enol; thus, endocyclic double bond strain alone could account for the observed results.

A study of solvolysis rates of 1-chloro-1- methylcycloalkanes by Brown (5,6) has shown that 1-chloro-1-methylcyclopentane solvolyzes some 125 times more rapidly than 1-chloro-1-methylcyclohexane, since in going to the trigonal transition state a relief of non-bonded interaction in the 5-ring system would be expected to lower the activation energy considerably, while in the 6-ring system, the introduction of a trigonal atom would not be favored.

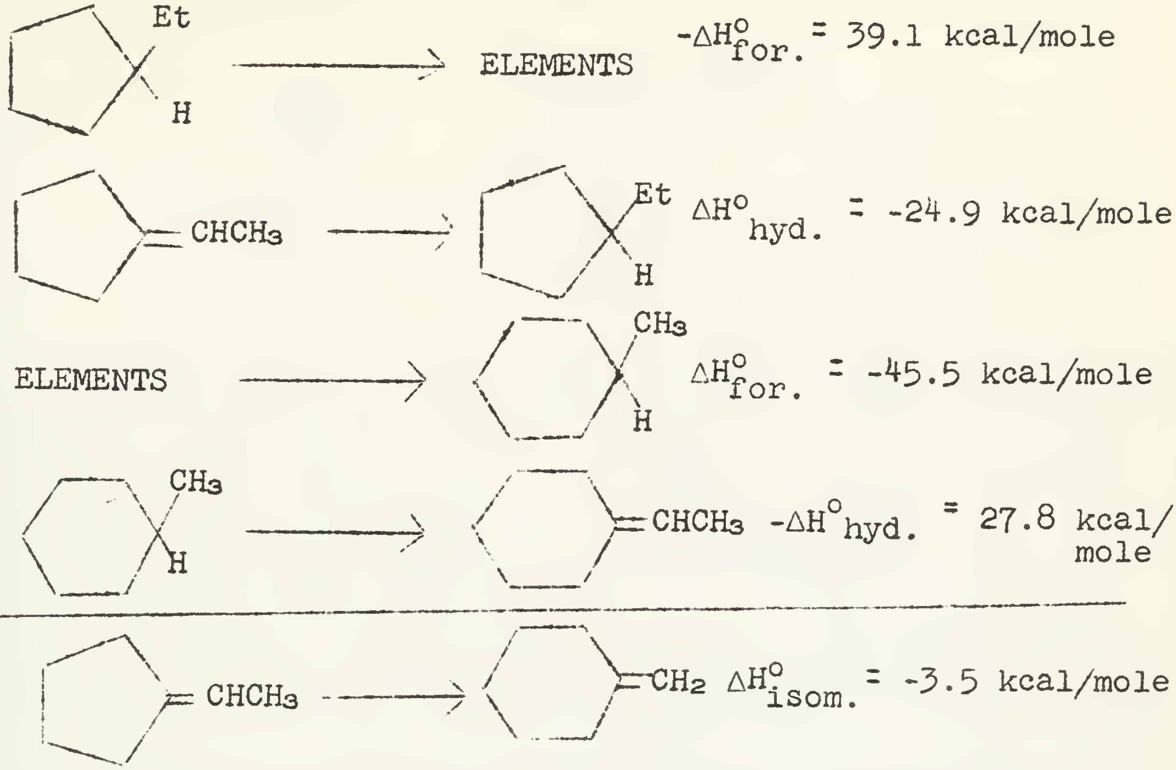


Additional data on the relative ease of introduction of a double bond into the 5-ring system has been obtained from studies of olefin formation in the dehydration of monocyclic terpenes (27,28), ring cleavage reactions (7,30), semicarbazone formation (29), and observations of specific products formed in certain Aldol condensations (25), and thermal condensations (26). In many cases a lack of information on the mechanism or the relative importance of steric factors, lessen the overall usefulness of the data.

In 1954 Brown (7) made a survey of the previously mentioned equilibrium and rate controlled reactions involving the formation or loss of an exocyclic double bond, and proposed a statement later reworded (6) after a criticism by B. R. Fleck (8): "Double bonds which are exo to a 5-ring are less reactive and more stable (relative to the saturated derivatives) than related double bonds which are exo to a 6-ring. Reactions which involve the formation or retention of an exo double bond in a 5-ring derivative will be favored over corresponding reactions which involve formation or retention of an exo double bond in a 6-ring derivative. Reactions which involve the loss of an exo double bond will be favored in the 6-ring as compared to the 5-ring derivative." One must consider that Brown's statement was based primarily on observations in the cycloalkanone series and might not be expected to be of general validity with regards to the carbon-carbon double bond (3).

Turner (3) has made a calculation of the isomerization enthalpy from ethylidenecyclopentane to methylenecyclohexane using known enthalpies of formation (48) and measured heats of hydrogenation as indicated below. The enthalpy difference of -3.1 kcal/mole clearly indicates the greater stability of the 6-ring exocyclic carbon-carbon double bond with respect to the 5-ring structure, in spite of the stabilizing influence of the methyl group on the 5-ring double bond (32). A similar calculation for the isomerization enthalpy of the corresponding endocyclic isomer results in a value of -4.6 kcal/mole in going from ethyl-Δ^1-cyclopentene to methyl-Δ^1-cyclohexene. The isomerization enthalpy for ethylcyclopentane going to methylcyclohexane is -6.4 kcal/mole (48). The greater absolute value for the isomerization of the saturated hydrocarbon is consistent with the idea that the introduction of a trigona

carbon atom in the ring reduces non-bonded interactions in the 5-ring system and slightly increases these interactions in the 6-ring system, causing the overall difference in enthalpy between the 5- and 6-ring systems to decrease (3,12). On the basis of these calculations, and



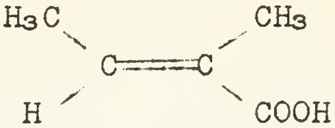
the previously discussed hydrogenation data, Turner (3) has indicated that for carbon-carbon double bonds," angular strain in placing a double bond exocyclic or endocyclic with respect to a 5-ring will make the double bond less stable than a similarly situated double bond in a 6-ring system."

With regards to the relative stability of endocyclic double bonds placed in 5- and 6-membered rings, Wheeler (36) has found that the dissociation constants (measured in 50% aqueous ethanol at 25°) of Δ^1-cyclobuten- and Δ^1-cyclopentencarboxylic acids were larger than that of Δ^1-cyclohexencarboxylic acid, the latter having about the same value as the open chain analog, tiglic acid. These results have been explained by considering that the additional strain imposed upon the 4- and 5-ring systems by the introduction of an endocyclic double bond leads to an increase in the s-character of the bond to the carboxyl group, producing a slight negative inductive effect which would be expected to increase the dissociation constant value in the strained ring compounds. This is parallel to the argument of Roberts (36) in explaining the relatively higher acidity of cyclopropanecarboxylic acid over cyclobutanecarboxylic acid. The normal negative inductive effect due to the presence of the α,β-unsaturation is considered to be approximately constant for each of these compounds. The acid weakening cross conjugation must not be significant in the strained rings, since the exocyclic contributing structure which can be written for this type of participation should be relatively more favored in the highly strained systems, and this would result in a trend opposite to that which was observed.

The ultraviolet absorptions of these α,β-unsaturated acids are given in the following table (34). Similar results were obtained for

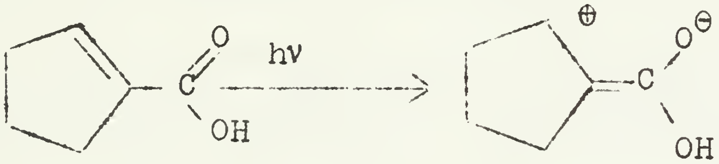
the corresponding amides. Light absorption in the near ultraviolet

I


II


	n	λ(mμ)	molar extinction coefficient
I	3	222	9,500
I	4	216	9,800
I	5	222	9,900
II	--	214	12,800

leads to an excited state which is thought to have greater contributions from charged structures (35) such as those indicated below. Structural changes resulting in an increase in the energy of the excited state over the ground state would be expected to move the absorption wavelength to lower values, and this has been observed in molecules which offer steric inhibition to resonance in the excited state (33). On the other hand, an effect which either destabilizes the ground state or stabilizes the excited state should shift the absorption to longer wavelength; thus, Wheeler (34) has indicated that introducing strain into the cyclopentane ring by means of an endocyclic double bond should decrease the energy difference between the ground and the excited state causing the observed ultraviolet shifts (compared to the 6-ring system). One must realize however, that since the Franck Condon principle applies for electronic excitations, the strain present in the ground



[excited state contributing structure]

state molecule will not be relieved upon excitation. The longer absorption wavelength of the 5-ring and 7-ring α,β-unsaturated acids compared to the acyclic or 6-ring acids must be accounted for by steric or electronic considerations, not by differences in strain between the ground and excited states.

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THE THERMAL QUINONE DEHYDROGENATION REACTION

Reported by W. S. Chilton November 14, 1960

Introduction

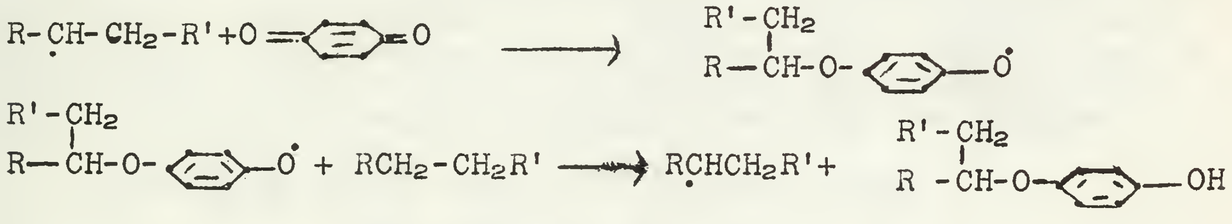
Quinones of sufficiently high potential can abstract hydrogen and its bonding electrons from carbon in certain organic compounds to yield carbonium ions which, by loss of a proton, form a double bond. The mechanism of this dehydrogenation has been the subject of a recent study by Braude, Jackman and Linstead and co-workers. Its utility in the selective partial dehydrogenation of steroids was pointed out by Agnello and Laubach in 1957 and has been demonstrated by a number of workers in the past year.[1] Jackman has cited examples of dehydrogenation with quinones in a review of hydrogenation and dehydrogenation reactions.[2]

Scope of the Reaction

Dehydrogenation of hydroaromatic hydrocarbons has been commonl carried out in refluxing amyl alcohol, benzene, phenetole, or xylene in the presence of chloranil, 3,4,5,6-tetrachloro-1,2-benzoquinone, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 1,4-naphthoquinone, ar 3,3',5,5'-tetrachloro-4,4'-diphenoquinone as hydrogen acceptor. The most reactive quinones are those with the highest oxidation potential. The oxidation potential is enhanced by electron withdrawing groups such as the cyano or halo substituent. In hydrocarbons the hydrogen donating position must be activated by the presence of an allylic or benzylic group. Heterocyclic hydroaromatic compounds are particularly reactive and may often by quantitatively dehydrogenated in a few minutes at room temperature. Acyclic alkyl amines and unsaturated alcohols may be dehydrogenated to enamines and aldehydes.

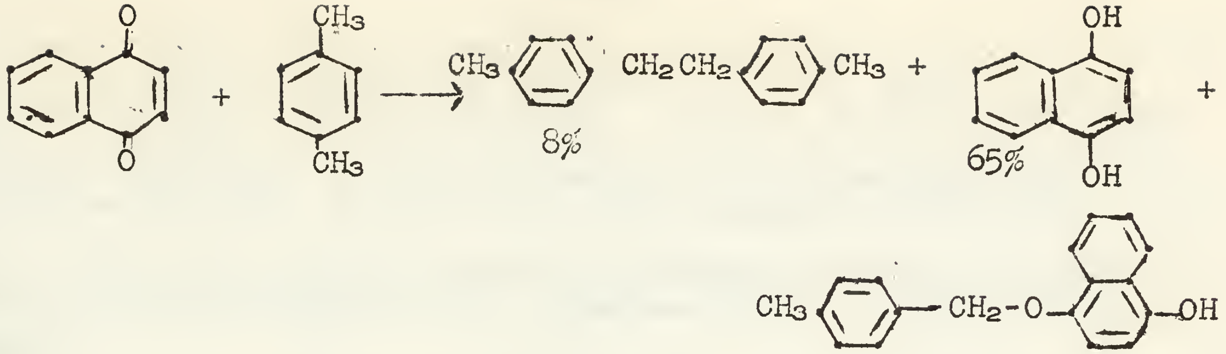
Mechanism

A radical mechanism for the thermal quinone dehydrogenation of hydroaromatics and alkyl side chains of aromatic compounds has been proposed in which a semi-quinone radical is the intermediate:

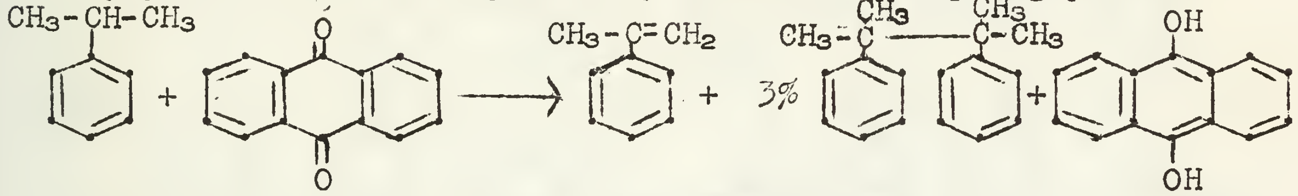


However neither added peroxide nor illumination has any effect on the yields of acenaphylene or naphthalene from acenaphthene and tetralin with chloranil in refluxing xylene.[3]

A photochemical dehydrogenation with quinone is known in which small amounts of hydrocarbon dimers are formed. In general small yields of dimers were observed in those cases where formation of an additional double bond was not possible.[4] Xylene is coupled in 8% yield after irradiation by a 500 watt light source placed 25 cm from a sealed quartz tube containing the reactants:



Only in the case of cumene did a compound capable of forming a conjugated double bond yield any detectable coupling product:



Unfortunately no control experiments were run to determine the effect of the absence of light.

A heterolytic mechanism has been proposed in which the rate determining step is the transfer of hydrogen with its two bonding electrons from the hydroaromatic compound to the quinone, followed by rapid proton transfer from the conjugate acid of the aromatic hydrocarbon to the hydroquinone anion:[5]

$$RH_2 + Q \xrightarrow{\text{slow}} RH^{\oplus} + QH^{\ominus} \xrightarrow{\text{fast}} R + QH_2$$

Kinetic studies of the dehydrogenation of a number of hydroaromatic hydrocarbons have shown that the reaction follows strict second order kinetics.[5,6] The rate of dehydrogenation of 1,4-dihydronaphthalene by thymoquinone at 100°C is doubled on going from decalin solvent to o-dichlorobenzene and quadrupled in dimethylformamide.[5] Radical-producing agents, benzoyl peroxide and light, are without influence on the reaction, and no hydrocarbon coupling products are found.[3,5] A close correlation exists between the oxidation potential of the particular quinone and the rate of reaction.[5,6] Catalysis has been observed in non-polar solvents with proton donors capable of forming molecular complexes with the quinone, in which case the conjugate acid of the quinone, a hydroquinone cation would be formed.[5] The cation has an even higher affinity for anionic hydrogen than does the quinone.

$$Q + HX \underset{}{\overset{\text{fast}}{\rightleftharpoons}} QH^{\oplus}X^{\ominus}; \quad RH_2 + QH^{\oplus} \xrightarrow{\text{slow}} RH^{\oplus} + QH_2$$

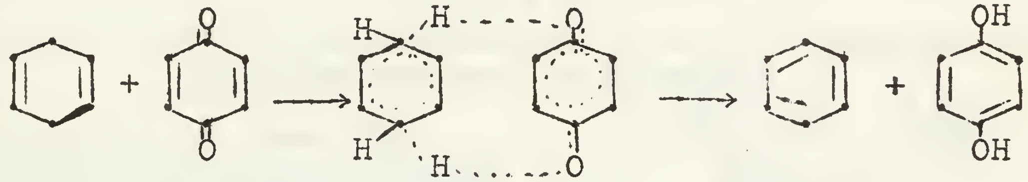
$$RH^{\oplus} + X^{\ominus} \xrightarrow{\text{fast}} R + HA$$

Further evidence of acid catalysis is offered by the observation of a two fold acceleration of the reaction between 1,4dihydronaphthalene and thymoquinone by 0.1 molar trichloroacetic acid in propionic acid solvent and a thousand fold acceleration by 0.070<u>M</u> perchloric acid.[5] Product calaysis, due to the formation of a molecular complex of quinone with the proton-donor hydroquinone during the course of the reaction, is observed only with quinones of low potential. Hydroquinone may form a complex with the quinone in solvents of low dielectric strength, partially transferring its proton to the quinone, to produce the hydro-

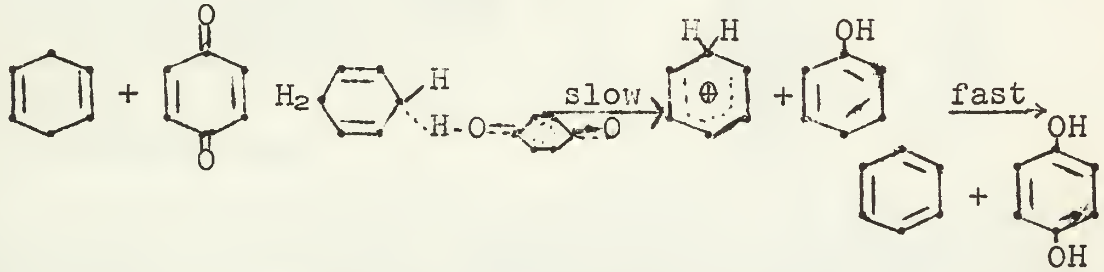
quinone cation. In line with this, p-nitrophenol but, not p-nitro anisole, both of which form complexes with the quinone, is a strong catalyst for the reaction.[5] Product catalysis decreases with increasing ionizing property of the solvent, which favors charge dispersal. It also decreases with increasing temperature which reduces the extent of molecular complex formation.[5]

Two mechanisms representing extremes in the time sequence of the two carbon-hydrogen bond cleavages are:

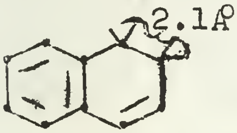
Path 1



Path 2

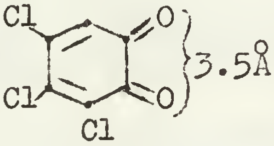


The concerted one-step mechanism (Path 1) would be expected to be partially dependent on steric considerations. Table 1 gives a comparison of the relative rate of dehydrogenation of hydrocarbon (I) and (II) by quinones (III)-(V) having varying separations between atoms involved in the reaction.[7]

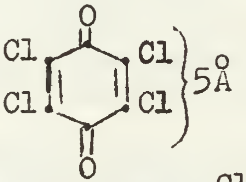


(I)

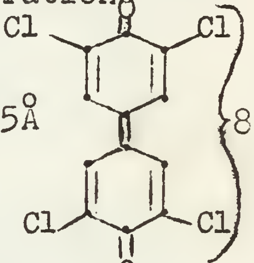
(II)



(III)



(IV)



(V)

Table 1

Relative rate of Dehydrogenation of (I) and (II) at 100°

	by:	(III)	(IV)	(V)
k_{II}/k_{I}		29.1±1.7	182±10	30.2±2.4

Models indicate that the one step mechanism would be most favorable for reaction of a 1,2-quinone (III) with a 1,2-dihydrosystem (I), whereas it is observed that the sterically quite dissimilar 1,8-diphenoquinone actually favors the 1,2 dihydrosystem to the same extent as does the 1,2-quinone; the sterically intermediate 1,4-quinone, with slightly lower potential than (III) or (V), is more discriminating.

For the dehydrogenation of (I) by five substituted 1,4-benzoquinones, there is a linear relationship between the free energy of activation, and the oxidation potential of the quinone, which is effectively a measure of the free energy change on reduction of the quinone by molecular hydrogen:[5] (eqn 1)

$$\Delta F^{\ddagger}_{25} = 38.0 - 16\ E^{0}_{25} \qquad \text{(Eqn 1)}$$

or in terms of free energy:

$$\Delta F^{\ddagger}_{25} = 38.0 - 0.07\Delta F^{0}_{25}$$

That 1,8-diphenoquinone also fits this equation is an argument against a one-step concerted mechanism in which steric effects would be expected to predominate.

Kinetic data on the dehydrogenation of a large number of hydroaromatics by high potential quinones have been obtained in phenetole solvent. Table 2 contains relative rate data and calculated resonance energy gains for the dehydrogenation of seven hydroaromatic hydrocarbons.[8] One of the main factors controlling the sequence of reactivity of hydrogen donors to a specific quinone wil be the lowering of the energy barrier by resonance energy gains in the transition state. The anomalies in the correlation of reaction rate with resonance energy gain in Table 2 appear to be acenaphthen and 1,2-diphenylethane. Resonance energy of acenaphthylene over acenaphthene is not accurately known. Estimates made do not take into consideration the effect of the increase in ring strain upon introduction of a double bond into the five member ring. The diphenyl ethane system will lose a degree of freedom of rotation on going to the planar stilbene, resulting in a decrease in the entropy of activation, and consequently, in a lower relative rate.

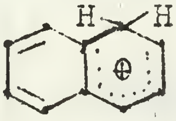
Table 2

Relative rate of dehydrogenation of various hydrocarbons by p-benzoquinone in phenetole

Donor	Rel. rate	ΔE_{res}
(I) 1,4-dihydrobenzene (DHB)	1	36
(II) 1,4-dihydronaphthalene (DHN)	0.57	30
(III) 9,10-dihydroanthracene (DHA)	0.015	20
(IV) 1,2-dihydronaphthalene	0.001	25
(V) Tetralin	10^{-4}	4
(VI) Acenaphthalene	10^{-5}	< 15
(VII) 1,2-Diphenylethane	10^{-6}	7

If the transition state of the hydrocarbon, after full or partial-transfer of a hydride ion to quinone to give the conjugate acid of an aromatic hydrocarbon, ressembles a sigma complex, the additional delocalization energy of the sigma complex over its hydroaromatic parent compound will contribute to lowering the energy of the transition state. Molecular orbital calculations show that this delocalization energy gain is greatest for 1,4-dihydrobenzene.[9] The predicted order of delocalization energy gains, 1,4-dihydrobenzene > 1,4-dihydronaphthalene > 9,10-dihydroanthracene, is consistent with the observed relative rate of aromatization of these hydrocarbons. (See Table 2)

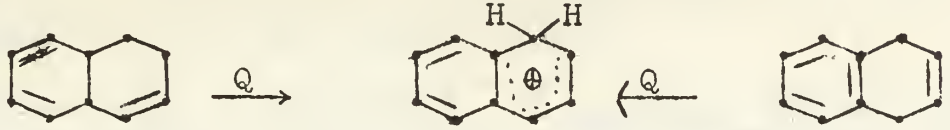
VIII



IX

Calculations for 1- and 2-naphthalenium ion predict that the 1-naphthalenium ion (VIII) has the higher resonance energy by somewhere between 2 and 13 kcal/mole.[9] This suggests that the 2-position is the preferred site of hydride abstraction in the dehydrogenation of 1,2-dihydronaphthalenes. The activation energy for the dehydrogenation of 1,2-DHN exceeds that of 1,4-DHN by 3 kcal/mole.[9c] Since they should both involve the same ionic intermediate, the difference in the resonance energy gain must arise from the difference in the resonance energy of the two hydroaromatic donors.

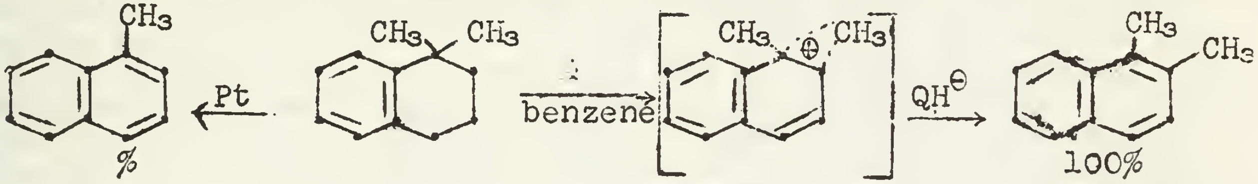
The difference in their heats of hydrogenation, 3.0 kcal/mole, is in excellent agreement with this explanation.



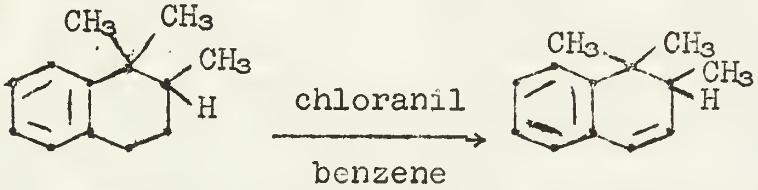
An ionic two step mechanism similar to Path 2, appears to be most probable on the basis of the available evidence. The rate determining step is the transfer of a hydride ion from a benzylic (allylic) position to quinone.

Dehydrogenation Reactions

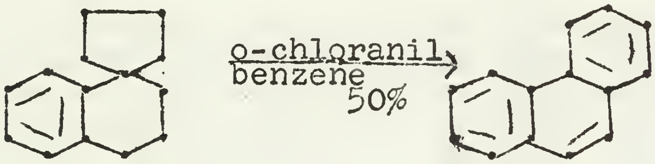
Aromatization of hydroaromatic compounds containing "blocking groups", such as the gem-dimethyl group in 1,1-dimethyltetralin, with platinum, selenium or sulfur usually proceeds with loss of one of the blocking groups.[10] Aromatization of blocked hydroaromatics with o-chloranil and other high potential quinones proceeds by a Wagner-Meerwein rearrangement retaining alkyl substituents:[11,]



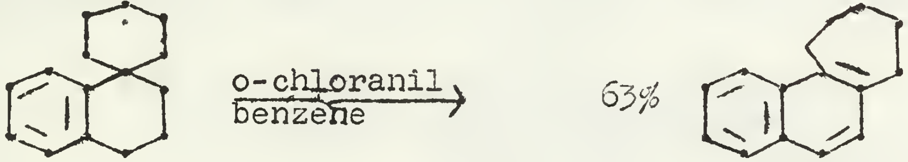
Dehydrogenation of 1,1,2-trimethyltetralin stops at the dihydro stage:[11]



Some spirohydroaromatics undergo alkyl migration with ring enlargement. Rearrangement and aromatization of 1,1-spirocyclopentanotetralin in benzene with o-chloranil produces phenanthrene:[12]



Spirocyclohexanotetralin undergoes rearrangement but only partial dehydrogenation:[12]



1-Methyl-1-phenyl tetralin undergoes phenyl migration exclusively. Since there are no clear examples of rearrangement of alkyl groups to radical ends,[13] the observation of a Wagner-Meerwein rearrangement strongly substantiates the ionic mechanism. The argument is strengthened by the observation that the stable radical, diphenyl picrylhydrazyl converts 1,2-DHN quantitatively to naphthalene but yields no naphalene product with 1,2-dihydro-1,1-dimethyl naphthalene.[12]

[illegible]

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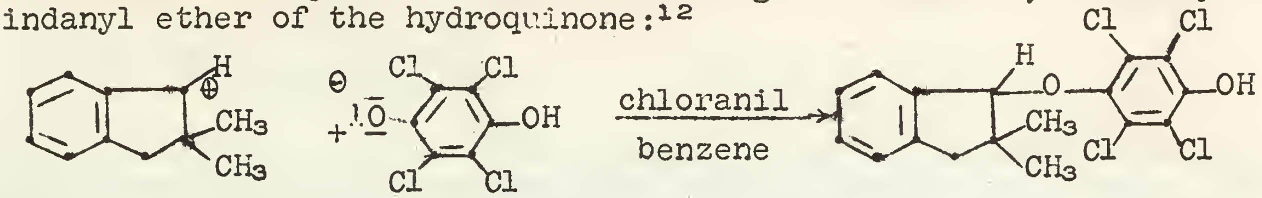
Indane gives a good yield of indene with dichloro-dicyanobenzoquinone, but 2,2-dimethyl indane apparently undergoes intermolecular nucleophilic substitution to give the bis-2,2-dimethyl indanyl ether of the hydroquinone:[12]



The octamethyl octahydroanthracene (X) was inert under conditions where all tetralins reacted with o-chloranil, showing that the reaction commences with attack at a benzylic or allylic position, all blocked.[12]

(X)

A kinetic study of the dehydrogenation of blocked hydroaromatic compounds such as 1,1-dimethyl tetralin reveals the first step to be rate controlling, since the rate of dehydrogenation of 1,1-dimethyl-1,2-dihydronaphthalene and of 1,2-dihydronaphthalene to their respective naphthalene derivatives is much greater than the rate of drhydrogenation of 1,1-dimethyl tetralin and tetralin to the naphthalenes.[14] A rate ratio of 20:1 for the initial step in the dehydrogenation of tetralin and 1,1-dimethyl tetralin is considerably greater than the expected electronic effect of replacing two hydrogens by methyl groups three carbons removed from the site of initial attack. However in formation of a carbonium ion by loss of hydride ion, it is necessary that the carbon atom adopt an sp^2 configuration coplanar with the benzene system, shifting the ring conformation from a half-chair toward a coplanar conformation. This is opposed by eclipsed hydrogen-hydrogen interactions in the planar conformation for unsubstituted tetralin. Consideration of the greater methyl-hydrogen interactions in 1,1-dimethyl tetralin suggests that the presence of alkyl substituents will raise the energy of the carbonium ion above that of a carbonium ion in an unsubstituted tetralin. This steric effect will therefore exercise an additional, retarding effect on the dehydrogenation of alkyl substituted tetralins.

The observation that several 1,1-dialkyl-1,2-dihydronaphthalenes have nearly the same second order reaction rate constants and energies of activation as unsubstituted 1,2-dihydronaphthalene is further evidence that initial hydride abstraction occurs at the 2-position as predicted by the M.O. calculations.[14] If initial attack were in the 1-position, the activation energy for the dehydrogenation of 1,2-dihydronaphthalene would be expected to be much less than that for 1,1-dialkyl-1,2-dihydronaphthalenes.

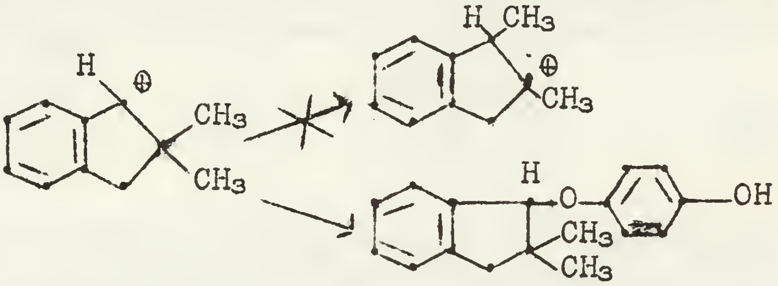
Table 3

Kinetic Data on the Dehydrogenation of Hydroaromatic Hydrocarbons

Donor	$10^3 k_2$(100°C)	E_A (kcal/mole)	$S^{\ddagger}$(E.U.)
Tetralin	5.86	15.6	29.0
1,1-dimethyl tetralin	0.29	16.2	33.7
1,2-dihydronaphthalene	41.1	15.4	25.7
1,2-dihydro-1,1-dimethyl-naphthalene	28.7	15.5	26.2
1,1-diethyl-1,2-dihydro-naphthalene	57.8	16.1	23.4

1,2-dihydro-1,1-diisopropyl naphthalene	40.8	15.1	26.5
1,2-dihydro-1-methyl-1-phenyl-naphthalene	18.7	15.9	26.2
1,2-dihydro-1,1-diphenyl-naphthalene	2.77	16.3	29.1

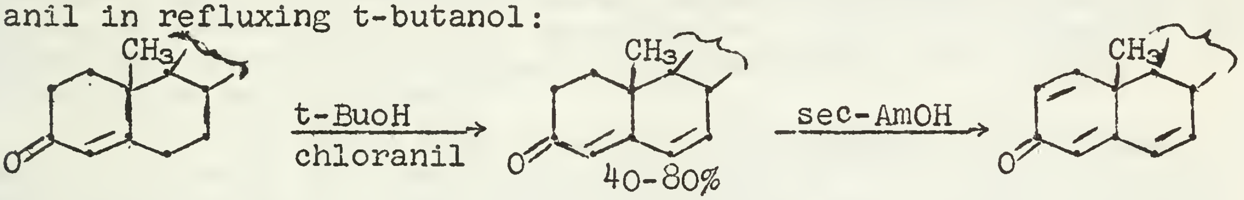
Introduction of the phenyl group in the 1-position of 1-methyl 1,2-dihydronaphthalene retards the dehydrogenation to a degree compatible with the inductive effect of this group.[14] Rate enhancement due to participation of the phenyl group is probably negligibl because the carbonium ion is well stabilized by resonance and the activation energy is low compared with that for reactions in which significant participation has been observed.[15] The 1,1-disubstitut -1,2-dihydronaphthalene system differs from cyclohexene and acyclic systems in that participating and leaving groups cannot adopt a truly axial configuration necessary for maximum participation. In the case of 2,2-dimethylindane, in addition to the conformational obstacle to methyl participation and rearrangement, the migration is further unfavored the loss of delocalization energy on migratio of the carbonium ion to the 2-carbon atom isolated from the pi electron system:



Instead hydroquinone ether is formed by direct nucleophilic attack on the unrearranged carbonium ion.

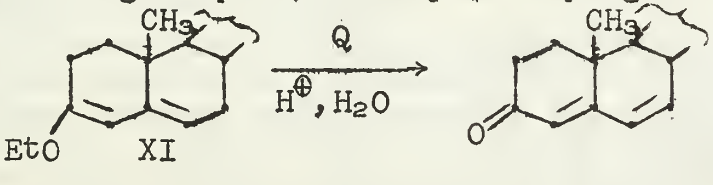
Dehydrogenation of Steroids

The thermal quinone dehydrogenation has been extended to steroids principally by Agnello and Laubach,[1,16] and Ringold and co-workers.[17,18,19] These and other workers have converted a great number of Δ^4-3-ketosteroids to $\Delta^{4,6}$-3-ketodehydrosteroids with chlo anil in refluxing t-butanol:



Dehydrogenation in the higher boiling sec.-amyl alcohol leads to the $\Delta^{1,4,6}$-trienone.

In the steroid dehydrogenation an enolization may be the rate determining step. 3-Ethoxy$\Delta^{3,5}$-pregnadiene-17α,21-diol-20-one (XI,



was dehydrogenated more readily than its parent Δ^4-3-ketone.[16]

Other Reactions

Viewed as a two step ionic process, the thermal quinone dehydrogenation ressembles a unimolecular elimination, E_1, in which the

[illegible]

[illegible]

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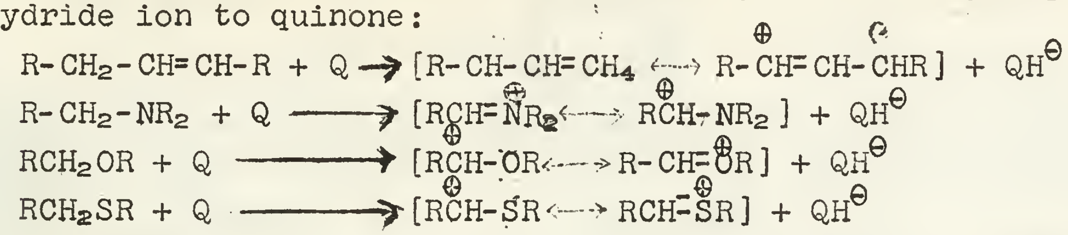
hydride ion is the leaving group and the quinone acts as a solvent or electrophilic catalyst. It is possible to envisage other dehydrogenations in which a carbon atom adjacent to an atom with an unshare electron pair is capable of transferring a bonded hydrogen as a hydride ion to quinone:



$$R\text{-}CH_2\text{-}CH{=}CH\text{-}R + Q \rightarrow [R\text{-}CH\text{-}CH{=}CH_4 \longleftrightarrow R\text{-}\overset{\oplus}{C}H{=}CH\text{-}\overset{\oplus}{C}HR] + QH^{\ominus}$$

$$R\text{-}CH_2\text{-}NR_2 + Q \longrightarrow [RCH{=}\overset{\oplus}{N}R_2 \longleftrightarrow R\overset{\oplus}{C}H\text{-}NR_2] + QH^{\ominus}$$

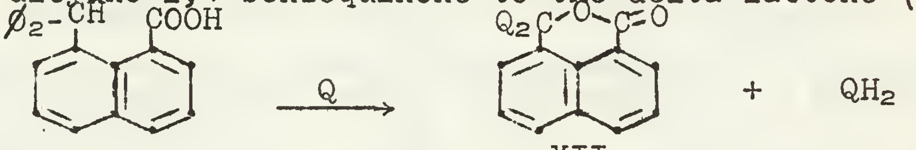
$$RCH_2OR + Q \longrightarrow [R\overset{\oplus}{C}H\text{-}OR \longleftrightarrow R\text{-}CH{=}\overset{\oplus}{O}R] + QH^{\ominus}$$

$$RCH_2SR + Q \longrightarrow [R\overset{\oplus}{C}H\text{-}SR \longleftrightarrow RCH\text{-}\overset{\oplus}{S}R] + QH^{\ominus}$$

Proton elimination is just one of the reactions which the resulting carbonium ion can undergo.

Nucleophilic Substitution

A compound containing a benzylic hydrogen, but no hydrogen on the alpha carbon atom, may form a carbonium ion but cannot form a double bond without rearrangement. It can, however, undergo nucleophilic substitution. If the molecule itself contains a suitably placed nucleophilic group, it should be possible to effect polymerization or cyclodehydrogenation by internal substitution. Thus 8-diphenylmethyl-1-naphthoic acid undergoes cyclodehydrogenation wit 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to the delta lactone (XII) in 85% yield:[20]

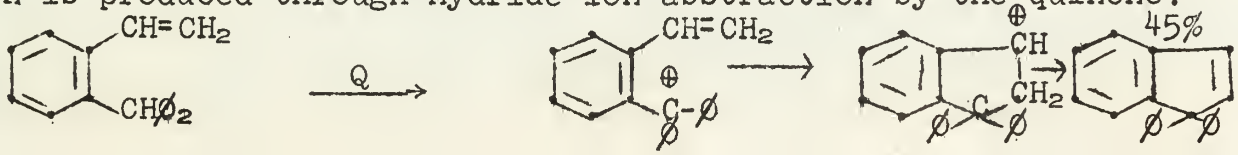


XII

In competition for 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, p-diphenylmethyl benzoic acid and o-diphenylmethyl benzoic acid reacted at similar rates although the ortho carboxyl group might be expected to inhibit formation of the nearly coplanar triphenyl methyl cation. Since the inductive effect should be parallel to the steric effect in the ortho isomer, it is probable that the carboxyl participates as a neighboring group, providing sufficient driving force to counter balance the steric and inductive effects. An example of steric inhibition of carbonium ion formation is provided by the two diphenylmethylbenzamide. Ortho-diphenylmethyl-benzamide does not react with the quinone in refluxing benzene, while p-diphenylmethyl-benzamide gives a quantitative yield of a polyamide which can be hydrolyzed to p-(α-hydroxy-diphenylmethyl)-benzamide in cold concentrated sulfuric acid.

It has been shown that carbonyl participation is stronger with amides than with carboxyl groups (21). However the ortho-benzamide does not participate under conditions where the benzoicacid does. This suggests that formation of the phthalide occurs through participation of carboxylate oxygen. If this is the case the phthalide-forming dehydrogenation would be expected to show a different dependence on the acidity.

The reaction of o-diphenylmethylstyrene with quinone is a cyclodehydrogenation resembling the acid catalyzed cyclization of alkadiene systems, which proceeds by carbonium ion attack on a double bond, the carbonium ion being formed by protonation of one of the double bonds. With o-diphenylmethylstyrene the carbonium ion is produced through hydride ion abstraction by the quinone:[22]



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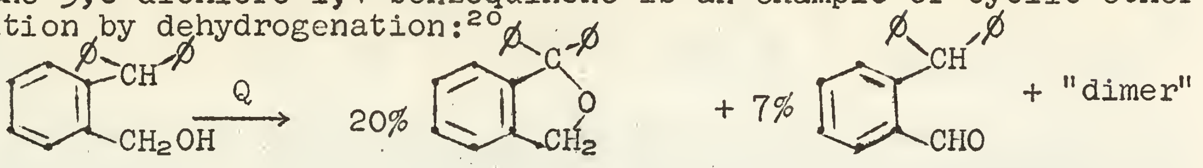
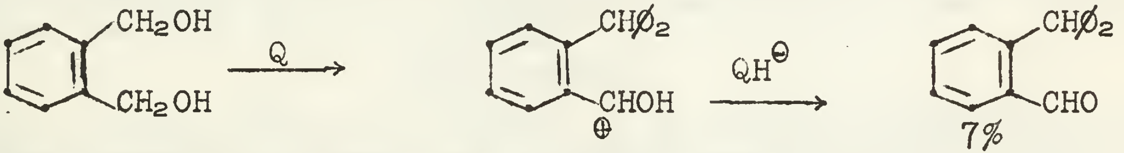
The reaction of o-diphenylmethyl-benzylalcohol with 2,3-dicyano-5,6-dichloro-1,4-benzoquinone is an example of cyclic ether formation by dehydrogenation:[20]



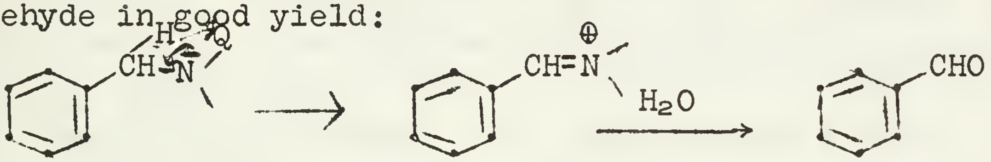
Side products included a dimer and a small amount of benzaldehyde arising from initial hydride abstraction from the alcoholic benzylic carbon atom:



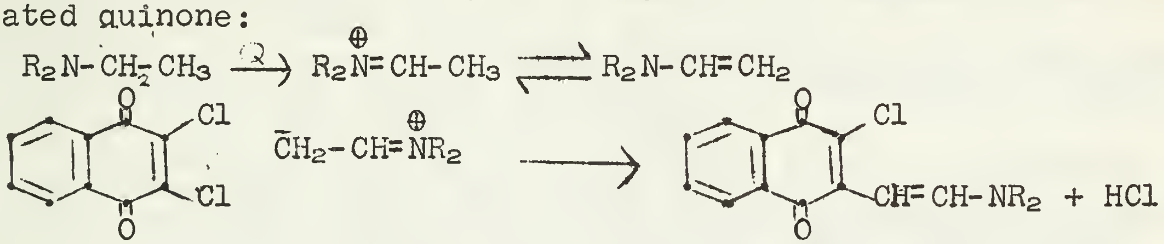
Dehydrogenation of Alcohols and Amines

The formation of aldehydes from benzyl alcohols, noted as a side reaction in the cyclodehydrogenation of o-diphenylmethylbenzyl alcohol, is a general reaction for primary and secondary allylic and propargylic alcohols as well.[23] Saturated alcohols do not undergo appreciable dehydrogenation in the dark. Cinnamyl alcohol with o-chloranil gives a quantitative yield of cinnamaldehyde at room temperature. Benzyl alcohol gives a 67% yield of benzaldehyde in three hours at 35°C. Benzhydrol gives a 42% yield of benzophenone.[23]

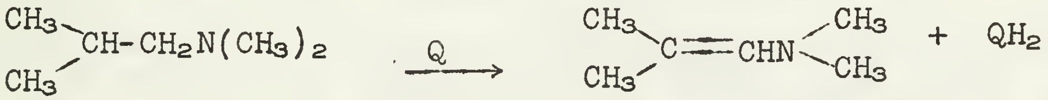
Benzylic amines are also readily dehydrogenated.[24,25] Quinone dehydrogenation of dimethylbenzylamine and tribenzylamine produces benzaldehyde in good yield:



Saturated alkyl amines as well as benzyl amines may be dehydrogenated. In contrast, alcohols must be benzylic or allylic. Tertiary amines containing a >N-CH-CH grouping are dehydrogenated to enamines. If the tertiary amine contains a >N-CH-CH₂- grouping, the dehydrogenated enamine reacts further, coupling with a second mole of halogenated quinone:



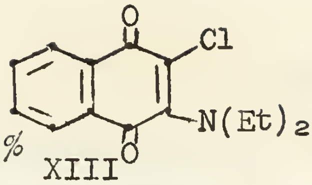
Dehydrogenation of N,N-dimethyl isobutyl amines gives an enamine which has no hydrogen on the beta carbon atom and cannot give a substitution product with the quinone. Isobutyraldehyde was isolated in 48% yield as its 2,4-dinitrophenylhydrazone:[24]



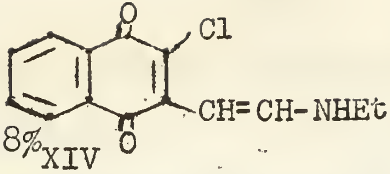
Dehydrogenation of secondary amines is complicated by reaction of the enamine dehydrogenation product with unreacted saturated amine to give the tertiary enamine:[25]

$$2CH_3CH_2-NHCH_2CH_3 \xrightarrow{Q} CH_3CH{=}NC_2H_5 + (C_2H_5)_2NH \rightleftharpoons CH_2{=}CH-N(C_2H_5)_2 + NH_2-C_2H_5$$

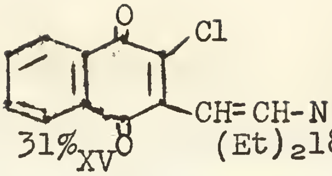
All four amines attack the quinone, displacing halogen to give products (XIII) - (XVI):



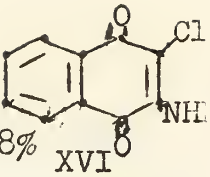
11% XIII



18% XIV



31% XV



18% XVI

Partially dehydrogenated heterocyclics are extremely reactive hydrogen donors. 3,5-Dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine is dehydrogenated quantitatively in 15 minutes at room temperature with chlorobenzoquinone.[26] The dihydropyridine is a sufficiently reactive hydrogen donor to hydrogenate maleic anhydride to succinic anhydride in good yield at 100°C.[26]

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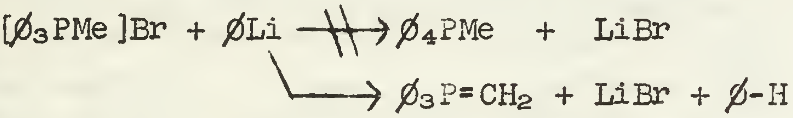
RECENT STUDIES OF THE WITTIG REACTION

Reported by R. C. Slagel November 17, 1960

INTRODUCTION: Phosphorous methylene (P-ylene) compounds have been known since 1919 when Staudinger and Meyer (1) reported that the phosphazine (I) obtained from triphenylphosphine and diphenyldiazomethane lost nitrogen on heating to give triphenylphosphinediphenylmethylene (II). This compound gave the keteneimine (III) with pheny isocyanate while eliminating triphenylphosphine.

$$\underset{(I)}{\phi_3P=N-N=C\phi_2} \xrightarrow[-N_2]{\Delta} \underset{(II)}{\phi_3P=C\phi_2} \xrightarrow{\phi NCO} \underset{(III)}{\phi N=C=C-\phi_2} + \phi_3PO$$

Very little work was done on this class of compounds then until Wittig and co-workers (2), in 1953, while trying to prepare ϕ_4PMe by the following path actually obtained triphenylphosphinemethylene.

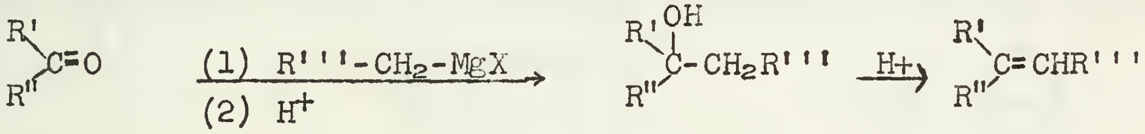


$$[\phi_3PMe]Br + \phi Li \not\longrightarrow \phi_4PMe + LiBr$$

$$\longrightarrow \phi_3P=CH_2 + LiBr + \phi-H$$

While trying to characterize this compound they allowed it to react with benzophenone which gave $\phi_3PO + \phi_2C=CH_2$ (84%) as products (3). Thus a new reaction of obtaining olefins from P-ylenes and aldehydes or ketones was discovered.

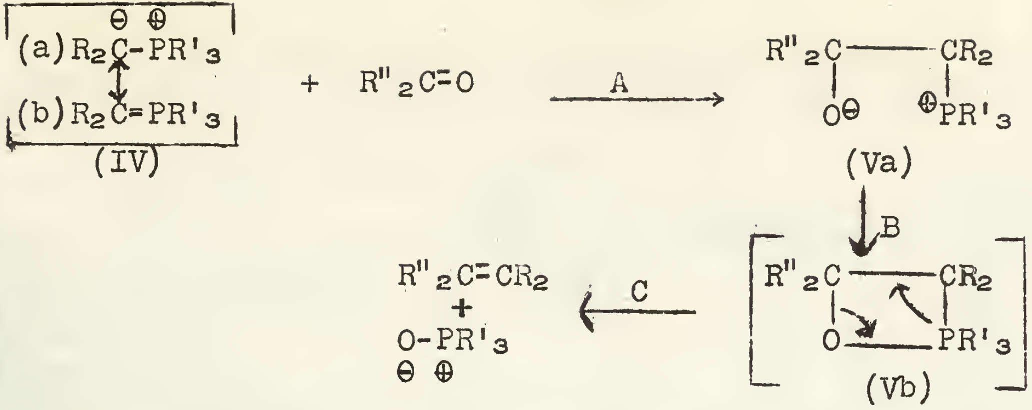
Probably the chief advantage this method of olefin preparation has over the older classical methods, such as the Grignard reaction, is that the position of the double bond is hardly ever in doubt, whereas with the Grignard reaction one cannot be sure of the exact position of the double bond if R' and R" are aliphatic groups. Another important factor is that the Wittig reaction proceeds normally under mild conditions. Thus the process offers access to sensitive olefins such as carotenoids, methylene steroids and other natural products.



$$R'R''C=O \xrightarrow[(2)\ H^+]{(1)\ R'''-CH_2-MgX} R'R''C(OH)-CH_2R''' \xrightarrow{H+} R'R''C=CHR'''$$

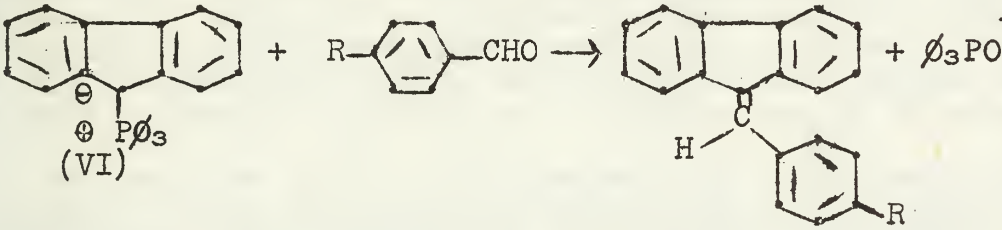
In the last three or four years this reaction has been extended into other general as well as specific syntheses. It is the purpose of this seminar to elaborate on the work done since the last seminar on this topic by B.D. Wilson (4) in 1956. Since two other general reviews, by Schollkopf (5) and Trippett (6), have appeared recently covering some of the work in 1957 and 1958, most emphasis will be given to the literature of the last two years.

MECHANISM: The triphenylphosphine alkylidenes, which are prepared by treating triphenylalkylphosphonium halides with a strong base, may be represented as resonance hybrids as shown by (IV) below. The triphenylphosphine methylene can now attack a carbonyl group forming a betaine (Va). The betaine is then probably closed to a cyclic intermediate or transition state (Vb) which breaks up to give the olefin and triphenylphosphine oxide (7,8).



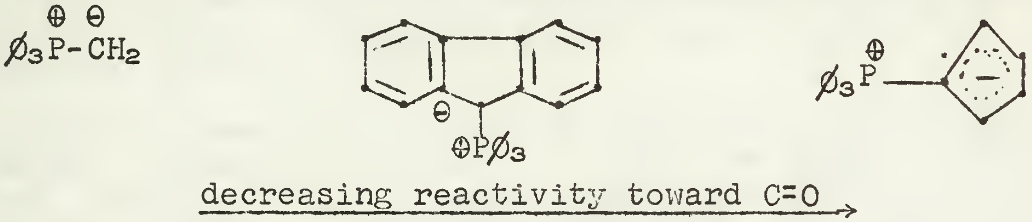
Recently Johnson and LaCount (9) have noted that there are several factors which control the course of the Wittig reaction.

1. The amount of positive charge on the carbonyl carbon: An electron-withdrawing group on the carbonyl carbon will increase its positive charge and facilitate the reaction. This effect is seen by treating triphenylfluorenylphosphine (VI) with substituted benzaldehydes under the same conditions (9,10).



R	% Yield
$-NO_2$	96
$-H$	84
$-OCH_3$	37
$-N(Me)_2$	0

2. The nucleophilic character of the attacking ylide (IV):
(a) This character will be decreased by resonance interaction (P-Pπ) with groups attached to the carbanion which tend to delocalize the negative charge as with phenyl or carbonyl groups. The reactivity of the ylide decreases in proportion to the electron-withdrawing power of the groups attached to the carbanion.



decreasing reactivity toward C=O →

(b) The extent of (2p-3d) d-orbital resonance (contribution of structure IVb to the resonance hybrid) between the carbanion and the phosphorus atom also affects the nucleophilic character of (IV). The less the amount of d-orbital resonance, the greater should be the reactivity. It is obvious that R' in (IV) can affect the extent of resonance by electronic interaction with the P atom. Jaffe (43) has argued from ultraviolet absorption spectra that phenyl groups are only very weakly conjugated with central P atoms having no unshared valence electrons. If this is true any interaction must be of the inductive type so we expect that the larger the electron-withdrawing power of the substituents on P, the greater the d-orbital resonance and the less the reactivity of the ylide in the Wittig reaction.

From these considerations one would expect the trialkylphosphine methylenes to be more reactive than triphenylphosphine methylenes. In comparing the reactions of triphenyl-, tri n-butyl-, and trimethylphosphine fluorenylides with various carbonyl compounds (Table I) it

is noted that the tri n-butyl ylide is more reactive than the triphenyl compound. However, the trimethyl ylide has lost the selectivity of the triphenyl ylide and in some cases gives a lower yield.

TABLE I (9)

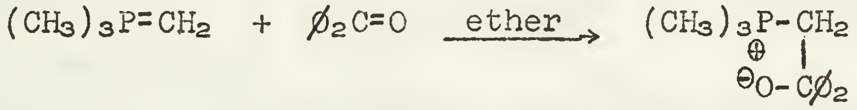
CARBONYL	RXN. TIME	YIELD %		
		Trimethyl	Tri n-butyl	Triphenyl
p-nitrobenzaldehyde	3 hr	74	99	96
p-chlorobenzaldehyde	"	--	96	93
Benzaldehyde	"	75	96	84
p-anisaldehyde	"	73	94	37
p-dimethylamino benzaldehyde	"	--	94	0
p,p-dinitrobenzophenone	24	--	93	0
Benzophenone	"	--	0	0

The low yield of the trimethyl compound has been explained as due to a weakening of the electron affinity of the P atom by hyperconjugation of the methyl groups (3) causing decreased reactivity for the trimethyl compound as compared to tri n-butyl. However, since the remaining 25% of the starting material in the trimethyl case was not accounted for and no rate studies were carried out, it is not safe to assume that the tri n-butyl compound is more reactive.

Trippett and Walker (12) prepared the compounds $Me_nØ_{3-n}P=CH-CO-$ (n=0,1,2,3) which all gave comparable yields (70-90%) of benzylidene acetophenone with benzaldehyde, and $Me_nØ_{3-n}P=CHØ$ (n=0,2,3) which gav with fluorenone about 60% and cyclohexanone 60-80% of the expected products.

Although there remains some question about the relative reactivities of alkyl and aryl ylides one can safely conclude from the above studies that the Wittig reaction is not restricted to tripheny phosphine ylides; the R groups in (IV) can be alkyl, aryl or a combination of these (44).

Little is known of the factors affecting steps B and C of the mechanism. Johnson and LaCount (9) feel the course of the reaction is best accounted for if step A is rate-determining. However, Wittig and Reiben (11) isolated the betaine (VII) from the reaction



$$(CH_3)_3P=CH_2 + Ø_2C=O \xrightarrow{ether} \begin{array}{l}(CH_3)_3\overset{}{P}-CH_2 \\ \quad\ \oplus \quad | \\ \quad\ {}^{\ominus}O-CØ_2\end{array} \quad (VII)$$

which was later shown to give the expected product in 40% yield (12) Clearly B or C is rate controlling at least in this case.

Needless to say, much more work needs to be carried out on the mechanism of the Wittig reaction.

STEREOCHEMISTRY: If the ylides and the carbonyl components are unsymmetrically substituted there is normally obtained a mixture of two cis-trans isomeric olefins indicating that the reaction is not stereospecific. However, the ratio of cis and trans isomers may vary with several factors.

1. The direction of coupling. Reaction (a) gives only the trans hydrocarbon (VIII) while reaction (b) gives a mixture of cis and

trans (13). No explanation has been offered for this surprising result.

(a) $$\mathrm{MeCH{=}CH(C{\equiv}C)_2CH{=}CH{-}CH{=}P\emptyset + OHC{-}CH{=}CH_2 \longrightarrow MeCH{=}CH(C{\equiv}C)_2CH{=}CH{-}CH\overset{t}{=}CH{-}CH{=}CH_2}$$
(VIII)

(b) $$\mathrm{MeCH{=}CH(C{\equiv}C)_2CH{=}CH{-}CHO + \emptyset_3P{=}CH{-}CH{=}CH_2 \longrightarrow (VIII)}$$ cis and trans

2. The base-solvent mixture. If benzyltriphenylphosphonium bromide is treated with phenyl lithium and benzaldehyde in ether ther is obtained 30% cis and 70% trans stilbene (IX) while the ratio is 53% cis and 47% trans if sodium ethoxide in ethanol is used (14). Trippett (6) believes this change is due to the base used.

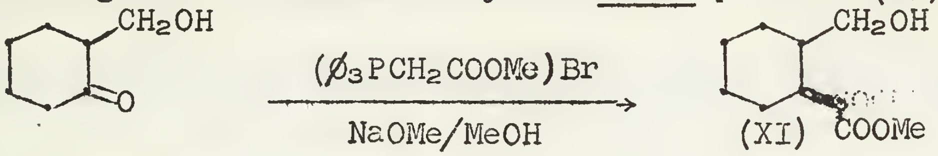
$$\mathrm{[\emptyset_3P{-}CH_2{-}\emptyset]Br \xrightarrow[solvent]{base} \emptyset_3P{=}CH{-}\emptyset \xrightarrow{\emptyset CHO} \emptyset{-}CH{=}CH{-}\emptyset}$$
(IX)

It is also possible that the solvent effects this change. The mixture of isomers possibly equilibrates to a greater extent in ether to give more of the thermodynamically more stable trans isomer. Also, the rates of reaction may be different with the two solvents. Since studies were not made of these possibilities, no real conclusions can be drawn.

3. The termperature of the reaction. At room temperature the reaction of the bisphosphorane (X) with benzaldehyde gives a mixture of three geometric isomers, but after heating under reflux in ether for one hour only the trans-trans isomer is recovered (15). Again this is probably due to equilibration to the thermodynamicall more stable trans isomer.

$$\mathrm{\emptyset_3P{=}CH{-}CH_2{-}CH_2{-}CH{=}P\emptyset_3 \xrightarrow{\emptyset CHO} \emptyset CH{=}CH{-}CH_2{-}CH_2{-}CH{=}CH\emptyset}$$
(X)

4. Steric hindrance. The compound 2-hydroxymethyl cyclohexanone with carboxymethyltriphenylphosphonium bromide and sodium methoxide in methanol gives almost entirely the trans product (XI) (6).



(XI)

RECENT APPLICATIONS:

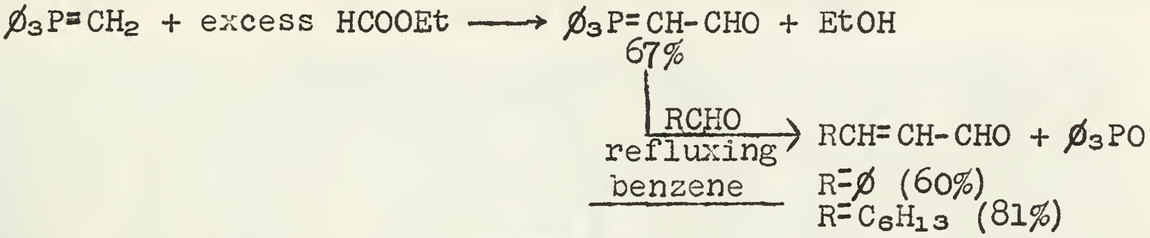
A. New Preparative Methods for Aldehydes: Simultaneous publications by Wittig (16) and Levine (17) describe a reaction which makes it possible to transform a carbonyl compound into an aldehyde which has one more carbon atom than the starting material. The P-ylene, triphenylphosphine methoxymethylene, is treated with a carbonyl compound giving an enol ether which is then hydrolyzed to the desired aldehyde. The yield of the enol ether depends on the

$$\mathrm{\emptyset_3P{=}CH{-}OCH_3 + R_2C{=}O \longrightarrow R_2C{=}CH{-}OCH_3 \xrightarrow{H_3O^+} R_2CH{-}CHO + HOCH_3}$$

nature of the carbonyl compound. In the case of benzophenone and tigogenone the yield is about 85% while with benzaldehyde and acetophenone the yield is about 40%. The hydrolysis is usually quantitative.

This reaction has several advantages over the glycidic ester method, the main ones being milder reaction conditions and avoidance of certain side reactions (17).

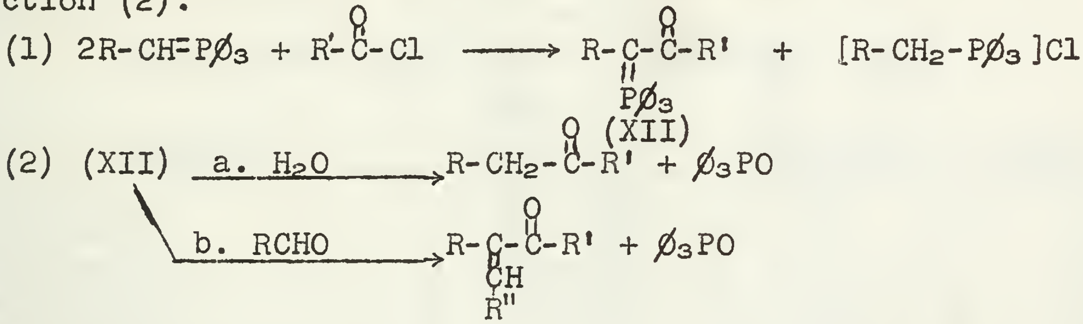
Trippett and Walker (41) have devised a scheme for obtaining α,β-unsaturated aldehydes. They first form triphenylphosphine formyl methylene from triphenylphosphine methylene and ethyl formate. This can then react with aldehydes in a normal Wittig fashion. Ketones will not react, however.



$$\emptyset_3P{=}CH_2 + \text{excess } HCOOEt \longrightarrow \underset{67\%}{\emptyset_3P{=}CH{-}CHO} + EtOH$$

$$\xrightarrow[\text{refluxing benzene}]{RCHO} RCH{=}CH{-}CHO + \emptyset_3PO \qquad R{=}\emptyset\ (60\%) \quad R{=}C_6H_{13}\ (81\%)$$

B. <u>A New Route to Ketones</u>: Bestmann (18) has shown reaction (1) to occur giving a new acyl alkylene (XII) in 60-80% yield. This compound can then be hydrolyzed to the corresponding ketone or treated with aldehydes to give α,β-unsaturated ketones as seen in reaction (2).



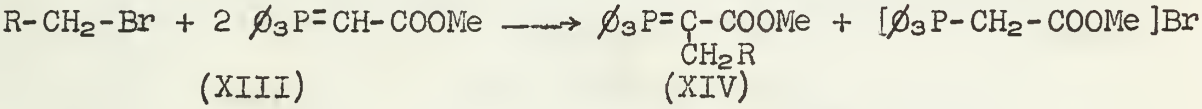
$$(1)\ 2R{-}CH{=}P\emptyset_3 + R'{-}\overset{O}{\overset{\|}{C}}{-}Cl \longrightarrow R{-}\underset{\underset{P\emptyset_3}{\|}}{C}{-}\overset{O}{\overset{\|}{C}}{-}R' + [R{-}CH_2{-}P\emptyset_3]Cl \quad (XII)$$

$$(2)\ (XII) \xrightarrow{a.\ H_2O} R{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}R' + \emptyset_3PO$$

$$(XII) \xrightarrow{b.\ RCHO} R{-}\underset{\underset{\underset{R''}{CH}}{\|}}{C}{-}\overset{O}{\overset{\|}{C}}{-}R' + \emptyset_3PO$$

The compound (XII), where R is aromatic, is stable to hydrolysis so that the results desired are obtained only if R is non-aromatic, preferably an alkyl group. With R=H, R=Me reaction (2a) gives acetone in 83% yield; R=H, R=Ø gives acetophenone (93%); and R=Me, R=Ø gives propiophenone (85%).

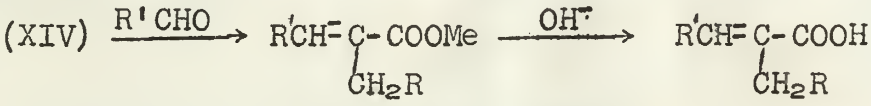
C. <u>A New Synthesis of Carboxylic Acids</u>: The reaction between a substituted methyl halide and triphenylphosphine carbomethoxymethylene (XIII) was shown by Bestmann (19) to give the compound (XIV).



$$R{-}CH_2{-}Br + 2\ \underset{(XIII)}{\emptyset_3P{=}CH{-}COOMe} \longrightarrow \underset{(XIV)}{\emptyset_3P{=}\underset{CH_2R}{C}{-}COOMe} + [\emptyset_3P{-}CH_2{-}COOMe]Br$$

When R=COOMe, the yield of (XIV) was 80% and with R=Ø, 75%. With alkaline hydrolysis the former gives succinic acid and the latter gives hydrocinnamic acid with yields of 90-100%.

One can also obtain α,β-unsaturated-α-branched carboxylic acids by the treatment of (XIV) with an aldehyde via the Wittig reaction.



$$(XIV) \xrightarrow{R'CHO} R'CH{=}\underset{CH_2R}{C}{-}COOMe \xrightarrow{OH^-} R'CH{=}\underset{CH_2R}{C}{-}COOH$$

In another paper Bohlmann (20) reports the treatment of ring substituted benzaldehydes with the ylide (XV), obtainable from γ-bromo crotonesters, and found that the results compared very favorably to those of the Reformatsky reaction. The Wittig method is preferred because it is experimentally simpler.

(XV)

D. <u>New General Synthesis of Substituted Vinyl Chlorides and Vinylidene Chlorides and Bromides:</u> Three research groups, Speziale et al. (21), Seyferth et al. (22) and Wittig et al. (23) have recently found that triphenylphosphine halo methylenes can be prepared via the reaction of a suitable carbene with triphenylphosphine. The carbene is generated by treatment of a halo-substituted methane with a strong base such as butyl lithium (22) or potassium t-butoxide (21). From these ylides a variety of substituted vinyl

$$CH_2Cl_2 + n\text{-BuLi} + \phi_3P \xrightarrow[-30^\circ]{\text{ether}} \phi_3P{=}CHCl + LiCl + C_4H_{10}$$

$$CHCl_3 + KO_tBu + \phi_3P \xrightarrow[0\text{-}5^\circ]{C_5H_{12}} \phi_3P{=}CCl_2 + KCl + t\text{-BuOH}$$

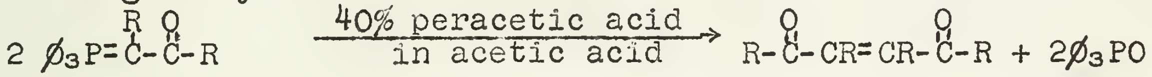
and vinylidene halides were prepared.

$$\phi_3P{=}CHCl + R_1R_2C{=}O \longrightarrow R_1R_2C{=}CHCl + \phi_3PO$$

TABLE II

CARBONYL	YLIDE	%YIELD	REF.
Benzophenone	$\phi_3P{=}CHCl$	31	23
Benzophenone	$\phi_3P{=}CCl_2$	46	21
Acetophenone	$\phi_3P{=}CBr_2$	--	22
Acetophenone	$\phi_3P{=}CHCl$	80-90	22
Cyclohexanone	"	--	22
Methyl isobutyl ketone	"	--	22
Diethyl ketone	"	--	22

E. <u>Method of Preparing Symmetrical Olefins:</u> Denney and Smith (24) found that weakly basic phosphine methylenes reacted with peracetic acid to give symmetrical olefins.



$$2\,\phi_3P{=}\overset{R}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}-R \xrightarrow[\text{in acetic acid}]{\text{40\% peracetic acid}} R-\overset{O}{\overset{\|}{C}}-CR{=}CR-\overset{O}{\overset{\|}{C}}-R + 2\phi_3PO$$

Bestmann (25) discovered that the autooxidation of triphenylphosphine benzylene produced a 55% yield of stilbene (35% <u>trans</u> and 20% <u>cis</u>.)

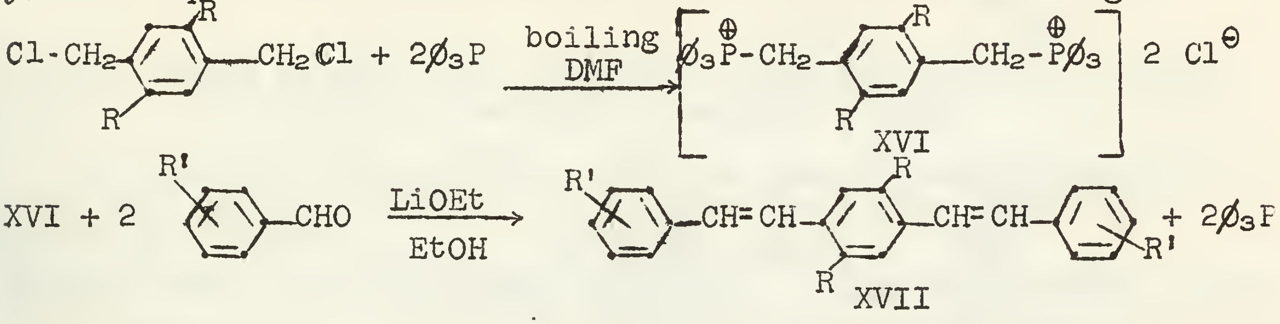
$$\underset{(XVI)}{\phi\text{-}CH{=}P\phi_3} \xrightarrow{O_2} \phi_3PO + \phi\text{-}CHO \xrightarrow{(XVI)} \phi\text{-}CH{=}CH\text{-}\phi + \phi_3PO$$

TABLE III

YLIDE	%YIELD	REF.
$\phi_3P{=}CHCO\phi$	73% <u>trans</u>	24
$\phi_3P{=}CHCOOCH_3$	52% <u>trans</u>	24
$\phi_3P{=}CHCOOEt$	41% -----	24
$\phi_3P{=}C(CH_3)_2COOEt$	7% -----	24
$\phi_3P{=}CH\text{-}CH{=}CH\text{-}\phi$	----------	25

F. <u>Synthesis of Polyphenyl Polyenes:</u>

1. Distyrylbenzenes: Campbell and McDonald (26) found that the Wittig reaction could produce good yields of distyrylbenzenes. This method is a great improvement over the previous pathways (via Grignard, Perkin-Kuhn condensation and Meerwein condensation) because of the ease of reaction, ease of work-up and the good yields acquired even with various substituents on the rings.

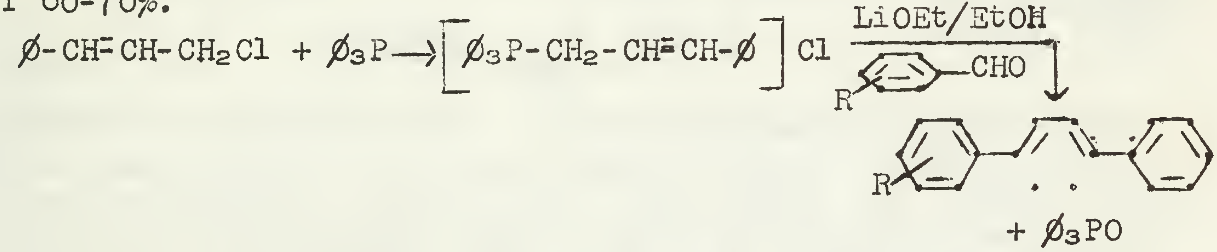


The products were a mixture of cis and trans isomers and were converted to all trans by heating with xylene containing a trace of I_2.

TABLE IV

R'	YIELD OF XVII R=H
H	88%
m-NO_2	83
p-CH_3	81
p-OCH_3	61
p-NO_2	60
p-$NHCOCH_3$	73
p-CO_2CH_3	80
p-Cl	14

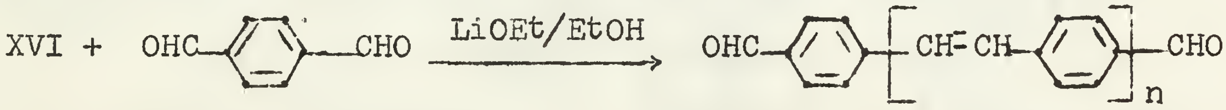
2. Diarylbutadienes: The same authors (27) showed that 1,4 Diphenylbutadienes, previously prepared via the Perkin-Kuhn condensatic in 25% yields, could be produced via the Wittig reaction in yields of 60-70%.



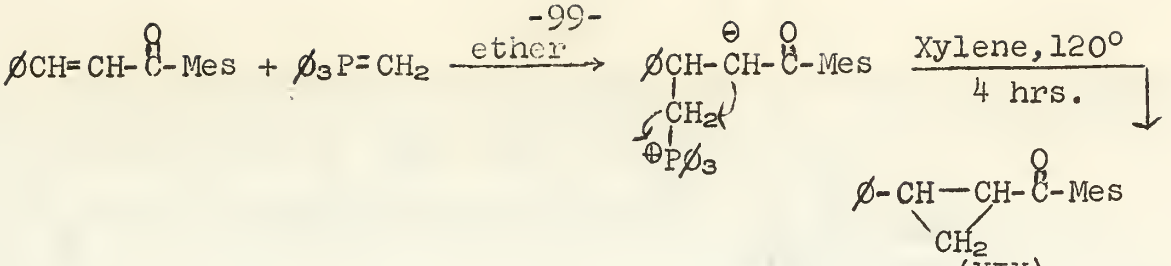
By similar reactions Drefahl et al (28) have prepared a serie of substituted butadienes.

3. Through reactions similar to those in parts 1 and 2 polyphenyl polyene-ynes (29) and vinyl styrenes (30) have been synthesized in 65-80% yields.

G. Method for Polymerization (31): Poly-xylylidenes were prepared giving a polymer with a molecular weight of about 1200 (n=9) and having an intense yellow color due to high conjugation.



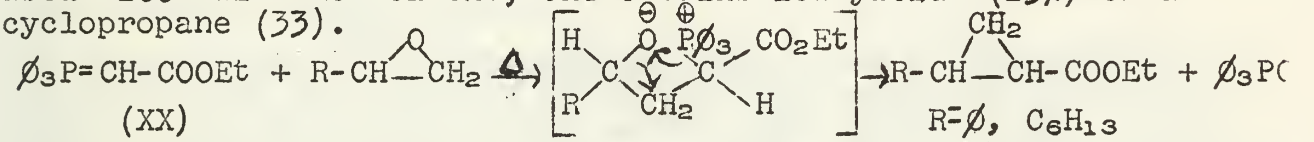
H. Formation of Cyclopropanes: Freeman (32) has shown in preparing the cyclopropane (XIX) that 1,4 addition is favored in the Wittig reaction by hindrance about the carbonyl group. This is



(XIX)

only the third example of 1,4 addition reported; usually 1,2 addition to α-β unsaturated carbonyl compounds occurs.

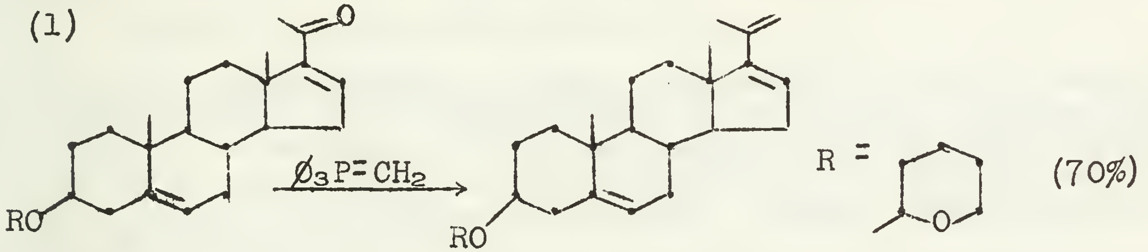
By heating the ylide (XX) with an epoxide under nitrogen at about 200° with no solvent, one obtains low yields (25%) of a cyclopropane (33).


(XX)

$R = \phi$, C_6H_{13}

I. Application to Steroids: In the last few years a good many keto steroids have been converted to otherwise hard to obtain methylene derivatives by the Wittig reaction.

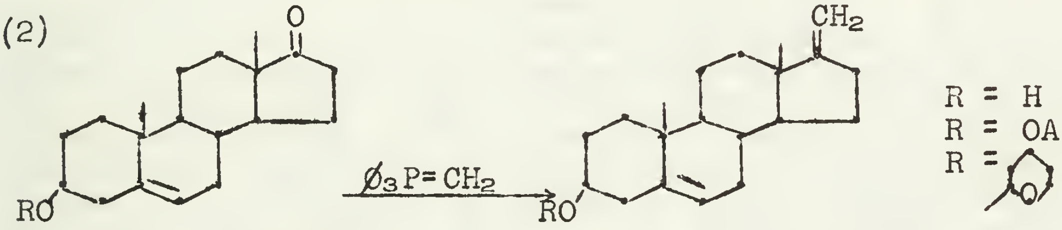
(1) Ref.



(70%) 36

16-dehydropregnenolone 20-methyl-5,16,20-pregnatriene-3β-ol

(2)

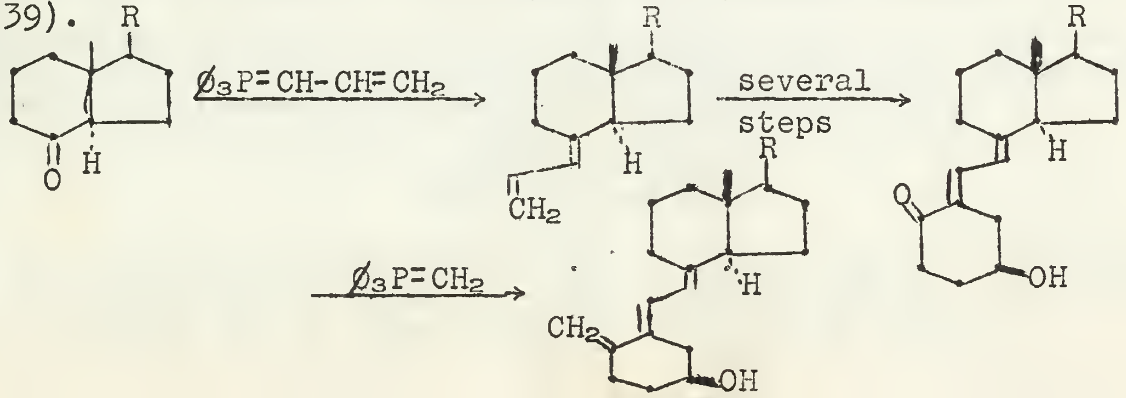


R = H (36%)
R = OAc (27%) 35
R = (44%)

Δ^5Androstene-3β-ol-17-one 17 methylene-Δ^5-androsten-3β-ol

These reactions show the great specificity of the Wittig reaction. As seen by reaction (2) the ylide will choose the carbonyl even though there are hydroxyl and double bond functions present. Reaction (1) again shows the reluctance of this reagent to undergo the 1,4 addition. Additional recent work on this subject can be found in references (34,37).

J. In Syntheses in the Vitamin D Series: The Wittig reaction has proved very valuable in two steps of the pathway in this series (38,39).



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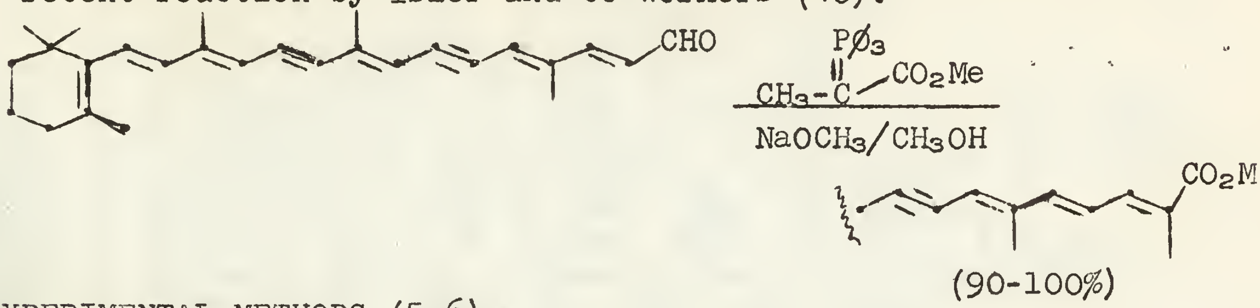
K. In the Synthesis of Carotenoids: Many examples are summarized in the review article by Schollkopf (5). An illustration is a recent reaction by Isler and co-workers (40).



EXPERIMENTAL METHODS (5,6):

A. Preparation of The Phosphonium Salt: The triphenylalkylphosphonium salts are prepared by the reaction of triphenylphosphine and the desired primary or secondary alkyl halide. The iodide reacts faster than the bromide or chloride but the resulting salt does not always give the normal Wittig reaction (42). A list of phosphonium salts may be found in reference (45).

B. Execution of the Wittig Reaction:

1. The organometallic method: This method employs phenyl or butyl lithium as a proton acceptor and ether or tetrahydrofuran (THF) as a solvent. Water and oxygen must be excluded from the system. Water destroys the organolithium compound and hydrolyzes the ylide to $\varnothing_2\mathrm{POCHR}_2$ and benzene. Oxygen reacts with the ylide as shown previously (25).

One equivalent of the base is added slowly to a suspension of the phosphonium salt in solvent and shaken. Usually the ylide formation is over within a few minutes and there is obtained a red to orange color. The carbonyl compound in the desired solvent is then added. The reaction usually can be carried out at room temperature. However, in more difficult cases betaine cleavage requires a temperature of 60-70°. In the latter case THF has an advantage over ether because of its higher boiling point. However, THF has a disadvantage in that it dissolves considerably more $\varnothing_3\mathrm{PO}$ This makes isolation of the product more difficult.

2. The Alcoholate Method: This method, which involves the use of sodium or lithium ethylate or methylate and the corresponding alcohol as a solvent, is being used more and more because of its simplicity.

3. The Sodium Amide Method: This method involves the use of sodium amide in liquid ammonia but is not widely used.

CONCLUSION: It must be said in concluding that the scope of the Wittig reaction is only at this time being realized. Many more valuable syntheses can be expected in the near future.

****

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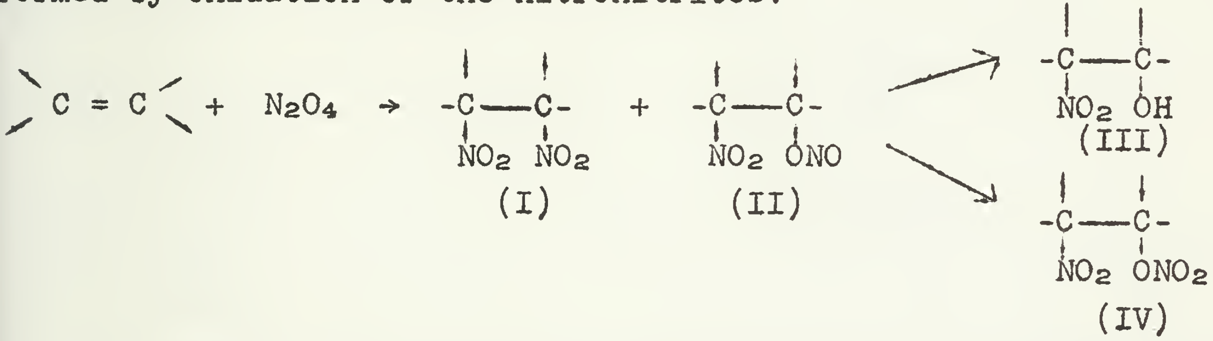
ADDITION OF DINITROGEN TETROXIDE TO OLEFINS

David L. Lydy November 28, 1960

The reaction of dinitrogen tetroxide with simple olefins was extensively investigated in 1946 by Levy, Scaife and collaborators (1-5). The facts then known of the orientation of the reaction led these investigators to propose a heterolytic addition of the tetroxide as $NO_2^+NO_2^-$. The earlier work in this area has been reviewed and will not be considered in this seminar (6). The purpose of this seminar is to consider recent investigations of this reaction and their contributions to the understanding of its mechanism.

Addition of the lower olefins to pure liquid N_2O_4 or to N_2O_4 dissolved in an ether or ester solvent produces dinitroparaffins, nitroalcohols and nitroalkyl nitrates in 65-80% yields. The reactants are carefully dried prior to use, and the reaction is run at -10 to 25°. Sodium-dried diethyl ether is the most suitable solvent, and normally the concentration of tetroxide is limited to 40% by weight to minimize oxidizing side reactions. Under these reaction conditions, addition takes only two forms: 1) as two nitro-groups, giving dinitro-compounds (I), and 2) as one nitro- and one nitrite group, giving nitronitrites (II), which are unstable and require conversion into nitroalcohols (III) by reaction with water or methanol as an essential first stage in satisfactory recovery of pure products. The nitronitrates (IV), are formed by oxidation of the nitronitrites.

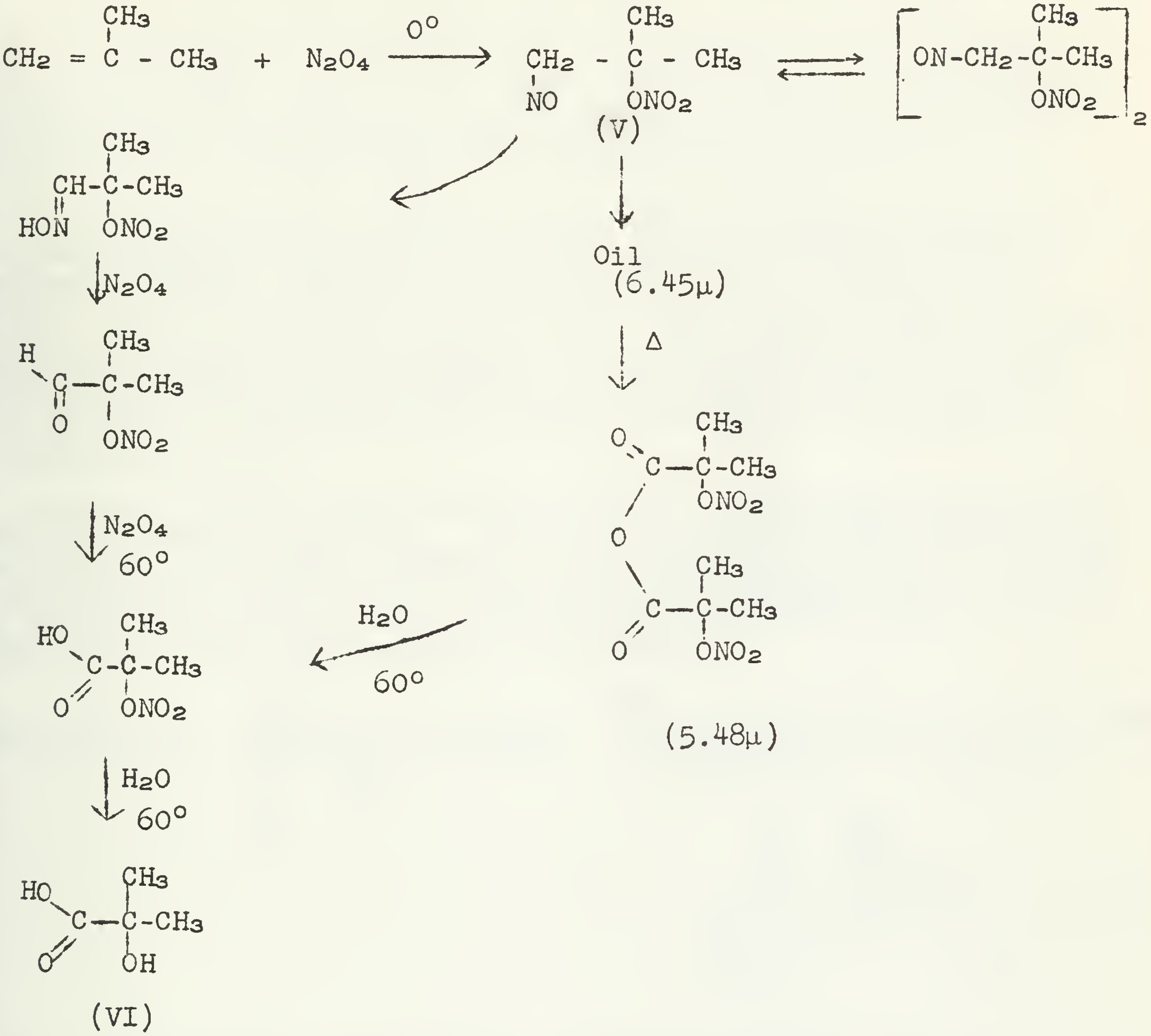


For unsymmetrical alkyl-substituted olefins, the second mode of addition always results in attachment of the nitro-group to the carbon with the greater number of hydrogen atoms and the nitrite group to that with the smaller number. For example, propene yields 1,2-dinitropropane, 1-nitro-2-propyl nitrite, 1-nitro-2-propyl nitrate and 1-nitro-2-propanol (7).

After completion of the reaction, excess of N_2O_4 and solvent, if used, may be removed by evaporation at water-pump vacuum from a falling-film, allowing the solvent-free product to drop into water or methanol for immediate conversion of the nitronitrite component into nitroalcohol. A convenient and simple form of evaporator is provided in the ordinary double-surface condenser by passing warm water through the jacket (1).

Ethylene (2), cyclohexene (5), and 2,4,4-trimethylpent-1- and 2-ene (5) may be suitably nitrated in the absence of solvent, i.e. by direct addition to liquid N_2O_4, yet propylene (3) and isobutylene (4) give rise to partly oxidized substances containing little or no dinitroparaffin unless an ether- or ester-type solvent, e.g., ethyl ether, dioxane or ethyl acetate, is used. Schoenbrunn and Gardner (8) have shown the products of the tetroxide-isobutylene reaction, in the absence of solvent, can be regarded as derivatives of isobutylene nitrosonitrate

(V). Good yields of α-hydroxyisobutyric acid (VI) were obtained (69-74%) when isobutylene was added to liquid N_2O_4 at 0°, and the resulting mixture was allowed to undergo oxidative and hydrolytic reactions.



If primary nitro-compounds had been formed in this reaction, they would have been isolated since they have been shown to be relatively stable to further reaction with N_2O_3 or N_2O_4 under these conditions. When ethers are used as solvent, isobutylene nitrosonitrate is not found nor can the observed products be derived from it under the reaction conditions. Therefore, the nitrosonitrate probably is the initial product when weakly basic solvents are not used.

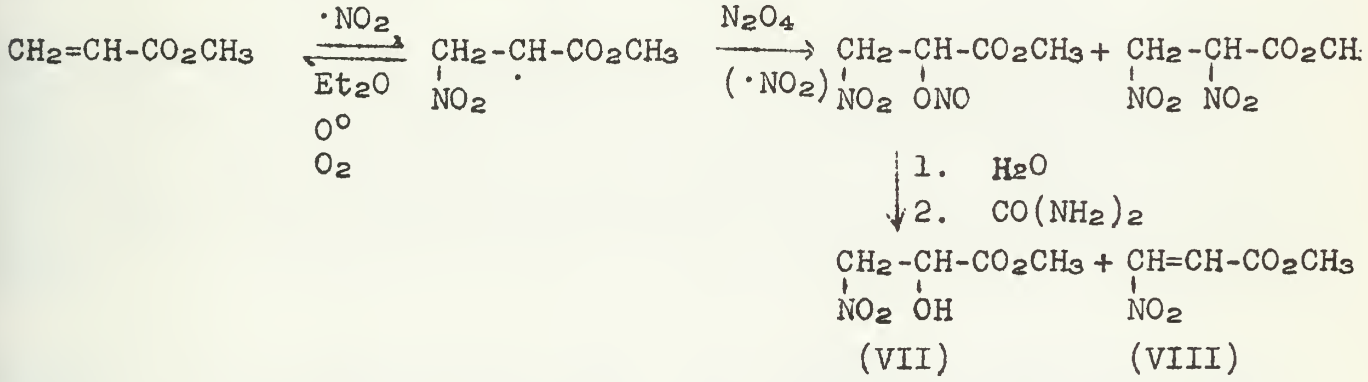
With ether- and ester-type solvents, probably depending on electron availability at the oxygen atom, the oxidation reactions are largely prevented, even in very concentrated solutions, thus permitting formation and survival of the normal addition products. The isolation of the dioxane-N_2O_4 complex (9) and the gradation of solvent effect with the nature of the side groups about the oxygen atom. seem to establish that these solvents act by molecular association with the tetroxide. Ethers with electron-attracting substitutents, i.e. with reduced electron availability at the oxygen atom, e.g., 2,2'-dichlorodiethyl ether, are

unsuitable media.

A further variable is introduced through reduction of some of the tetroxide to trioxide which can give rise to undesirable or unstable side products (e.g. nitronitroso-compounds). The introduction of oxygen into the reaction or the use of excess tetroxide gives a product which is more stable to distillation and relatively free from N_2O_3 addition products. In the absence of oxygen, the amount of dinitrocompound is of the same order as the combined amounts of nitroalcohol and nitronitrate (both derived from nitronitrite). Oxygen addition tends to favor the last component to a marked extent.

On the basis of the directive influence of unsymmetrical olefins, the specific solvent effect of certain ethers and esters, and the function of oxygen, previous investigators (1-5,10) proposed that addition of N_2O_4 to olefins involved initial dissociation of the tetroxide into nitronium and nitrite ions. The initial step of the addition was thought to be attachment of the electropositive nitrogen atom of NO_2^+ to the unsaturated center; the second group, as NO_2^-, was then attached through C-N to yield dinitroalkane or through C-O to yield nitronitrite.

Results of more recent studies, however, have been interpreted in terms of a homolytic process. Shechter and Conrad (7) observed that the production of methyl 2-hydroxy-3-nitropropionate (VII) and methyl-3-nitroacrylate (VIII) in the tetroxide-methyl acrylate reaction can not be explained on the basis of heterolytic addition, but is to be expected if a homolytic process is operating.



The initial attack is represented as being reversible, for it has been found (11) that NO_2 radicals catalyze the *cis-trans* isomerization of olefins. It is not known whether the resulting nitroalkyl radical then reacts with another NO_2 radical, with N_2O_4, or with both (12).

Brown (13) observed that the reaction of the nitronium ion with olefins has different characteristics from those of N_2O_4-olefin additions. With 100% nitric acid, low temperatures and excess olefin, the nitration shows a tendency toward rearrangements and elimination of protons distant from the incoming nitro-group. Cyclohexene, for example, gives only the rearranged products; *trans*-3-nitrocyclohexyl nitrate, *trans*-4-nitrocyclohexyl nitrate, and 4-nitrocyclohexene.

Bachman and Chupp (14) studied the vapor phase nitration of olefin in the presence of chlorine in more than catalytic amounts. This chlorine can react with the olefin producing a bond which is not readily susceptible to either oxidation or hydrolysis. In the vapor

phase reaction (260-275°) with propene and 1-butene, only one isomer is produced, 1-chloro-2-nitropropane and 1-chloro-2-nitrobutane, respectively. This indicates that the reaction may proceed by a single specific mechanism. If it is assumed to be a free radical process, the following sequence of reactions may be postulated.

$$\begin{array}{l} RCH{=}CH_2 + \cdot Cl \longrightarrow R\underset{\cdot}{C}H{-}CH_2Cl \\ R\underset{\cdot}{C}H{-}CH_2Cl + \cdot NO_2 \longrightarrow RCH(NO_2)CH_2Cl \\ R\underset{\cdot}{C}H{-}CH_2Cl + Cl_2 \longrightarrow RCH(Cl)CH_2Cl + \cdot Cl \end{array}$$

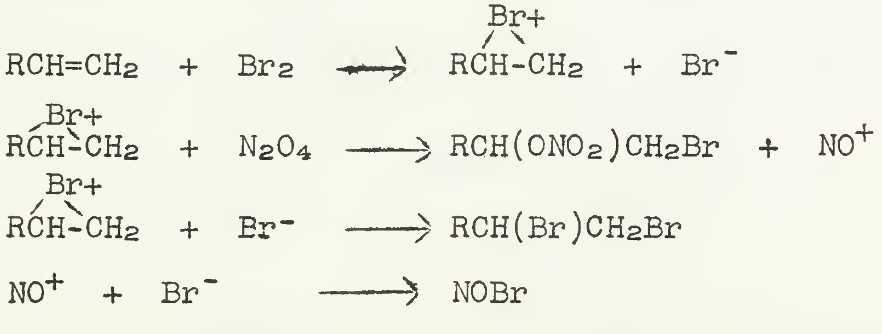
In these vapor phase reactions, the conversions to chloronitroalkanes are low (about 10%) since several important side reactions can occur. Dinitrogen tetroxide alone can react, forming additional nitrogen containing materials and oxidation products or chlorine can react to form 1,2-dichloropropane. Liquid phase reactions produce only this 1,2-dichloropropane.

Vinyl bromide was found to react (15) with dinitrogen tetroxide and chlorine at 250° to give 1-bromo-1-chloro-2-nitroethane. Similarly vinyl bromide, N_2O_4, and bromine gave 1,1-dibromo-2-nitroethane.

$$\begin{array}{l} CH_2{=}CHX + \cdot NO_2 \xrightarrow[\text{temp.}]{\text{low}} CH_2(NO_2)\underset{\cdot}{C}HX \\ CH_2(NO_2)\underset{\cdot}{C}HX + X_2 \longrightarrow CH_2(NO_2)CHX_2 + \cdot X \\ CH_2{=}CHX + \cdot X \xrightarrow[\text{temp}]{\text{high}} CH_2(X)\underset{\cdot}{C}HX \\ CH_2(X)\underset{\cdot}{C}HX + \cdot NO_2 \longrightarrow CH_2(X)CH(NO_2)X \quad X{=}Cl \text{ or } Br \end{array}$$

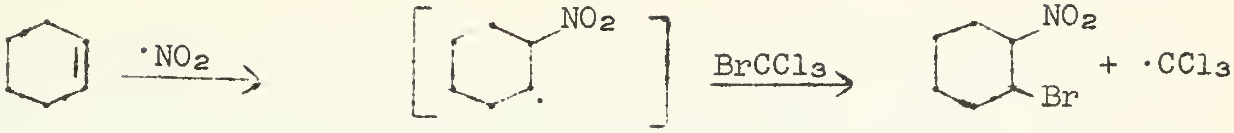
When vinyl chloride was treated at 325° with mixtures of dinitrogen tetroxide and chlorine or bromine, the nitrogen containing products were 1,2-dichloronitroethane and 1-chloro-2-bromo-1-nitroethane, respectively. The orientation of the entering groups is reversed in this latter investigation, since sufficient quantities of halogen atoms are formed at this higher temperature to initiate the addition process. The major side product in both of these studies was the trihalogenated olefin.

Bachman and Logan (16) report that ethylene, propylene, 1-butene, 2-butene, and 2-methylpropene react with mixtures of tetroxide and bromine or iodine to form β-haloalkyl nitrates to the practical exclusion of nitro compounds. The olefin is passed into a liquid mixture of halogen and tetroxide at ice-bath temperatures. Under these conditions the reaction appears to involve initial attack by the halogen on the olefin.



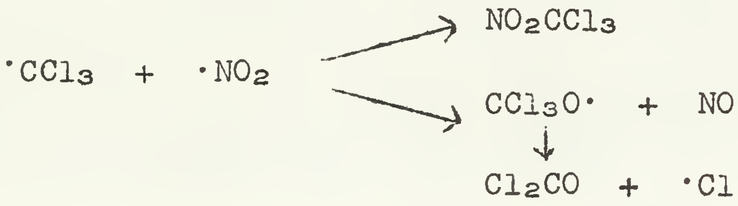
$$\begin{array}{l} RCH{=}CH_2 + Br_2 \longrightarrow \overset{Br^+}{RCH{-}CH_2} + Br^- \\ \overset{Br^+}{RCH{-}CH_2} + N_2O_4 \longrightarrow RCH(ONO_2)CH_2Br + NO^+ \\ \overset{Br^+}{RCH{-}CH_2} + Br^- \longrightarrow RCH(Br)CH_2Br \\ NO^+ + Br^- \longrightarrow NOBr \end{array}$$

The principal side reaction is the formation of the corresponding alkene dihalide. An alternate mechanism employing $BrNO_2$, formed in

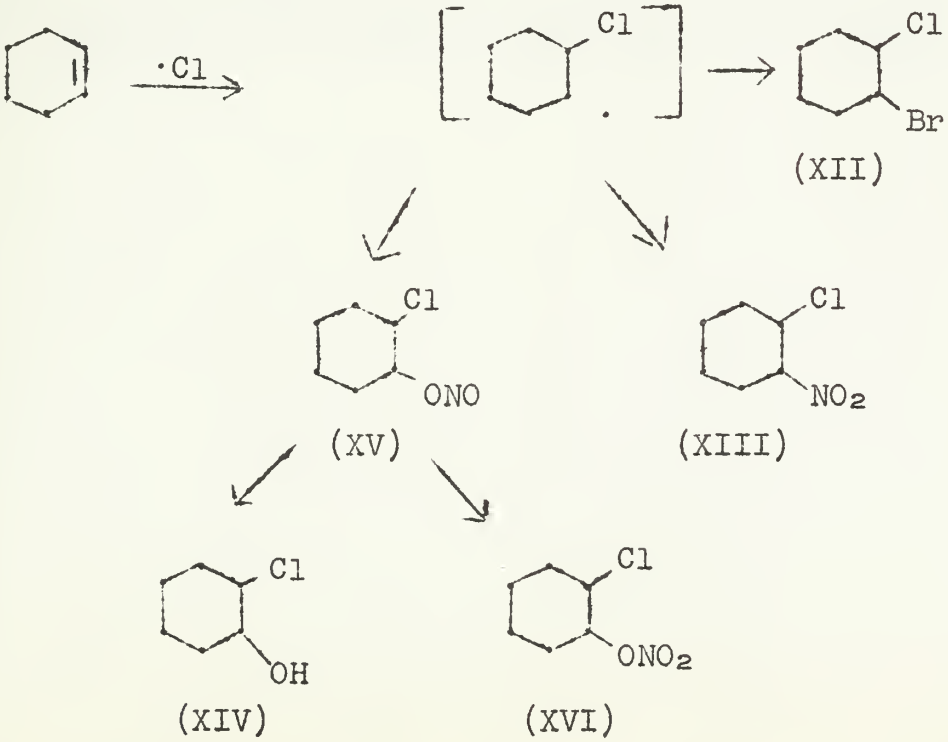


Since the reaction was protected from light, the bromotrichloromethane can only have altered the character of the product in its capacity as a radical-transfer agent. Therefore, the absence of the normal addition products must mean that the heterolytic reaction, if it operates at all, is of very minor importance.

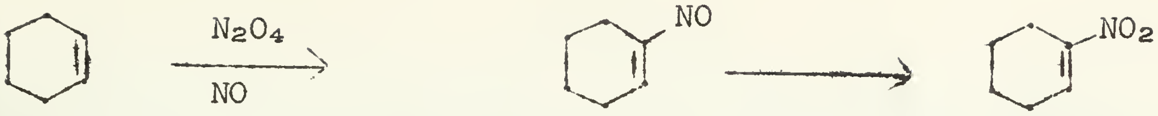
No products of addition of free trichloromethyl radicals to cyclohexene were isolated, presumably because a more rapid reaction occurs with N_2O_4 ($\cdot NO_2$).



The chlorine atoms produced initiate addition to cyclohexene, forming 2-chlorocyclohexyl radicals which are the precursors of 2-bromochlorocyclohexane (XII), 2-chlorocyclohexanol (XIV), 2-chlorocyclohexyl nitrate (XVI), and possibly 2-chloronitrocyclohexane (XIII). Compounds (XIV) and (XVI) are derivatives of 2-chlorocyclohexyl nitrite (XV) by hydrolysis (in working up) and by induced oxidation (during reaction), respectively. Nitric oxide, N_2O_4 and cyclohexene form the cyclohexene nitroso-compound (XVII). 1-Nitrocyclohexene (XVIII) results from oxidation of the nitroso-compound in working up. All the products therefore involve fragments of the radical chain mechanism involving $BrCCl_3$, and it seems impossible to explain them except by a free radical mechanism.



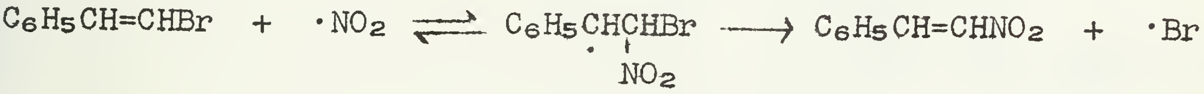
(IV)



(XVII) (XVIII)

Addition of free radical reagents to halogenated olefins has been known to lead to adducts that have lost a halogen atom (22). For instance, various alkyl radicals and 1,2-dichloroethylene react to produce 1-chloro-2-alkylethylenes (23).

The slow addition of dinitrogen tetroxide to an ether solution of β-bromostyrene gives β-nitrostyrene (67%) as the major product and saturated compounds which arise from the addition of bromine or tetroxide to the bromostyrene as by-products (24). If a radical mechanism is assumed, the relatively stable intermediate radical may then reversibly eliminate the NO_2 radical or may eliminate a bromine atom to give the unreactive β-nitrostyrene.



$$C_6H_5CH{=}CHBr + \cdot NO_2 \rightleftharpoons C_6H_5\underset{\cdot}{C}H\underset{NO_2}{\underset{|}{C}}HBr \longrightarrow C_6H_5CH{=}CHNO_2 + \cdot Br$$

Only one of the possible by-products, a dibromonitrophenylethane was isolated. The nitro group absorption at 1540 cm^{-1} in the infrared spectrum of this adduct indicated it was 1,1-dibromo-2-nitro-2-phenylethane; absorption at higher wave length would be expected for the isomeric 1,2-dibromo-1-nitro-2-phenylethane (25).

The work on the stereochemistry of the dinitrogen tetroxide addition to olefins is too extensive to be considered in this seminar. References to recent publications in this area are included in the bibliography (26-31).

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SOME REACTIONS IN STRONG ALKALIES

Reported by V. F. German December 1, 1960

INTRODUCTION

The ability of fused alkali to serve as a strong oxidizing agent has long been known. Unfortunately, much of the work conducted in this system has been done with little care and almost no concern as to the by-products of the reaction. Isolation and purification of the major products and by-products presented an insurmountable problem to early investigators. However, the advent of new isolation and purification techniques now allows the investigation of various reactions in fused alkalies. Identification of by-products is possible by means of counter current distribution, paper chromatography, and gas chromatography.

UNSATURATED ACIDS

Treatment of an unsaturated acid with molten potassium hydroxide or a eutectic mixture of potassium hydroxide and sodium hydroxide results in the formation of a saturated acid with two fewer carbon atoms than the parent unsaturated acid. Acetic acid is also isolated as a major product in the reaction.

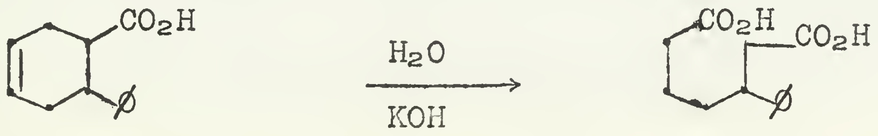
$$CH_3(CH_2)_mCH{=}CH(CH_2)_nCO_2H \xrightarrow[H_2O]{KOH} CH_3(CH_2)_{m+n}CO_2H + CH_3CO_2H.$$

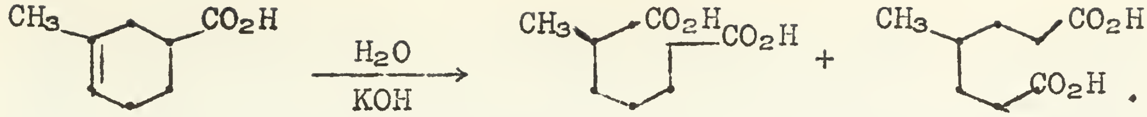
Oleic acid (n=7,m=7) yields hexadecanoic and acetic acid when treated with molten potassium hydroxide. The corresponding trans isomer gives hexadecanoic acid in approximately equal yields. Thus, the reaction is general for both cis and trans isomers of unsaturated acids (1). When the fusion is conducted in an inert atmosphere, yields of the saturated acid are high and approximately the same regardless of the location of the double bond. (See Table I).

Table I
Yields from Alkaline Fusion

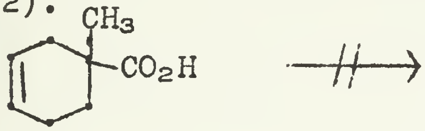
Starting Acid	Product (Acid)	Yields%	Temp./Time (min.)
9-octadecenoic	Hecadecanoic	80-85	360/60
6-octadecenoic	Hexadecanoic	78	360/30
10-undecenoic	Nonanoic	80	360/30
2-nonenoic	Heptanoic	80	300/5

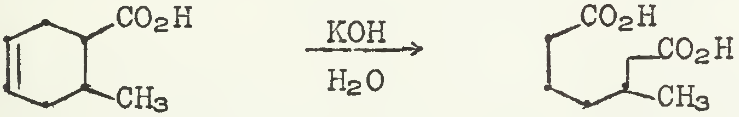
Cyclic unsaturated carboxylic acids are cleaved without the loss of two carbon atoms (2,3). The corresponding dicarboxylic acid is the main product isolated. A synthetic route to substituted pimelic and adipic acids is provided by fusion of the appropriate cyclohexene or cyclopentene carboxylic acids. The cyclohexene carboxylic acids are readily obtained from the Diels-Alder synthesis. Fusion of cyclohexene carboxylic acids with alkyl groups in positions 3, 4, and 5 of the cyclohexene ring yields mixtures, since cleavage of either the bond between carbon atoms 1 and 6 or the bond between carbon atoms 1 and 2 can occur.





The formation of a saturated carboxylic acid with two carbon atoms fewer than the parent unsaturated acid suggests that migration of the double bond into conjugation with the carboxyl group is necessary before cleavage of the carbon-carbon bond. This was demonstrated by the following observations. Unsaturated acids with the α or β positions to the carboxyl group blocked were recovered as isomeric unsaturated acids. Migration of the double bond had occurred but no fission products resulting from cleavage of a carbon-carbon double bond could be detected. Under similar conditions an unsaturated acid, in which the formation of α,β-unsaturated acid is possible, was degraded to a saturated acid. The momomethyl derivatives of cyclohexene carboxylic acid are an example of this (2).





The cleavage of an α,β-unsaturated acid is usually more rapid than the cleavage of an unsaturated acid with the double bond isolated by several carbon atoms from the carboxyl group. Yields are usually higher and at the end of the fusion smaller amounts of isomeric unsaturated acids remain. For maximum cleavage of oleic acid a temperature of 360° for 60 min. was required. For cleavage of 2-nonenoic acid only 5 min. at a temperature of 300° was necessary. (See Table I).

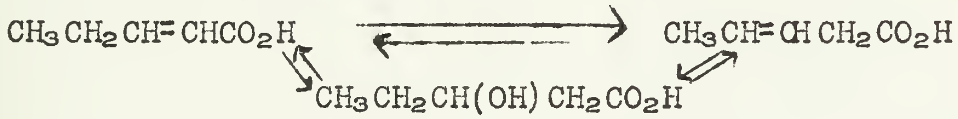
The isomerization of 1,4-dienes to the corresponding conjugated dienes is well known and is used extensively as an analytical tool. Isomerizations of this type are carried out in boiling solutions of glycerol or ethylene glycol with sodium or potassium glycolate or glycerolate. Methyl linoleate, for example, is completely isomerized at 180° to a mixture of the conjugated dienoic acids (4,5). The isomerization of an isolated double bond, however, occurs only under drastic conditions. Migration of an isolated double bond into conjugation with the carboxyl group could proceed by a series of prototropic or three carbon changes (6). Isomerizations

$$-\text{CH}=\text{CH}-\text{CH}_2- \underset{H_2O}{\overset{OH^-}{\rightleftarrows}} -\overset{\ominus}{\overline{\text{CH}-\text{CH}-\text{CH}}}- \underset{OH^-}{\overset{H_2O}{\rightleftarrows}} -\text{CH}_2-\text{CH}=\text{CH}-$$

of this type have been studied in metalation reactions. Treatment of 1-decene with sodium and o-chlorotoluene gave a dialkyl substituted ethylene in 99% yield. No attempt was made to determine the exact location of the double bond (7). Incomplete reaction of oleic acid with molten potassium hydroxide gave isomers with the double bond distributed in each position along the carbon chain from between carbon atoms 12 and 13 to between carbon atoms 4 and 5. (8). The amount of isomeric acids with unsaturation in any given position was determined by ozonolysis of the fusion products and isolation of the mono and dicarboxylic acid. The amount of

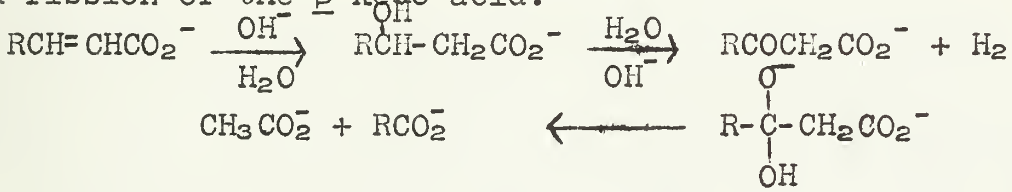
each isomer was a function of time, and with increased reaction time approximately equal amounts of each isomer were obtained. Initial migration of the double bond appears to occur both toward and away from the carboxyl group. The absence of the isomer with the double bond between carbon atoms 3 and 4 may be explained by rapid isomerization of this isomer to the α,β-unsaturated isomer under the influence of the carboxyl group. The lack of the α,β-unsaturated acid suggests that cleavage of the conjugated acid is more rapid than migration of the double bond. The more stable trans olefins were the major isomers present.

Attack of a hydroxide ion on the β-carbon of the conjugated unsaturated acid probably occurs before fission of the carbon-carbon bond. Attempts to isolate the β-hydroxy acid from the reaction mixture were not successful. However, in dilute aqueous alkali the β-hydroxy acid has been shown to exist in equilibrium with both the β,γ-unsaturated acid and the α,β-unsaturated acid. Ives and Kerlogue found that the equilibrium could best be described by a triangular equilibrium diagram (9). The system studied was the isomeric pentenoic acids.



$$\begin{tikzcd} \mathrm{CH_3CH_2CH{=}CHCO_2H} \arrow[rr, shift left] \arrow[dr, leftrightarrow] & & \mathrm{CH_3CH{=}CHCH_2CO_2H} \arrow[ll, shift left] \arrow[dl, leftrightarrow] \\ & \mathrm{CH_3CH_2CH(OH)CH_2CO_2H} & \end{tikzcd}$$

It has been suggested that fission of the β-hydroxy acid could occur by two possible routes (8). One route proceeds through the formation of a β-keto acid. Cleavage would occur by the normal acid fission of the β-keto acid.

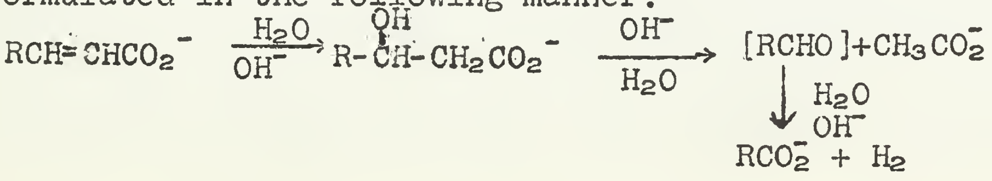


$$\mathrm{RCH{=}CHCO_2^-} \xrightarrow[\mathrm{H_2O}]{\mathrm{OH^-}} \mathrm{R\overset{OH}{C}H{-}CH_2CO_2^-} \xrightarrow[\mathrm{OH^-}]{\mathrm{H_2O}} \mathrm{RCOCH_2CO_2^-} + \mathrm{H_2}$$

$$\mathrm{CH_3CO_2^-} + \mathrm{RCO_2^-} \longleftarrow \mathrm{R{-}\underset{OH}{\overset{O^-}{C}}{-}CH_2CO_2^-}$$

In this scheme of fission the formation of a ketone is assumed to occur by dehydrogenation of a secondary alcohol. Such dehydrogenations are throught to occur. Treatment of 10-hydroxy and 12-hydroxyoctadecanoic acids with eutectic mixtures of potassium and sodium hydroxide gave considerable quantities of 10-oxo-octadecanoic and 12-oxo-octadecanoic acids (10). However, the evolution of hydrogen was not definitely established. Complete fusion of both the keto acid and the corresponding hydroxy acid gave identical products in similar yields. However, fusion of a β-keto acid and its corresponding α,β-unsaturated acid gave different minor products. Fusion of acetoacetic acid gave small amounts of acetone entrained in a stream of nitrogen swept through the reaction vessel. Under similar conditions no acetone could be isolated from the fusion of crotonic acid. Formation of 2-nonanone was observed in the fusion of 3-oxodecanoic acid.

The second possible route of cleavage of unsaturated acids proceeds through the formation of an aldehyde followed by rapid conversion to the observed acid. Such a retro-aldol route could be formulated in the following manner:



$$\mathrm{RCH{=}CHCO_2^-} \xrightarrow[\mathrm{OH^-}]{\mathrm{H_2O}} \mathrm{R{-}\overset{OH}{C}H{-}CH_2CO_2^-} \xrightarrow[\mathrm{H_2O}]{\mathrm{OH^-}} \mathrm{[RCHO]} + \mathrm{CH_3CO_2^-}$$

$$\mathrm{[RCHO]} \xrightarrow[\mathrm{OH^-}]{\mathrm{H_2O}} \mathrm{RCO_2^-} + \mathrm{H_2}$$

The rapid conversion of aldehydes to acids has been demonstrated by Fry and Schultze (11). Nearly quantitative amounts of acetic acid and hydrogen were obtained from the treatment of acetaldehyde with fused potassium hydroxide. Under conditions of the fusion reaction no aldehyde could be isolated from the fusion of β-hydroxybutyric acid (8). Less drastic conditions gave small amounts of acetaldehyde.

Small amounts of saturated acids with four carbon atoms fewer than the major product were isolated in the potassium hydroxide fusion of the saturated acids. Fusion of oleic acid gave tetradecanoic acid in yields of 2-3%(8). It has been suggested that this by-product comes from further attack of a hydroxide ion on the major product, hexadecanoic acid, formation of 2-hexadecenoic acid, and subsequent cleavage to tetradecanoic acid. Experiments with decanoic and hexadecanoic acid gave similar results. However, these by-products may come from dienoic acids. Linoleic acid is difficultly separable from oleic acid. Fusion of the acid would give tetradecanoic acid. One possible explanation for the small amounts of cyclohexanone observed in the fusion of cyclohexene-1-carboxylic acid is cyclization of the pimelic acid to give the observed cyclohexanone. In the presence of no water Werber and co-workers found this to be the case(3). However, further investigation showed that the amount of cyclohexanone formed was highly dependent on the presence of water. To account for this they assumed that at least part of the cleavage was occurring by decarboxylation.

Treatment of dienic and acetylenic acids with molten potassium hydroxide yields saturated carboxylic acids with four fewer carbon atoms than the parent unsaturated acids (12). Linoleic acid on treatment with fused potassium hydroxide gives tetradecanoic acid in 60% yield. Small amounts of hexadecanoic acid were also obtained. Under some conditions small quantities of butyric acid were isolated. Acetic acid was also isolated.

$$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H \longrightarrow CH_3(CH_2)_{12}CO_2H$$

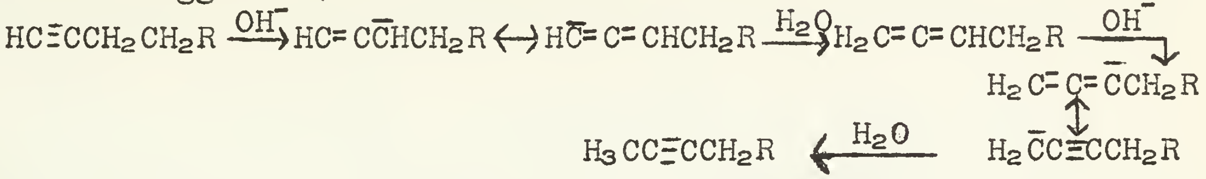
In a system which has a 1,4-diene system, initial isomerization to the more stable 1,3-diene would be expected before further isomerization occurred. Subsequent migration could occur by removal of a proton in a position α to either double bond.

$$-CH{=}CH-CH{=}CH-CH_2 \underset{H_2O}{\overset{OH^-}{\rightleftharpoons}} -CH{\cdots}CH{\cdots}\overset{\ominus}{CH}{\cdots}CH{\cdots}CH- \underset{OH^-}{\overset{H_2O}{\rightleftharpoons}} -CH_2-CH{=}CH-CH{=}CH-$$

Incomplete fusion of linoleic acid indicated that migration of the conjugated diene system had occurred both toward and away from the carboxyl group(12). Examination of the infrared region between 600 and 1000 cm^{-1} and the ultraviolet region between 200 and 300 mμ showed that the trans-trans isomer was the predominant isomer. Also found were small quantities of cis-trans and the trans unconjugated isomers. During the course of the reaction extensive polymerization had occurred.

Migration of an acetylenic bond along a carbon chain is thought to occur by a series of acetylenic-allenic-acetylenic rearrangements(12,13). Equilibration of 1-pentyne in alcoholic potassium hydroxide gave a large amount of 2-pentyne in equilibrium with 1-pentyne and the 1,2-diene. The more stable 1,3-diene was not present in the equilibrium mixture, and the equilibrium was not

effected when quantities of 1,3-pentadiene were added to solutions of 1-pentyne, and the system equilibrated. The 1,3-pentadiene could be recovered in quantitative amounts. The following scheme has been suggested:



$$HC\equiv CCH_2CH_2R \xrightarrow{OH^-} HC{=}C\bar{C}HCH_2R \longleftrightarrow H\bar{C}{=}C{=}CHCH_2R \xrightarrow{H_2O} H_2C{=}C{=}CHCH_2R \xrightarrow{OH^-} H_2C{=}C{=}\bar{C}CH_2R \longleftrightarrow H_2\bar{C}C\equiv CCH_2R \xrightarrow{H_2O} H_3CC\equiv CCH_2R$$

In contrast to this type of migration, aliphatic acetylenic acids with the acetylenic bond near the carboxyl group form conjugated dienes (14,15). Jones and co-workers found that treatment of 4-pentynoic acid with 9N potassium hydroxide gave almost complete isomerization to the 2,4-pentadienoic acid. The intermediate 3,4-pentadienoic acid was not isolated under the reaction conditions, but was shown to isomerize smoothly to the 2,4-pentadienoic acid under mild conditions.

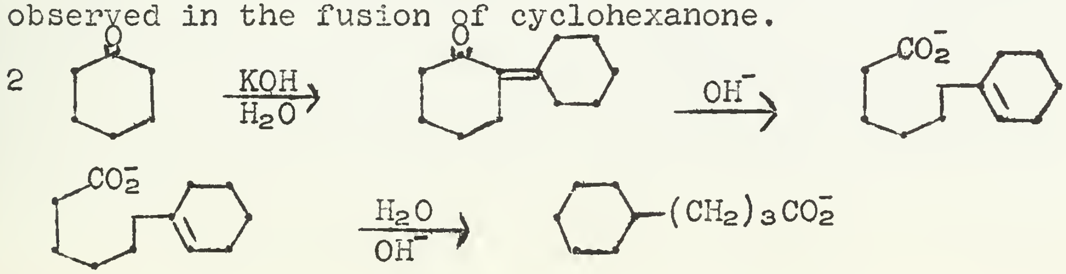
Cleavage of the 2,4-dienoic acid could proceed in two ways. An attack of a hydroxide ion at the β-carbon and cleavage would give acetic acid and an unsaturated acid of two fewer carbon atoms. A second attack on the unsaturated acid by a hydroxide ion and cleavage would give the observed acid. The second possibility would be attack of a hydroxide ion at the δ-carbon and cleavage to give the observed saturated acid. The crotonic acid could then cleave to give two moles of acetic acid. No mention of crotonic acid having been isolated was made (12).

Acetylenic acids with the acetylenic bond in the 2 or 3 position are thought to cleave by hydrolysis to the keto acid and fission. In concentrated aqueous alkali, 3-butynoic acid gave acetone and acetoacetic acid (14).

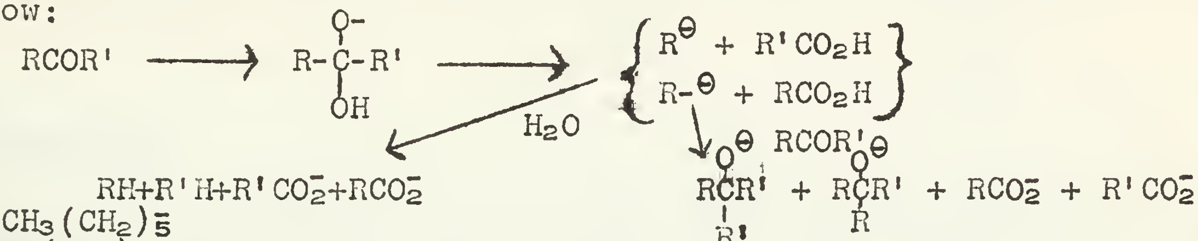
KETONES AND KETOACIDS

Reaction products and intermediates isolated in the treatment of ketones and keto acids with molten alkali can be explained in several ways, some of which can not be distinguished from each other. The possible explanations range from an initial aldol condensation to simple hydrolytic cleavage.

Fusion of cyclohexanone with molten potassium hydroxide gave γ-cyclohexylbutyric acid (16,17). Under incomplete reaction conditions appreciable quantities of 1-cyclohexenehexanoic acid were isolated. Further reaction would proceed by migration of the double bond into conjugation with the carboxyl group and fission of the carbon-carbon bond. It has been suggested that 2-cyclohexylidenecyclohexanone is first formed by an aldol condensation. However, the proposed intermediate has not been isolated. Fusion of a sample of 2-cyclohexylidenecyclohexanone gave the products observed in the fusion of cyclohexanone.



A recent investigation of the fusion of 12-oxo-octadecanoic acid gives an insight into the cleavage of aliphatic straight chain keto acids (10). Heptanoic, undecanoic, and dodecanedioic acids were the major products formed in the reaction. Hexane was also isolated in small amounts. One possible mechanism is shown below:



$R = CH_3(CH_2)_5$
$R' = -(CH_2)_{10}CO_2H$

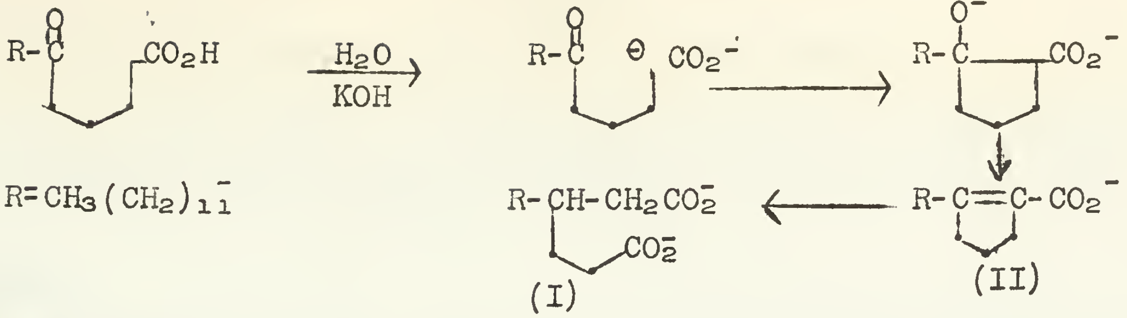
In the above scheme the reaction would proceed by the initial attack of a hydroxide ion on the carbonyl carbon of the ketone. Cleavage would occur with attack of the carbanion on another molecule of the ketone or abstraction of a proton from a water molecule. It is unlikely that the carbanion would have a long life time. Cleavage and nucleophilic attack would probably occur simultaneously. The tertiary alcoholate, formed by attack of the carbanion on the ketone, would either react with another proton source giving the observed acids, remain as a high molecular weight residue observed in the reaction, or undergo fission to give the observed high molecular weight acids. Meyer has indicated that such reactions do occur (18). The olefin produced in the reaction of laurone with potassium hydroxide could either occur by an aldol type reaction and cleavage of ketone, or it could be formed from a tertiary alcohol during the course of the reaction (19,20).

$[CH_3(CH_2)_{10}]_2CO \qquad [CH_3(CH_2)_{10}]_2C{=}CH(CH_2)_9CH_3$

In keeping with this scheme, a considerable decrease in the amount of high molecular weight residue formed during the reaction was observed with dilution of the ketone. In the fusion of 10-oxo-heptadecanoic acid a dilution of the ketone by increasing the weight ratio of alkali decreased the quantity of acidic residue formed in the reaction from 0.35 to 0.21 moles per mole of starting keto acid (10).

The small quantities of valeric and sebacic acid formed in the reaction are not accounted for by this reaction scheme (10). The conversion of heptanoic acid to pentanoic acid by formation of 2-heptenoic acid and cleavage is unlikely. In the reaction no nonanoic acid was isolated, and fusion of undecanoic acid under similar conditions gave no trace of nonanoic acid. The formation of small quantities of the two possible α,β-unsaturated ketones and cleavage to give both sebacic and valeric acids has been suggested.

As the keto group is moved closer to the acid group in the straight chain aliphatic series, products are formed which suggest the interaction of the carboxyl group with the keto group (10). Fusion of 6-oxo-octadecanoic acid gives 3-dodecylhexanedioic acid (I). The intermediate 2-dodecyl-1-cyclopentenecarboxylic acid (II) was isolated in 50% yield when the reaction was run under suitable conditions.

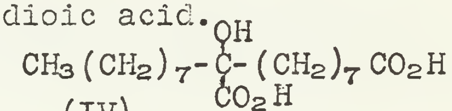


1,2-GLYCOLS

Glycols undergo a rearrangement similar to the benzil-benzilic acid type rearrangement when treated with either molten potassium hydroxide or strongly aqueous alkalies at high temperatures. (21, 22). The reaction appears to work equally well for both erythro and threo isomers. Since few examples exist, there is doubt as to the general nature of this reaction. Le Suer and Withers found that 9,10-dihydroxyoctadecanoic acid (III) when treated with molten potassium hydroxide at 200-250° gave 2-hydroxy-2-octyldecanedioic acid (IV). Under similar conditions 13,14-dihydroxydocosanoic acid gave 2-hydroxy-2-octyltetradecanedioic acid.

$CH_3(CH_2)_7CHOHCHOH(CH_2)_7CO_2H$

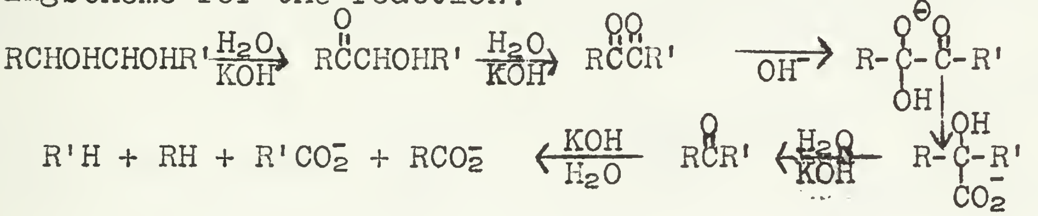
(III)



$$CH_3(CH_2)_7-\underset{CO_2H}{\overset{OH}{C}}-(CH_2)_7CO_2H$$

(IV)

Conflicting reports of the products of this reaction led to an investigation of the reaction under various conditions. The fusion of 9,10-dihydroxyoctadecanoic acid was selected as a representative example (22). During the reaction hydrogen was evolved. As might be expected, no hydrogen was given off during low temperature fusion of the diketone (23). Weedon has proposed the following scheme for the reaction:



R' = $-(CH_2)_7CO_2^-$
R = $CH_3(CH_2)_7-$

He has suggested that the reaction would proceed by initial dehydrogenation of the diol to the mixed 9-hydroxy-10-oxo-octadecanoic or 10-hydroxy-9-oxo-octadecanoic acids. Both were isolated in small quantities when the reaction was carried out at temperatures below 240°. Fusion of mixed samples of both yielded the α-hydroxy acid. The origin of the diketone is in question. It could arise from further dehydrogenation of the isomeric hydroxy ketones. Fusion of the diketone also yielded the 2-hydroxy-2-octyldecanedioic acid. At temperatures above 260° the α-hydroxy acid was rapidly converted into 9-oxoheptadecanoic acid, and fusion of 9-oxoheptadecanoic acid gave quantities of octanoic, nonanoic, and azelaic acids.

At temperatures favoring the formation of 2-hydroxy-2-octyldecanedioic acid, octanoic acid was usually not isolated from the reaction mixture. This would indicate formation of the octanoic acid entirely from the cleavage of 9-oxoheptadecanoic acid. Under the same conditions nonanoic and azelaic acids are formed, possibly

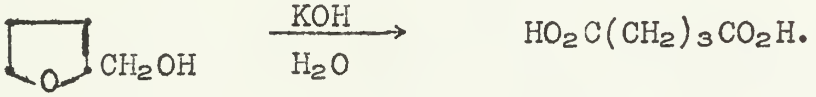
by fission of the hydroxyketo acid or the diketone.

In Weedon's reaction scheme the mechanism of initial dehydrogenation of the glycol is not analogous to any low temperature aqueous alkaline reaction where oxidation of the alcoholate occurs by hydride transfer to a carbonyl compound.

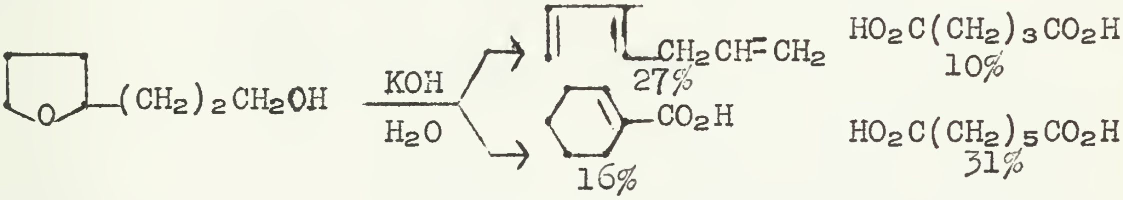
ALCOHOLS

The action of fused alkalies containing small quantities of water on primary alcohols was first observed by Dumas and Stass in 1840 (24). Treatment of a primary alcohol with molten potassium hydroxide or a eutectic mixture of potassium and sodium hydroxides leads to the corresponding acid salt and hydrogen. The mechanism by which this reaction proceeds is in doubt, but early investigators assumed that at high temperatures water was acting as an oxidizing agent. An example of this is the conversion of butyl alcohol to sodium butyrate in high yields (25). However, other methods of effecting this transformation are preferred.

One interesting variation of this method is the production of various diacids from the fusion of substituted tetrahydrofurans. For example, tetrahydrofurfuryl alcohol gave glutaric acid in 59% yield (26).



Runge and co-workers have suggested that ring opening is accomplished by either attack of a hydroxide ion on the ether linkage or hydride transfer. The n-propyl alcohol derivative gave a mixture of products on treatment with a eutectic mixture of potassium and sodium hydroxide. The following products were isolated.

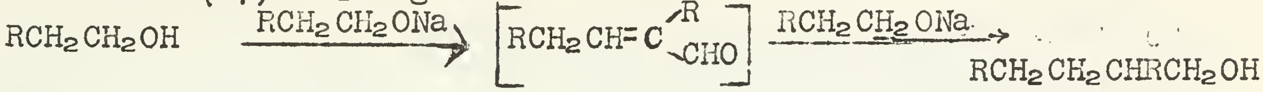


Secondary alcohols yield the corresponding ketone. Best results were obtained by Weedon when a concentrated aqueous solution of potassium hydroxide and cadmium oxide was used (10). Fusion of 12-hydroxyoctadecanoic acid gave the same products observed during the fusion of 12-oxo-octadecnoic acid. Under suitable conditions the keto acid was isolated in 60% yield. In this case, however, the evolution of hydrogen was not definitely established.

$$CH_3(CH_2)_5CHOH(CH_2)_{10}CO_2H \xrightarrow[H_2O]{CdO\text{-}KOH} \left|\begin{array}{l} CH_3(CH_2)_5CO_2H \\ HO_2C(CH_2)_{10}CO_2H \\ CH_3(CH_2)_9CO_2H \\ CH_3(CH_2)_4CH_3 \end{array}\right|$$

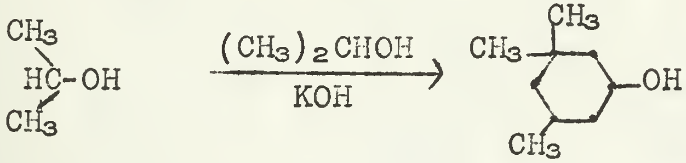
Closely related to the action of fused alkali on alcohols is the action of alkalies on an excess of an anhydrous alcohol. The sodium or potassium salt of the alcohol is frequently used in place of the alkalies. Primary alcohols yield the corresponding dimeric alcohol and considerable higher molecular weight products. The reaction is thought to proceed through an aldol condensation and subsequent reduction of the α,β-unsaturated aldehyde by hydride transfer

Blocking of the α position to the alcohol group prevents the condensation and the corresponding ether is obtained instead of the dimeric alcohol. Treatment of 2-ethylhexanol with the corresponding sodium salt of the alcohol gave the bis-ether in place of the dimeric alcohol (27). The general reaction scheme is shown below:



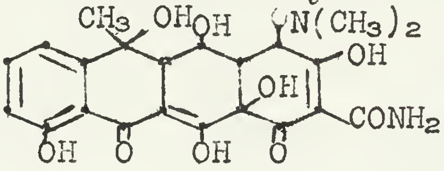
$$RCH_2CH_2OH \xrightarrow{RCH_2CH_2ONa} \left[RCH_2CH{=}C\begin{smallmatrix}R\\ CHO\end{smallmatrix}\right] \xrightarrow{RCH_2CH_2ONa} RCH_2CH_2CHRCH_2OH$$

Secondary alcohols frequently undergo repeated internal aldol condensations to give cyclic alcohols. Isopropyl alcohol, when treated with potassium hydroxide under anhydrous conditions gave, in addition to 4-methyl-2-pentanol, small amounts of 3,3,5-trimethylcyclohexanol (28).



NATURAL PRODUCTS

The use of fused alkalies has long been a standard tool in studies on natural products. Discretion must be used in determining which part of the molecule gives rise to the observed products. The study of Terramycin can serve as an illustration. From Terramycin (V) Woodward and co-workers obtained acetic, salicyclic (VI), m-hydroxybenzoic (VII), and succinic acids (29). Kuhn and Dury conducted the fusion at lower temperatures and obtained 6-acetylsalicylic acid (VIII), which could be further converted to the observed aromatic acids and acetic acid under more drastic fusion conditions (30). From aqueous alkaline hydrolysis of Terramycin another fragment was isolated(IX), which when subjected to fusion conditions gave the observed salicylic acid and acetic acid (31).



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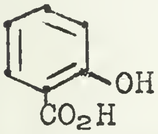
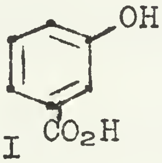
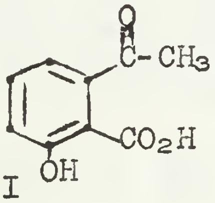


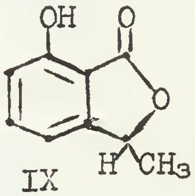
VI



VII



VIII



IX

From this it was concluded that the salicylic and m-hydroxybenzoic acids came from an aromatic system in the Terramycin molecule and not from aromatization of some part of the molecule.

Studies in the alkaloid field give similar results. Folkers found that alkaline fusion of β-erythroidine gave indole and postulated that the indole fragment came from rings B and C, since it was known that the $\rangle N-\underset{|}{C}-\underset{|}{C}-CO-O-$ grouping was particularly labile under the action of strong alkalies (32).

The structure of β-erythroidine has been completely elucidated by Boekelheide and co-workers (33).

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PERIODATE OXIDATION OF PHENOLS

Reported by A. F. Ellis December 5, 1960

INTRODUCTION

Selective oxidation of organic compounds with aqueous periodate has been a most versatile tool for organic structure determination and synthesis. The oxidations can be divided into two types: first, those producing carbon-carbon bond cleavage, and second, those where no such cleavage takes place.

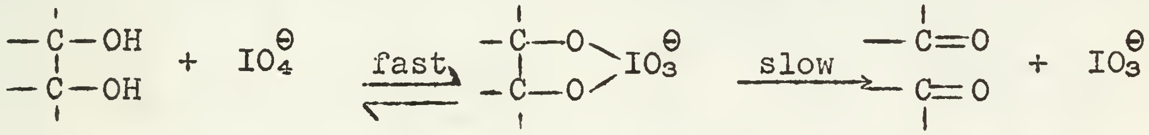
The first type of periodate oxidation is the well known α-glycol cleavage, discovered by Malaprade (1) in 1928 and initially developed into an analytical and synthetic method by Fleury (2). A review of early work on this first type of oxidation was made by Jackson (3).

The second type of oxidation was discovered by Heubner and Bubl (4) in 1946. While investigating the reason for an excessive uptake of periodate in the oxidation of an aldonic acid benzimidazole, they found that the excess periodate was reduced by an activated methylene group.

More recent reviews on both types of periodate oxidation have been made by Bobbitt (5) and Dyer (6).

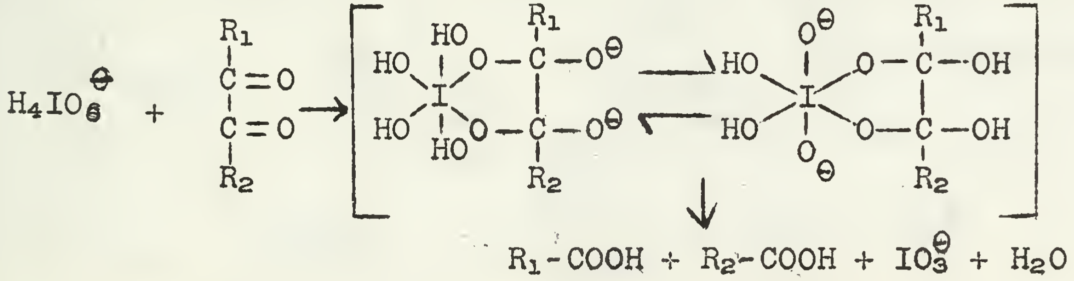
Mechanisms of Carbon-Carbon Bond Cleavage Reactions

The mechanisms for these types of periodate oxidations have been thoroughly discussed by Taylor (7) and Dyer (6). The presently accepted mechanism for oxidation of α-glycols was proposed by Criegee in 1933 (8). This mechanism consists of a fast reversible formation of a complex between the glycol and the various periodate species. This is followed by a slower rate-determining decomposition of this complex to yield the oxidized products and the reduced periodate.



The exact manner of formation of the intermediate and the effect of the periodate hydration-dehydration equilibria are not fully understood.

The mechanism for the oxidation of α-diketones is thought, by Shriner and Wasmuth (9), to involve nucleophilic attack of each of the various paraperiodate species at the carbonyl carbon atom.



The following periodate equilibria are thought to be important in neutral and acid solution (10):

$$H_5IO_6 \xrightleftharpoons{k_1} H_4IO_6^{\ominus} + H^{\oplus} \xrightleftharpoons{k_2} H_3IO_6^{\ominus} + 2H^{\oplus}$$

$$H_4IO_6^{\ominus} \xrightleftharpoons{k_D} IO_4^{\ominus} \rightarrow 2H_2O$$

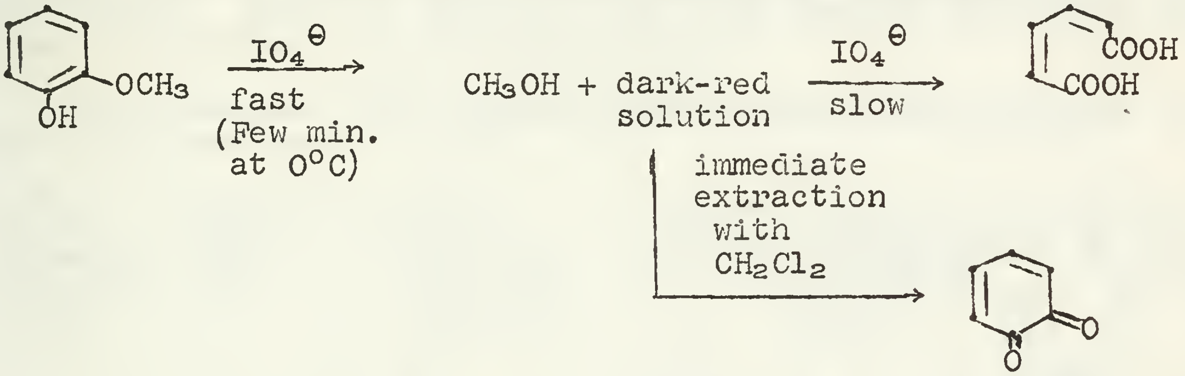
$$k_1 = 2 \times 10^{-2},\ k_2 = 4 \times 10^{-9},\ k_D = 40$$

In basic solution a third ionization can occur where $K_3 = 10^{-12}$. All of the various species are present to degrees varying with the conditions and all may enter into the oxidation process. The most pro ably species in neutral or acid solutions is some form of the monevalent ion.

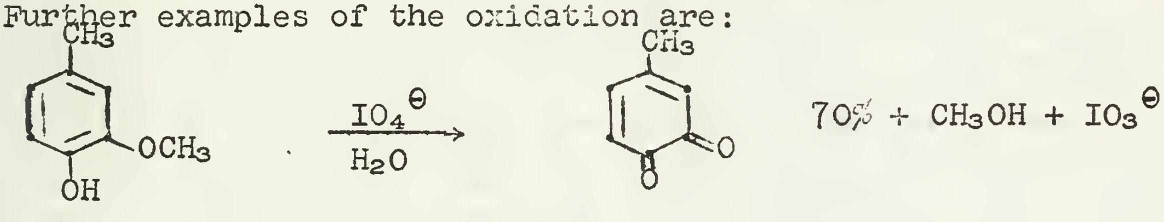
Periodate Oxidation of Phenols

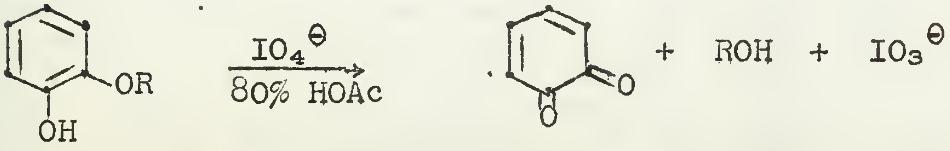
In the course of the investigation of periodic acid oxidation of lignin sulfonic acids, Pennington and Ritter (11) oxidized severa structures related to lignin. They found that, under conditions thought to be specific for oxidation of α-glycols, some substituted phenols were attacked by periodic acid. The reactions were complete in a few hours and yielded solutions of yellow and red colorations. They were not able to explain what was occurring. In 1955, Adler(12 noticed the rapid formation of methanol in the oxidation of guaiacol with periodate. He then developed a method of estimating the number of guaiacyl residues with a free phenolic -OH group in lignin based on this discovery (13). Adler then began a general investigation of the oxidation of phenols by periodates.

Oxidation of Monoethers of Pyrocatechol and Hydroquinone (14)

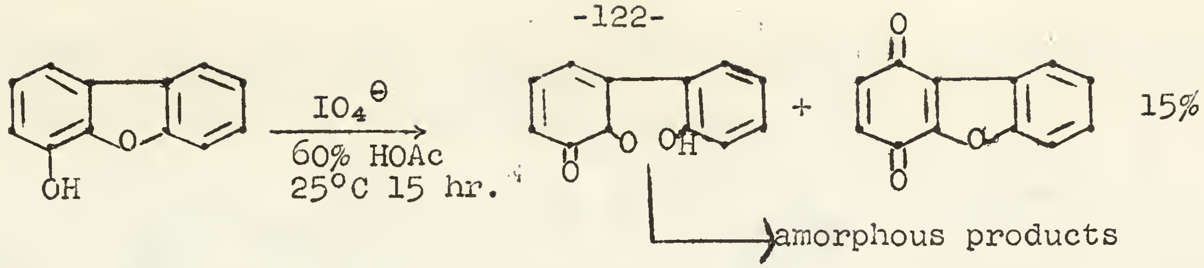


When periodate was added to a solution of guaiacol in water, the solution immediately turned dark red. On standing, this gradually decomposed to the acid residues, but if extracted immediately with methylene chloride, o-benzoquinone could be isolated in 64% yield. This reaction was found to be general for pyrocatechol monoethers. Further examples of the oxidation are:

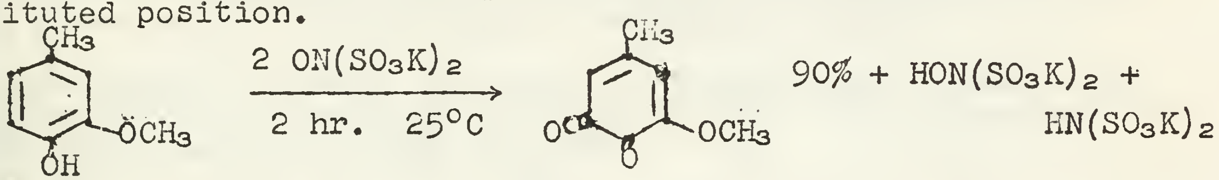




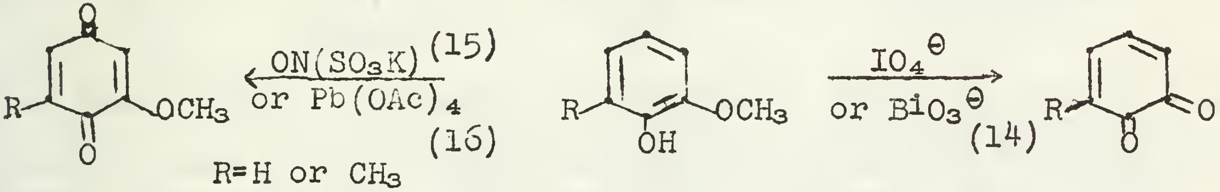
If R = C_2H_5, the reaction proceeds as fast as with guaiacol.
If R = C_6H_5, the reaction is slower but free phenol is formed.



This rapid oxidative dealkoxylation with periodate appears to open a new method for preparation of orthoquinones. This method can be considered complementary to the method of Teuber (15) for oxidation of p-substituted phenols by Fremy's salt [$ON(SO_3K)_2$]. Unlike periodate, Fremy's salt attacks the free o-position rather than the methoxy-substituted position.

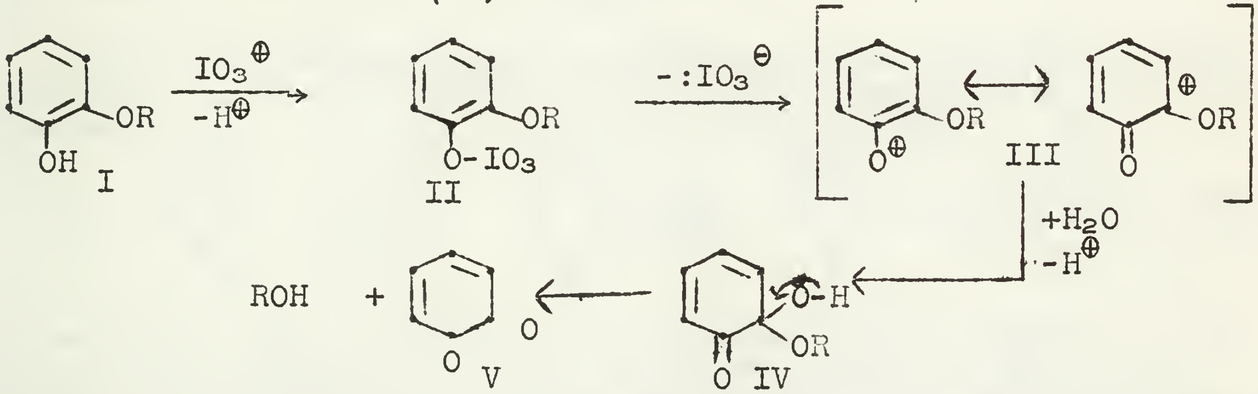


Periodate and Fremy's salt also differ with respect to their behavio toward guaiacols with a free p-position.



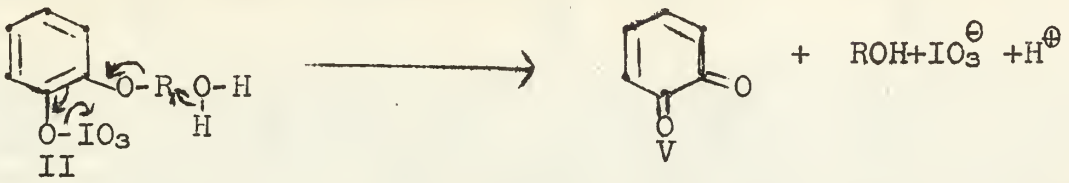
Two other glycol splitting reagents, $KBiO_3$ and $Pb(OAc)_4$, also react with phenols. However, $Pb(OAc)_4$ acts like Fremy's salt (16), while $KBiO_3$ acts similarly to periodates (14).

Adler proposes that the pyrocatechol monoether oxidation occurs by an ionic mechanism. (14).



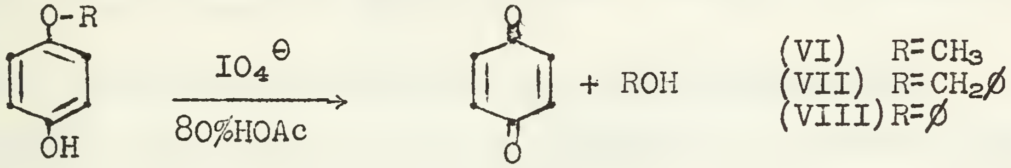
According to Levitt (17), the active species in the periodate oxidation is the periodonium ion or its hydrates. This cation would attact the phenol at the site of the highest electron density, the phenolic OH group, yielding the periodic acid aryl ester. However, Adler gives no evidence for the existence of the IO_3^+ species, nor does he explain how it could be such a specific reagent and why it doesn't attack the aryl nucleus. A more probable first step would involve formation of the periodic acid aryl ester from the phenol and some form of periodic acid. The ester could then decompose, forming IO_3 and the mesomeric aroxyl cation (III). Addition of a mole of water to the cation would then give the o-quinone-like hemiketal and a proton. Finally, the spontaneous decomposition of the hemiketal would give the o-quinone and the alcohol.

Alternatively, the ester (II) or cation (III) may decompose directly without formation of the hemiketal in a concerted reaction with a molecule of water as a nucleophile.

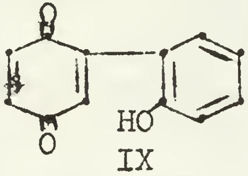


The remarkable ease of formation of the pyrocatechol monoethers might suggest complex formation between the two o-oxygens and the periodate, but the equally facile oxidations of hydroquinone monoethers gives support to the acyclic mechanisms proposed above.

Hydroquinone, itself, is almost instantaneously oxidized by periodate giving p-benzoquinone in high yield. The following hydroquinone monoethers also were oxidized.

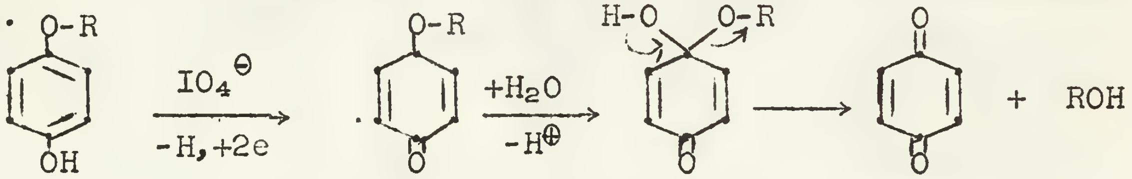


The phenyl ether underwent, in addition, a more complicated oxidation. In 80% acetic acid it rapidly consumed 1.4 moles of periodate. The products were p-benzoquinone and phenol (in amounts indicating 60% normal ether cleavage) and a brick-red substance (IX) $C_{12}H_8O_3$. This substance was later identified as (o-hydroxyphenyl)-p-benzoquinone.

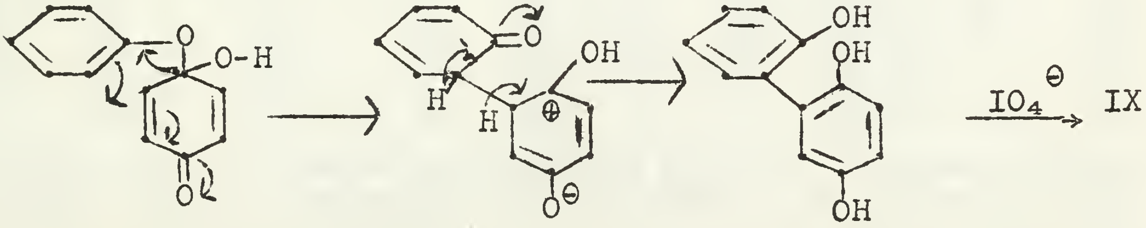


IX

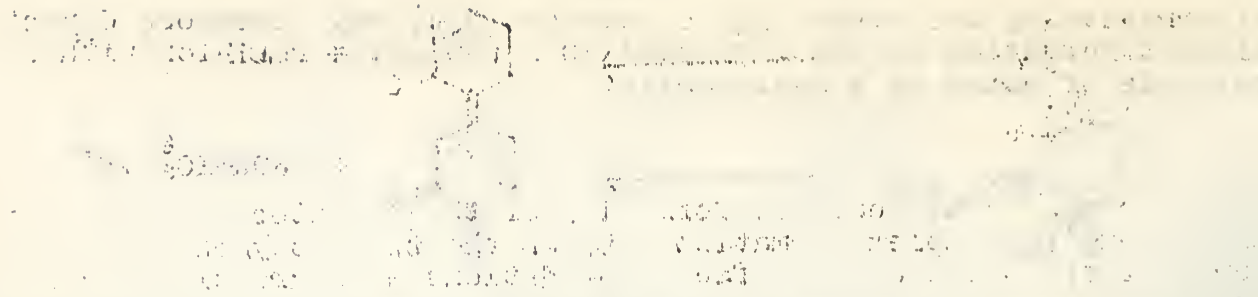
Adler (14) proposes that the mechanism of the oxidation of the hydroquinone monoethers should be similar to that for the pyrocatechol monoethers.



The reaction could also occur in a concerted manner similar to the pyrocatechol compounds. The side reaction producing (o-hydroxyphenyl)-p-benzoquinone is proposed to proceed via a cyclic mechanism. This rearrangement is comparable to that undergone by ordinary p-quinones, although here this reaction requires the presence of a strong acid (18,19).



The relative ease of the various types of phenol oxidations was indicated by oxidation of 2-methoxy- and 2,5-dimethoxyhydroquinones and 2,4-dimethoxyphenol.



[illegible]

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[illegible]

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[illegible]

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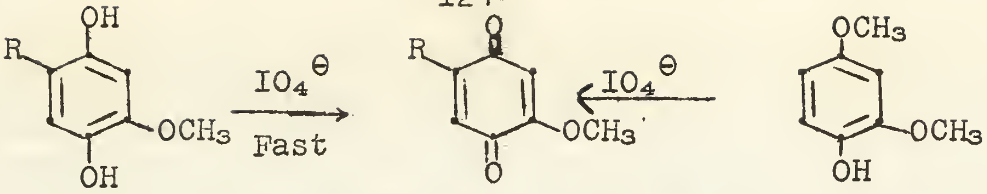
A. R=H

B. R=OCH3



The two hydroquinones (A and B) were oxidized to the p-benzoquinone in over 90% yield indicating that the hydroquinone group is oxidized in preference to the pyrocatechol monoether group. The 2,4-dimethoxyphenol was oxidized to the same benzoquinone indicating that the hydroquinone monoether is oxidized in preference to the pyrocatechol monoether. It was also noted that m-methoxyphenol is only oxidized very slowly by periodate forming small amounts of methoxy-o-and p-benzoquinone.

No systematic comparison has been made between the action of periodate and other specific oxidants on p-hydroquinone derivatives; however, Fremy's salt is known to react, forming 4-methoxy- and 4-benzyloxy-o-quinones in high yield.

Oxidation of 2,6-dimethoxyphenol and 3-methoxycatechol

Further investigation of the oxidation of phenolic compounds produced some interesting reactions (20).

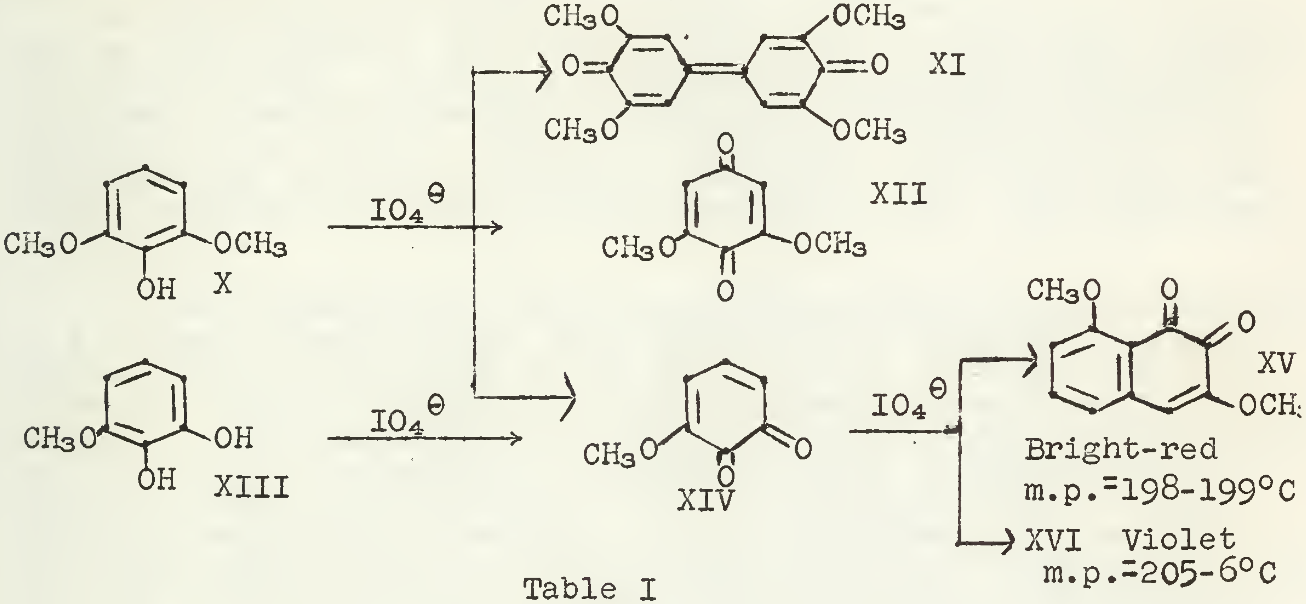
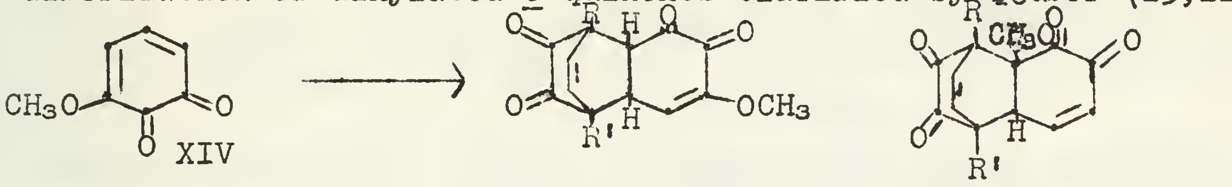


Table I

Experiment Number	Compound	Concentration in reaction mixture in mmoles/l	Temp. °C.	Time min.	XI	XII	XIV	XV	XVI	Total XI-XVI
1	X	8	4	2	7	5	58	7	2	79
2	X	8	20	10	12	3	35	15	7	72
3	X	80	20	10	31	3	5	25	2	66
4	XIII	80	20	10	-	-	12	48	2	62
5	XIV	40	20	10	-	-	21	51	2	74

The oxidation of 2,6-dimethoxyphenol led to three expected products (XI,XII,XIV) and two unexpected C_{10} compounds. The fusion of two C_6 compounds could be assumed to arise via a spontaneous dimerization of 3-methoxy-1,2-benzoquinone. The red product XI was shown to be the 3,8-dimethoxy-1,2-naphthoquinone The violet product XVI is thought to be the isomeric 3,5-dimethoxy-1,2-naphthoquinone.

The investigation of the route of the reaction became experimentally possible when Adler (20) found that a dimer of XIV was easily formed. When XIV was allowed to stand in solution, (in acetone, methylene chloride, chloroform, ethyl acetate or dioxane) a yellow precipitate settled out. On purification, this was a yellow compound M.P. 139-140°C. The infrared spectrum showed absorption bands at 1760, 1740 and 1715 $cm.^{-1}$ indicating the presence of three isolated carbonyl groups, a band at 1690 $cm.^{-1}$ indicating an α,β-unsaturated carbonyl group and a band at 1615 $cm.^{-1}$ for the olefinic part of the conjugated system. These bands were almost identical to those reported by Harley-Mason and Laird (21) for the dimer of unsubstituted o-benzoquinone. The structure of this dimer was recently elucidated by considering a diene addition of two molecules of o-benzoquinone in a manner analogous to the dimerization of alkylated o-quinones clarified by Teuber (15,22).



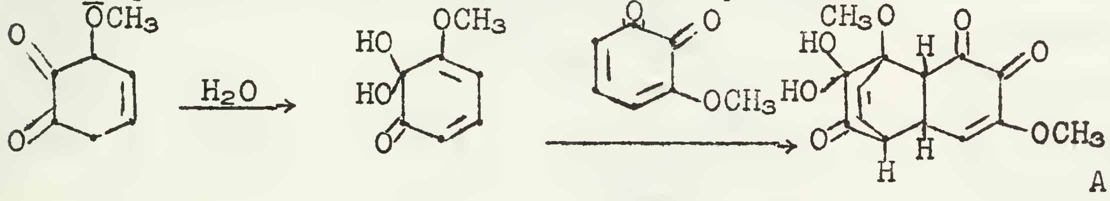
XIV

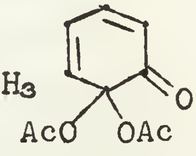
XIX R=CH_3O,R'=H
XIXa R=H,R'=CH_3O

XIXb R=CH_3O,R'=H
XIXc R=H,R'=CH_3O

As will be shown later the correct structure for the β-naphthoquinone (XV) indicates that the structure XIX is the correct structure for the dimer. When XIX was treated with o-phenylenediamine, it formed 1-methoxyphenazine in 90% yield indicating a retrodiene cleavage occurs easily. When XIX was treated with periodate, the naphthoquinone (XV) was produced in 87% yield. Thus the formation of XV obviously involves oxidative removal of the keto group and two hydrogens.

As the oxidation of 3-methoxy-o-benzoquinone (XIV) is complete in a period of ten minutes, with some product detected after two minutes, the dimerization of XIV must occur at a rather high rate in water. This is not self evident as dimerization in organic solvents is a comparatively slow reaction. An investigation of the UV spectra of XIV in water and in organic solvents indicated that it rapidly formed a monohydrate in water. The large shift in λmax (+60mu) in comparing the maxima of the monohydrate with that of 2-acetoxy-o-quinol acetate XXXI indicated that the 1-carbonyl was the one most likely hydrated. It was also found that a concentrated solution of XIV in water formed a new dimer which was the monohydrate of XIX. The infrared spectrum of this dimer indicated that there were fewer carbonyl groups, but that the C=C-C=O chromophore was still present. Thus, the rapid dimerization of XIV in water was proposed to occur via diene addition between the o-quinol and the o-quinone to form the dimer monohydrate.

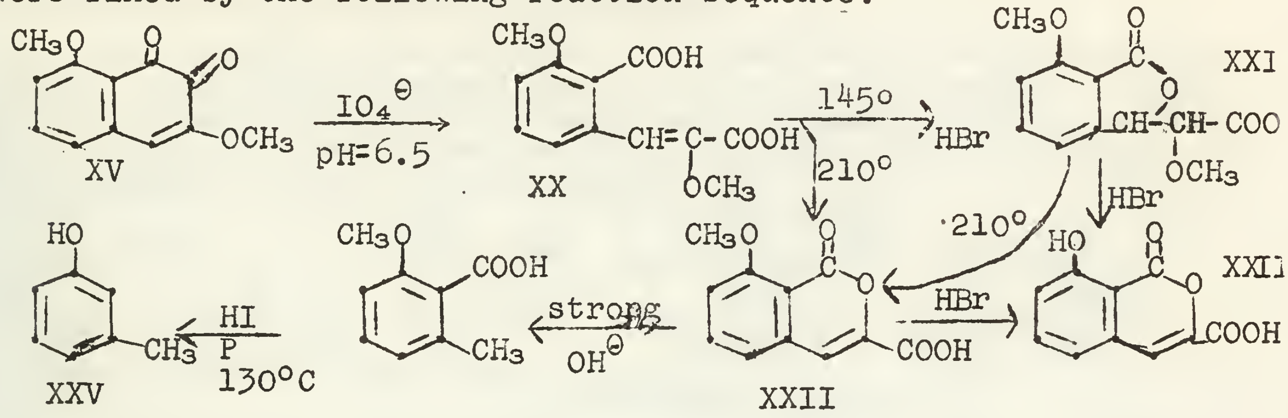




XXXI

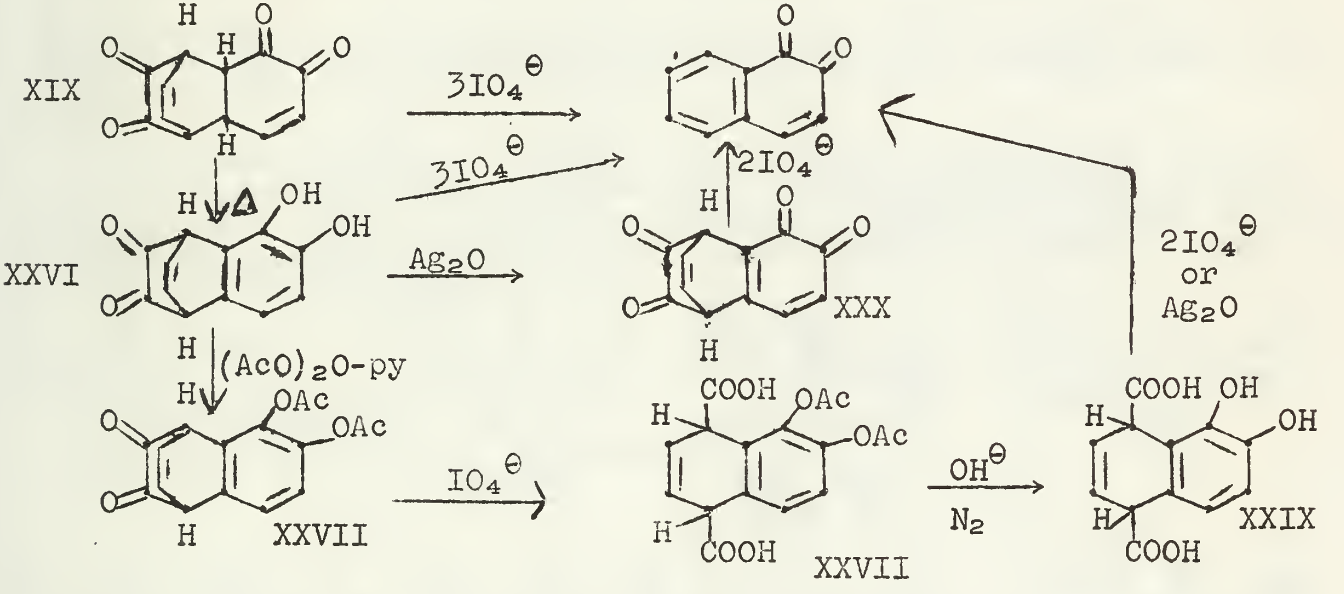
The structure of the β-naphthoquinone XV was elucidated in the following manner (23). The absorption spectrum of XV indicated a double carbonyl with bands at 1670 and 1660 $cm.^{-1}$ in the infrared and resembled known napthoquinones in the ultraviolet and visable

ranges. The o-quinone group was indicated by the formation of a phenazine derivative and, after reduction to a leuco compound, formation of a diacetate with a typical ultraviolet spectrum for a naphthoquinone derivative. XV was also oxidized with permanganate to 3-methoxyphthalic acid. The positions of the two methoxy groups were fixed by the following reaction sequence:

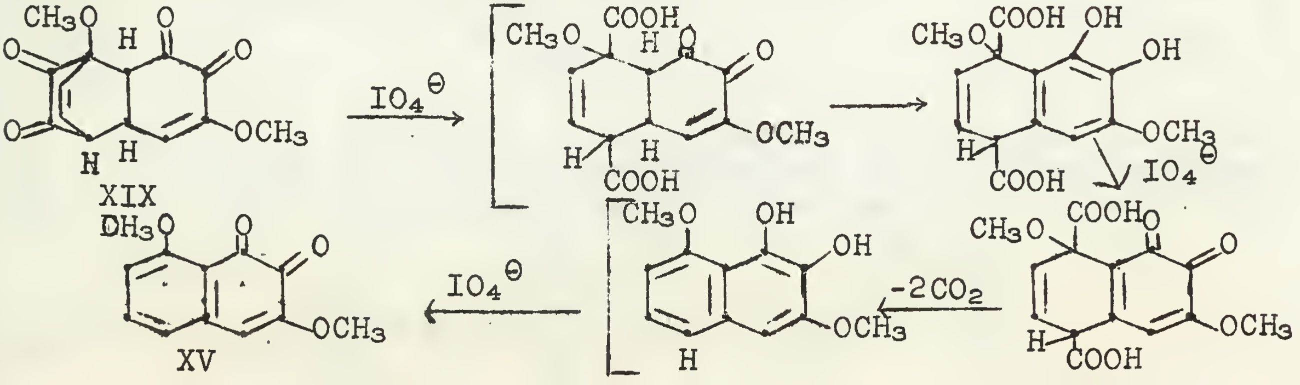


Absorption spectra of XX, XXI and XXII compared well with those for the known similar compounds without the nuclear methoxy group. The placement of the methoxy group on XXII was established by two methods, the most unequivocal being degradation to m-cresol.

The mechanism of the oxidative conversion of the dimer XIX into the β-naphthoquinone XV was elucidated by considering the following reactions: (24)



These reactions suggest that the periodate oxidation of the dimer XIX occurs by the following reaction sequence.



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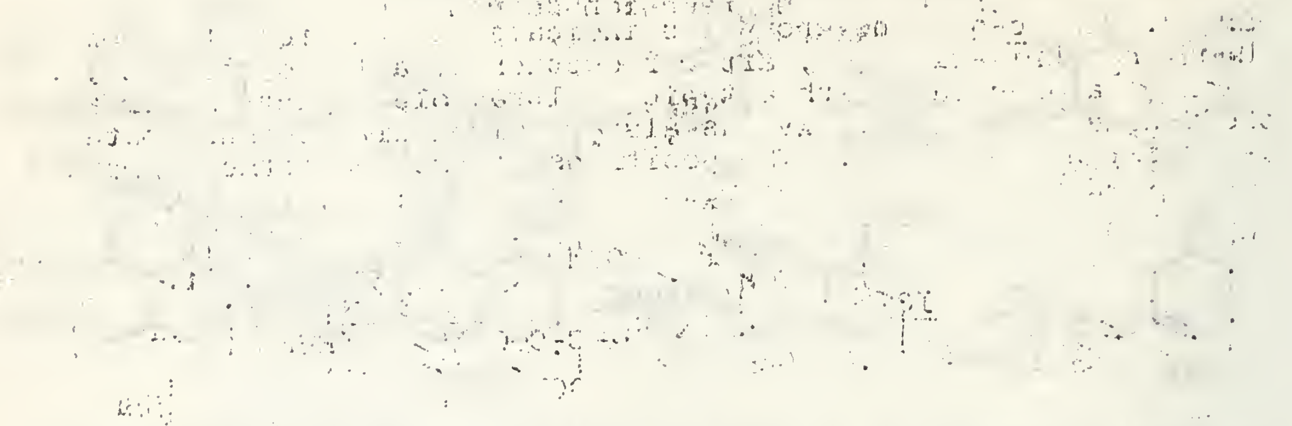

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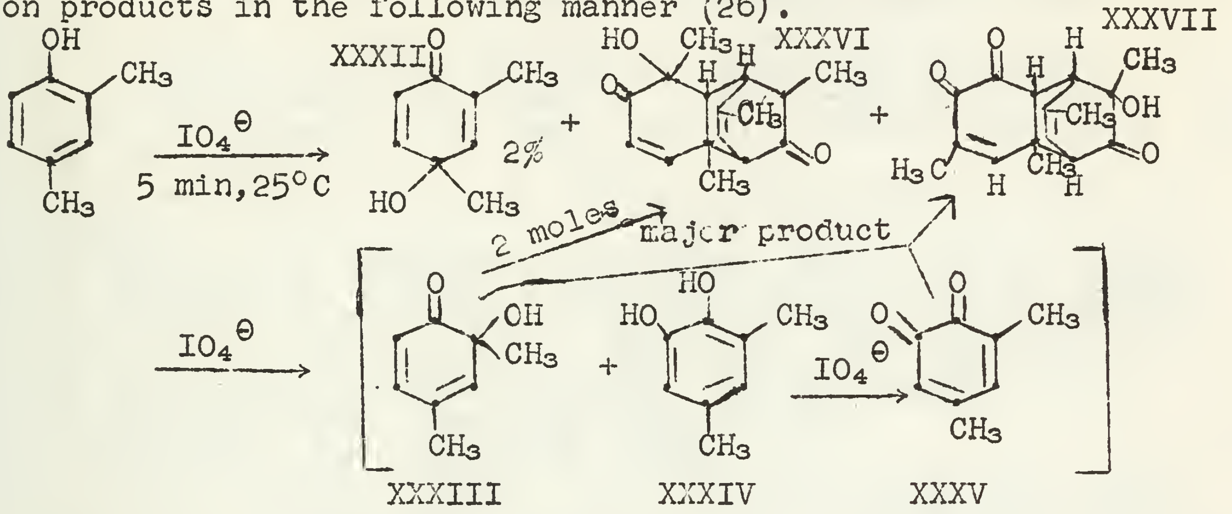
The spontaneous, rapid decarboxylation of the postulated *o*-quinoid intermediate can be attributed to the special position of the carboxyl groups, both of which are part of vinylogous β-keto acid structures.(25)

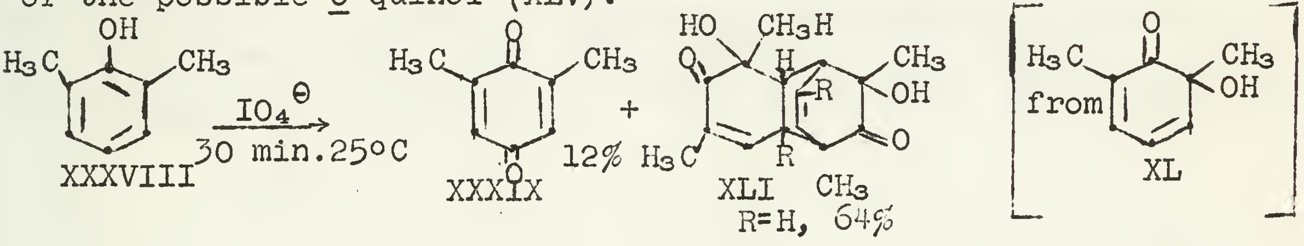
Oxidation of methyl substituted phenols

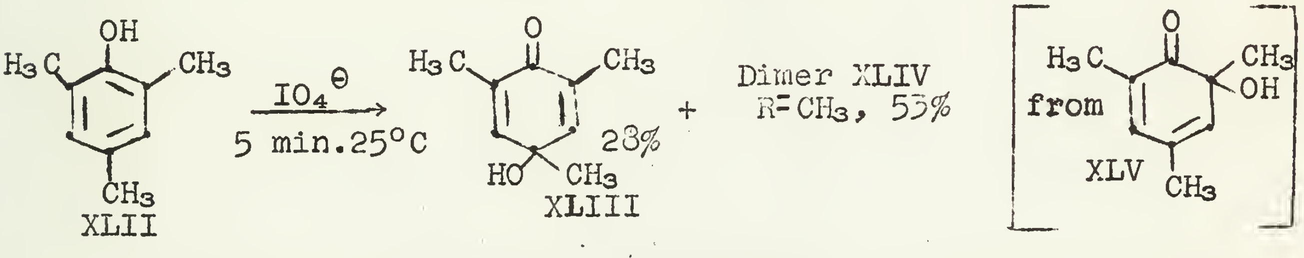
Adler has also investigated the oxidation of methyl substituted phenols. 2,4-Dimethylphenol was oxidized with periodate to form a stable *p*-quinone (XXXII) and two dimeric compounds (XXXVI,XXXVII). The dimeric compounds were found to be formed from two *ortho*-oxidation products in the following manner (26).



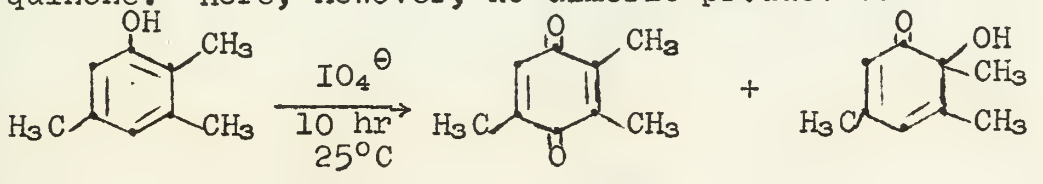
The fact that no product corresponding to a dimer of XXXV was found indicated that the *o*-quinone XXXV dimerized more readily with the *o*-quinol (XXXIII) than with itself.

2,6-Dimethylphenol XXXVIII was oxidized by periodate to 2,6-dimethyl-*p*-benzoquinone (XXXIX) and a dimer (XLI) of the possible *o*-quinol (XL) (27). 2,4,6-Trimethylphenol (XLII) is oxidized to 2,4,6-trimethyl-*p*-quinol (XLIII) and a dimer (XLIV), similar to XLI, of the possible *o*-quinol (XLV).





Adler found that 2,3,5-trimethylphenol was oxidized by periodate to a mixture of 2,3,5-trimethyl-*o*-quinol and 2,3,5-trimethyl-*p*-quinone. Here, however, no dimeric product could be isolated (27).



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APPLICATIONS OF LOW INTENSITY ULTRASONIC WAVES TO ORGANIC CHEMISTRY

Reported by D. Tuleen December 8, 1960

INTRODUCTION:

Sound is propagated through a medium by longitudinal compressions and rarefactions; these may be represented by sinusoidal waves in which the pressure is plotted against the distance. Frequency, wavelength and velocity have their usual meaning in such a representation, and are interrelated by the familiar expression: $f\lambda=c$. As the wave passes through the medium, a compression should bring about a temperature rise unless heat is somehow withdrawn. A rarefaction should, conversely, cause a decrease in temperature unless heat is added. For even the best heat conductors the wqvelength is too small, and the thermal conductivity too small for the flow of an appreciable amount of heat. The compressions and rarefactions of the sound wave are therefore adiabatic rather than isothermal.

The acoustical spectrum has been divided roughly into the three frequency regions of infrasonic, sonic and ultrasonic on the basis of detection by the human ear[1], much as the limitation of the human eye has led to a division of the electromagnetic spectrum into the infrared, visible and ultraviolet regions. This seminar will deal with applications of ultrasonic waves (frequency>20,000 cps) to organic chemistry. We shall need to consider first, however, some of the methods of generation and measurement of such waves.

GENERATION:

In the latter nineteenth century the Curie brothers[2] discovered that crystals of certain substances (e.g. quartz, tourmaline, topaz) which lack a center of symmetry develop positive and negative charges at different locations of the crystal when compressed along certain axes. These charges were found to be proportional to the applied pressure. This is electro-striction or the piezoelectric effect. The converse piezoelectric effect was discovered soon afterwards; changes in the dimensions of such crystals brought about by an applied potential difference. This converse effect has been applied to the generation of ultrasonic waves. One applies an alternating potential at a frequency which causes the crystal to resonate. This resonance frequency is related to the dimensions of the crystal. Thus, for the fundamental mode of vibration:

$$f = \frac{v}{2L} \tag{1}$$

where f is the frequency, v is the velocity of sound in the crystal and L is the "characteristic" length of the crystal.[3] The odd harmonic overtones may also be generated by this method. The usefulness of this procedure can be readily imagined, as ultrasonic waves of an accurately known frequency can be generated. Quartz is generally used as the piezoelectric transducer because it is resistant to fracture and economical. Methods for cutting and mounting the crystal, as well as applying the alternating potential are outside of the scope of this seminar, and are well reviewed.[2,3]

The intensity of a wave is proportional to the square of the amplitude. Sound waves of high or low intensity may be generated by varying the applied potential. Waves of high intensity have been

employed to bring about physical or chemical changes in such varied endeavors as oxidation in aqueous media, polymerization, de-polymerization, emulsification, initiation of reaction,[4] cleavage of aromatic and heterocyclic rings,[5-7] not to mention uses in laundering[4] and the enhancement of the mellowing rate of whiskey and sake.[8] Low intensity waves, the subject of this seminar, have been used as an analytical too in sonar, velocity and absorption measurement and the examination of relaxation processes.

MEASUREMENT:

The velocity of sound in liquids may be accurately determined by the use of an interferometer.[9,10] A piezoelectric plate, which is driven by an independent source, is coupled to a column of liquid in which is immersed a movable reflector. The plate is set in vibration, propagating longitudinal waves. Standing waves are set up at certain reflector settings. A dip in the current in an electrical circuit associated with the transducer is observed at reflector distances of (2n+1) one-quarter wavelengths from the plate, where n is integral. The frequency of generation is known; the wavelength may be determined from the reflector distances at which resonance occurs. The velocity of propagation is calculated from $f\lambda = c$.

The sound wave is absorbed as it passes through a medium. Measurement of absorption is based on the decrease of the amplitude from A_o to A after propagation through a known distance, x. The absorption coefficient, α, may be defined:[1]

$$A = A_o e^{-\alpha x} \tag{2}$$

All fluids absorb sound by a classical mechanism which involves loss by viscosity and heat conduction.[11] The classical absorption coefficient, α_{class}, is shown to be proportional to the square of the frequency, f,

$$\alpha_{class} = \frac{2}{3} \frac{f^2}{c^3 p} \left[\eta + \frac{3}{4} (\gamma - 1) \frac{\lambda}{c_p}\right] \tag{3}$$

where c is the velocity of sound; p, the density; η, the viscosity; γ, the ratio of heat capacities Cp/Cv; λ, the wavelength. The second term of (3), the absorption by heat conduction, is very small for all liquids except liquid metals. The quantity usually considered in absorption studies is α/f^2, which is constant with respect to frequency for most liquids (exceptions discussed later).

Measurement of absorption at sonic frequencies is extremely difficult because of the variation in absorption coefficient with the square of the frequency as expressed in (3). At sonic frequencies the value of α is very small, and the length of the medium necessary for accurate absorption measurements is on the order of kilometers. This practically limits the study of absorption by liquids at sonic frequencies to seawater. Even for seawater, the measurement is subject to experimental difficulty, because of the inhomogeneity of the medium.[12]

Absorption, or attenuation, in liquids is measured at low ultrasonic frequencies (50kc - 1 Mc) by the reverberation technique, and at higher frequencies (0.5 Mc - 300 Mc) by a pulse method. The reverberation method involves the acoustical excitation of a closed vessel and the observation of the exponential decrease of the amplitude. The loss

of energy consists of two parts, the volume loss and the wall or surface loss. These two losses can be separated by using several vessels of differing volume to surface ratios, but herein lies the source of most of the innacuracies of the method. Karpovich has shown that the wall loss is dependent not only on the dimensions of the container, but also on the volume loss.[13] Absorption measurements by reverberation are accurate only to 5-10%.

The pulse method eliminates standing waves and minimizes wall loss. The transducer emits a pulse of waves which are reflected and return to the transducer between pulses. The reflected wave is picked up by the same crystal and presented on the screen of an oscilloscope. Absorption measurements accurate to within 2% are achieved by this method.[14,15]

EARLY APPLICATIONS:

The first development in the application of the study of low intensity ultrasonic waves to organic chemistry was the accurate determination of sound velocity in a number of organic liquids,[16-19] and the linear decrease of velocity with increasing temperature[20]. As the number of liquids studied increased, various investigators attempted to generalize the effect of various structural features on velocity of sound. Parthasarathy, for example, concluded that velocity was enhanced by increasing the length of the molecule, or by introducing unsaturation. He also concluded that aromatic compounds propagate ultrasonic waves more swiftly than do aliphatic, highly viscous compounds more than mobile ones, and compounds with an electric moment more swiftly than those without.[17-19] Although these generalizations are usually true, they are not infallible. For instance, Lagemann and co-workers[21] found that velocity did not always correspond to a single value of molecular weight in homologous series; alkyl phenyl ketones exhibit a minimum in a plot of velocity vs. molecular weight.

Rao's empirical equation relating velocity, c, density ρ, and molecular weight, M, appeared in 1941.[22]

$$R = Mc^{1/3}/\rho \tag{4}$$

For most liquids R is nearly constant; variations in R have been interpreted as a qualitative measure of association.[23,24]

ADIABATIC COMPRESSIBILITY:

From a consideration of a plane longitudinal wave in a cylinder one can derive[25] an expression for the velocity in terms of the adiabatic compressibility, β_{ad}, and the density, ρ. (S = entropy)

$$c^2 = \frac{1}{\beta_{ad}} \quad \text{where } \beta_{ad.} = -\frac{1}{v}\left(\frac{\delta v}{\delta P}\right)_S \tag{5}$$

The isothermal compressibility is defined:

$$\beta_T = -\frac{1}{v}\left(\frac{\delta v}{\delta P}\right)_T \tag{6}$$

By mathematical identity:

$$\left(\frac{\delta V}{\delta P}\right)_S = -\left(\frac{\delta S}{\delta P}\right)_V \Bigg/ \left(\frac{\delta S}{\delta V}\right)_P \quad \text{and} \quad \left(\frac{\delta V}{\delta P}\right)_T = -\frac{\left(\frac{\delta T}{\delta P}\right)_V}{\left(\delta T/\delta V\right)_P} \tag{7}$$

Therefore:

$$\frac{\beta_{ad}}{\beta_T} = \frac{\left(\frac{\delta S}{\delta P}\right)_V \left(\frac{\delta T}{\delta V}\right)_P}{\left(\frac{\delta T}{\delta P}\right)_V \left(\frac{\delta S}{\delta V}\right)_P} = \left(\frac{\delta S}{\delta T}\right)_V \Bigg/ \left(\frac{\delta S}{\delta T}\right)_P \tag{8}$$

But by definition:

$$Cp = T\left(\frac{\delta S}{\delta T}\right)_P \quad ; \quad Cv = T\left(\frac{\delta S}{\delta T}\right)_V \tag{9}$$

Therefore:[26]

$$\frac{\beta_{ad}}{\beta_T} = \frac{Cv}{Cp} \tag{10}$$

and a knowledge of the velocity, (therefore β_{ad}), and the isothermal compressibility leads to an evaluation of the ratio of heat capacities.

CLASSIFICATION OF LIQUIDS:

The introduction of pulse techniques enabled chemists to determine accurately the absorption of sound, and to classify organic liquids on the basis of their absorption.[14,27,28] It was found that a few "normal" liquids displayed an absorption nearly that predicted by classical theory; examples of this class are helium and mercury. Most liquids are "abnormal" in that their absorption greatly exceeds the classical amount. The abnormal liquids are subdivided into three groups[27]. The non-associated polyatomic liquids, as benzene, hexane, CCl_4 etc. exhibit a positive temperature coefficient of absorption. The associated polyatomic liquids, mainly the alcohols, have a negative temperature coefficient of absorption. A third group of abnormal liquids was also classified; in this group α/f^2 is not independent of frequency. These liquids are the relaxing liquids. At the time of the classification the only relaxing liquids known were acetic acid and a few simple esters. Later studies demonstrated many anomalies within this classification.[29] As the experimentally available frequency was raised many more relaxing liquids were noted.

RELAXATION:

The energy of a sound wave alternates between kinetic energy and potential energy as the wave exhibits rarefactions and compressions. Consider the equilibrium:

$$\text{I} \quad \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \quad \text{II} \tag{11}$$

where II denotes the higher energy species. The potential energy brought about by a condensation may be transfered to a few molecules of I thereby exciting them to state II and perturbing the equilibrium. The system then re-equilibrates; its recently acquired excess energy is transformed into thermal energy and is absorbed by the medium. At sufficiently low frequencies the excitation and loss of energy occur between successive condensations, and the absorption is maximum. As the frequency is increased, a point is reached where the change from condensation to rarefaction is so rapid that the perturbed medium cannot re-equilibrate between successive condensations, so the absorption is decreased. At very high frequencies the equilibrium is unaffected by the variations in the wave. The relaxation process just described may occur when the molecules of the medium exist in an equilibrium between two or more states of different energy.[30] It is observed experimentally as a decrease in the value of α/f^2, from its low frequency value to a limiting value, B, at high frequencies, (Fig. 1),[31] and a maximum in the value of the absorption per wavelength, μ, at the characteristic frequency of the relaxation, f_c, (Fig. 2).[31]

Fig. 1

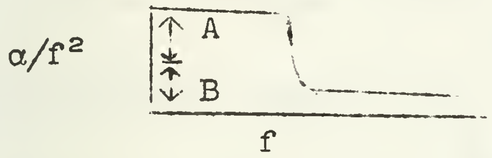
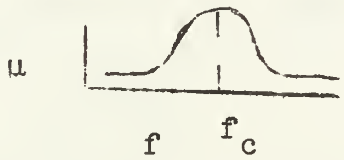


Fig. 2



Lamb has shown[32] that if the change in velocity with changing frequency (the velocity dispersion) is neglible, a relaxation process may be represented by (12) where A and B are constant:

$$\frac{\alpha}{f^2} = \frac{A}{1+(f/fc)^2} + B \tag{12}$$

The absorption per wavelength, μ, and u_m, its maximum value are defined by (13) and (14):

$$\mu = (\alpha - Bf^2)\lambda = \frac{Acf}{1+(f/fc)^2} \tag{13}$$

$$\mu_m = \frac{Acf}{2} \text{ ; where } f = f_c \tag{14}$$

Measurement of α, f, and c enables the calculation of A, B and μ to be made.[32] The energy difference between states I and II in equilibrium (11) can be evaluated from the variation of μ_m with temperature. The temperature variation of f_c determines the potential energy barriers between the two states.

For equilibrium (11) there is a contribution to the heat capacity arising from relaxation, δCp:30.

$$\delta Cp = R \left[\frac{\Delta H^\circ}{RT}\right]^2 \frac{e^{-\Delta F^\circ/RT}}{[1+e^{-\Delta F^\circ/RT}]^2} \tag{15}$$

If $\Delta F^\circ > 3RT$ we may approximate the squared term in the denominator as unity within an error of 5%.

$$\delta Cp = R \left[\frac{\Delta H^o}{RT}\right]^2 e^{-\Delta F^o/RT} = R \left[\frac{\Delta H^o}{RT}\right]^2 e^{-\Delta H^o/RT} e^{\Delta S^o/R} \qquad (16)$$

Furthermore, if the velocity dispersion is small, as is usually the case:[33]

$$\frac{2\mu m}{\pi} = \frac{\gamma-1}{Cp} \delta C_p \qquad (17)$$

$$\frac{2\mu m}{\pi} = \frac{\gamma-1}{C_p} R \left[\frac{\Delta H^o}{RT}\right]^2 e^{-\Delta H^o/RT} e^{\Delta S^o/R} \qquad (18)$$

where γ is the ratio of heat capacities, Cp/Cv. The heat of reaction, ΔH^o can be determined from the slope of the linear plot of $\ln T^2 \mu m\, Cp/\gamma-1$ vs. $1/T$. Substitution into (18) yields the value of ΔS^o. If, on the other hand, $\Delta F^o \underline{\quad} 3RT$, an assumption of a zero entropy change is made and the enthalpy difference is approximated.[33]

It can be shown that[30] $f_c = \dfrac{k_{12} + k_{21}}{2\pi}$ for eqn (11) $\qquad$ (19)

The equilibrium constant is:

$$K_{eq} = \frac{k_{12}}{k_{21}} = e^{-\Delta F^o/RT} \qquad (20)$$

If $\Delta F^o > 3RT$, $k_{21} \gg k_{12}$, and

$$fc = \frac{k_{21}}{2\pi} \qquad (21)$$

From the theory of absolute reaction rate[34]

$$k_{21} = \left(\frac{kT}{h}\right) e^{-\Delta F_2^{\ddagger}/RT} \qquad (22)$$

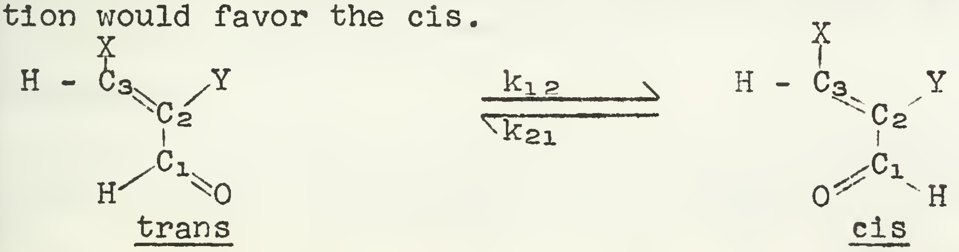
Therefore:

$$fc = \frac{1}{2\pi}\left(\frac{kT}{h}\right) e^{-\Delta F_2^{\ddagger}/RT} = \frac{1}{2\pi}\left(\frac{kT}{h}\right) e^{-\Delta H_2^{\ddagger}/RT} e^{\Delta S_2^{\ddagger}/R} \qquad (23)$$

and a plot of $\ln fc/T$ vs $1/T$ yields $\Delta H_2^{\ddagger}$, the enthalpy of activation for the reverse reaction, from the slope; substitution into (23) yields $\Delta S_2^{\ddagger}$

ALDEHYDES:

The pulse method has been employed[35-37] to study the equilibrium between rotational isomers of unsaturated aldehydes. Rotation about the C_1-C_2 bond is restricted, as resonance imparts partial double-bond character to this bond. Electric dipole moment studies[38] indicate that the trans form is the more stable, although electrostatic interaction would favor the cis.



Energy parameters have been evaluated for this equilibrium employing the methods outlined.

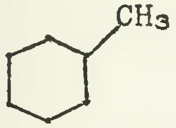
Table I.

aldehyde	f_c(Mc at 25°C.)	k_{21}(sec^{-1})	ΔH°(kcal)	$\Delta H_2^{\ddagger}$(reverse)
acrolein	176	11.1×10^{8}	2.1	5.0
crotonaldehyde	30.3	1.9×10^{8}	1.9	5.5
cinnamaldehyde	15.7	0.98×10^{8}	1.5	5.6
methacrolein	174	11.0×10^{8}	3.1	5.3

The energy difference between rotational isomers of aldehydes with extended conjugation, as cinnamaldehyde, is smaller than for acrolein. The increase in the energy difference noted in substituting a methyl group at C_2 (methacrolein) has been attributed[37] to a stabilization of the trans isomer by an attraction between the oxygen and the methyl group.

CYCLOHEXANES:

Certain cyclohexane derivatives exhibit relaxation phenomena in the range 100-200 kc. Relaxation has been observed, for example, in:[31,39,40]



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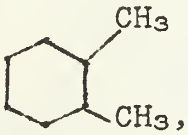
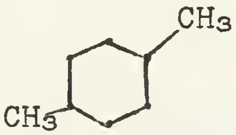


trans



trans

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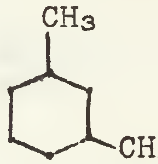
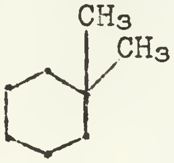


cis

whereas no relaxation is observed in:

,



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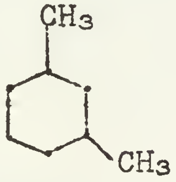

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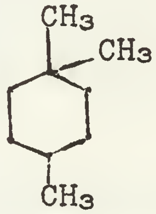
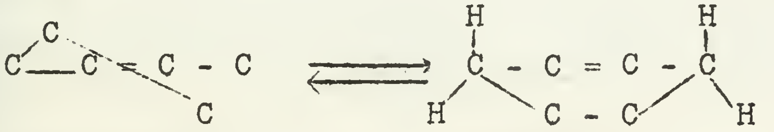


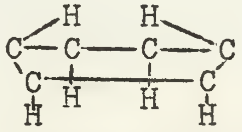
These results are consistent with the theory that the equilibrium between the two chair forms of the ring is perturbed. Thus cyclohexane, in which the two chair forms are of equal energy shows no relaxation, while the energy difference between an axial and an equatorial methyl group in methyl cyclohexane gives rise to a relaxation. The absence of relaxation in 1,1,3-trimethyl cyclohexane has been attributed to the large steric interaction of two exial methyl groups. Relaxation is therefore expected for this compound at higher frequencies; this has not been examined. The behavior of cyclohexane[41] is in agreement with the theory that the high energy boat form is present in very small amounts at equilibrium. Unfortunately, the ultrasonic data for cyclohexane derivatives has been achieved with a reverberation method. As this method is quite inaccurate, no attempt has been made to correlate the interesting relaxations observed with energy differences between the axial and equatorial conformers.

CYCLOHEXENE:

Karpovich[31] has observed relaxation in cyclohexene at 80 kc, presumably because of the equilibrium between pseudo boat and chair forms:



pseudo-chair pseudo-boat

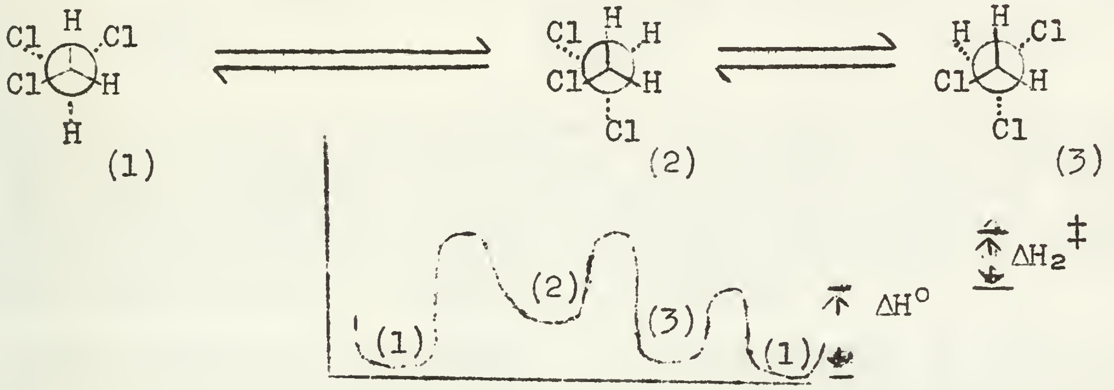


boat-cyclohexane

At first this may seem surprising, as cyclohexane shows no relaxation. The two hydrogens in the "fore" and "aft" positions in the boat form of cyclohexene are further apart than their counterparts in the saturated analog. Further, the four hydrogens below the cyclohexane boat tend to make it less stable.

ETHANE DERIVATIVES:

Ultrasonic absorption has been used to calculate the barrier to rotation about certain C-C single bonds.[42,43,44] Lamb noted a relaxation in 1,1,2-trichloroethane. The Newman projections of the three isomers interconverted by this restricted rotation are:



By modifying slightly the method outlined previously (to provide for three state equilibrium) values of $\Delta H^\circ = 2.1$ kcal, and $\Delta H_2^\ddagger = 5.8$ kcal (for the reaction of $2 \rightarrow 1$) have been determined. Spectroscopic measurements[45] indicate $\Delta H^\circ = 1.8 \pm 0.2$ kcal., while gas phase measurements[46] evaluate $\Delta H_2^\ddagger = 5.5$ kcal. Some of the compounds studied are indicated in Table II.

Table II

Compound	ΔH° (kcal)	$\Delta H_2^\ddagger$ (kcal) ($2\rightarrow1$)
1,1,2-trichloroethane	2.2	5.8
1,1,2-tribromoethane	1.6	6.4
sym-tetrabromoethane	0.9	4.3
1-bromopropane	1.3	3.6
1,2-dichloropropane	1.1	4.7
1,2-dibromopropane	0.9	4.9
2-methylbutane	0.9	4.7

CARBOXYLIC ACIDS:

The low frequency relaxations observed in acetic and propionic acids[47,32] were first interpreted as perturbations of monomer-dimer equilibria, and calculations of energy differences were made on the basis of this interpretation.[48] More recent evidence[49] shows two relaxations in acetic acid solutions. The low frequency relaxation is now interpreted as the cleavage of one hydrogen bond. The higher frequency relaxation is believed to represent the equilibrium between monomer and dimer.[50]

ESTERS:

The energy differences between rotational isomers of methyl and ethyl acetates and formates, including their investigation by ultrasonic waves, has been discussed in a recent seminar.[51]

SOLUTIONS:

The study of absorption of ultrasonic waves by binary solutions has indicated[49] three main types of behavior, as indicated by Figs. 3-5

Fig. 3
$CCl_4 + C_6H_6$

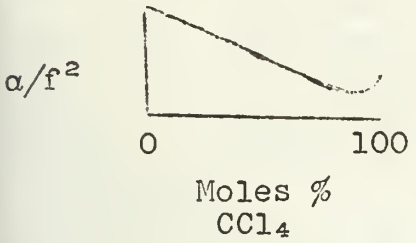


Fig. 4
$C_6H_5OH + CCl_4$

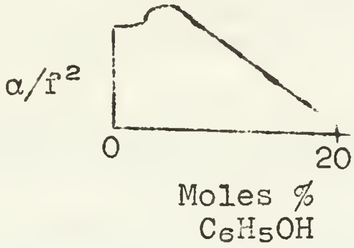
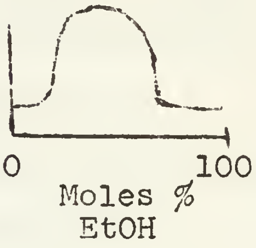


Fig. 5
EtOH + H_2O



The maximum in Fig. 4 is attributed to association of the phenol, perhaps in a monomer-dimer equilibrium; that in Fig. 5 is believed to be due to "some interaction" between the molecules of the two species. The three cases cited above are examples of the type of curve obtained when: a) neither of the liquids is associated, b) one is associated and the other is not, c) both are associated.

Some studies have been made of solvent effects on the dissociation of salts. The relaxations observed have been interpreted in terms of the dissociation mechanism believed to be operative. These studies have been limited to the present to inorganic salts.[52,53]

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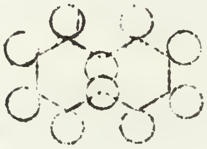
SYNTHESIS AND PROPERTIES OF CONJUGATED MACROCYCLES

Reported by J. R. Kuszewski December 15, 1960

This seminar concerns itself with the synthesis and properties of conjugated macrocyclic hydrocarbons $\left(CH=CH\right)_x$, where x is at least five. Some aspects of this subject have been treated in a Universit of Illinois Seminar (1), a Massachusetts Institute of Technology Seminar (2), a Pennsylvania State University Seminar (3), and in rather out-of-date reviews by Baker (4) and Baker and McOmie (5).

Hückel's Rule (6) states that stable monocyclic conjugated ring with all atoms equivalent have 4n+2 pi-electrons (where n=0,1,2...). Thus besides benzene, monocyclic hydrocarbon systems which might have aromatic character are the cyclopropenium cation (7), cyclopentadienyl anion (8), tropylium cation (9), and cyclooctatetraenyl dianion (10). The success of Hückel's Rule has spurred the search for larger conjugated monocycles.

Early calculations by Mislow (11) underlined the steric features to be expected of conjugated macrocycles having 10 to 30 carbon ring skeletons. Cyclodecapentaene ($C_{10}H_{10}$), although it contains 4n+2 pi-electrons, cannot fully obey Hückel's Rule because steric repulsions of the interior hydrogen atoms require the ring to be non-planar. The degree of this repulsion is evident from a scale drawing of the hypothetical planar conformation of this molecule, assuming the pertinent atomic dimensions: C-C 1.40 A, C-H 1.10 A, Van der Waals radius of H 1.0 A, and C-C-C bond angles 120°.

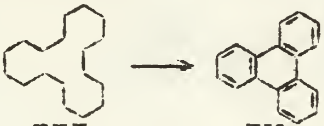


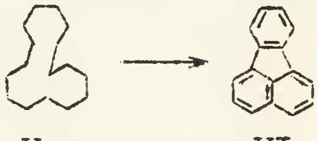
Similar scale drawings revealed that hydrogen repulsion subsides witl increasing size of the monocycle, and led Mislow to conclude that cyclotriacontadecapentaene ($C_{30}H_{30}$) would most likely be the smallest unstrained planar macrocycle having 4n+2 pi-electrons. It shoul be noted, however, that there is no intrinsic necessity that the bon angles in aromatic systems be 120°. The C-C-C bond angles in the cyclopropenium cation are 60°, and in the cyclopentadienyl anion, the tropylium cation, and the cyclooctatetraenyl dianion (assuming planarity) they are 108°, 128.6°, and 135° respectively. So if some variation in bond angles be allowed, it is conceivable that cyclic systems as small as cyclooctadecanonaene ($C_{18}H_{18}$) be planar, or nearly so.

The synthesis of simple conjugated macrocycles seemed an enormous task until a few years ago. Prelog, Boarland, and Polyak (12) studied the dehydrogenation over palladium-charcoal at 400° of cycloalkanes $\left(CH_2\right)_n$ where n=9-18. No conjugated macrocycles were obtaine polycyclic hydrocarbons were produced instead. The cycloparaffins could be classified into four groups according to the number of carbon atoms present. In group A were found cyclononane (C_9H_{18}), cyclotridecane ($C_{13}H_{26}$) and cycloheptadecane ($C_{17}H_{34}$), in each of which, after primary cyclization to benzene nuclei, there remained five carbon atoms to form a C_5 ring. For example, dehydrocyclizatior of cyclononane (I) gave indene (II). In group B were found cyclo-

decane ($C_{10}H_{20}$), cyclotetradecane ($C_{14}H_{28}$) and cyclooctadecane ($C_{18}H_{36}$), all of which could cyclize to aromatic hydrocarbons consisting of 1,2 condensed benzene nuclei. Thus cylooctadecane (III) cyclized to triphenylene (IV). Group C consisted of hydrocarbons in which, after formation of benzene nuclei, there remained a C_7 ring. However, under the stated reaction conditions no well-defined products could be isolated from cycloundecane ($C_{11}H_{22}$) and cyclopentadecane ($C_{15}H_{30}$). The hydrocarbons in group D were those in which a C_8 ring remained after formation of benzene nuclei. Rearrangement products were observed in this group. Cyclohexadecane (V), for example, gave fluoranthene (VI).

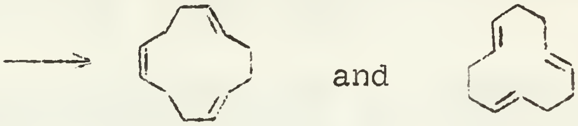

I II


III IV


V VI

In 1957, Wilke (13) reported the trimerization of 1,3-butadiene to both *cis,trans,trans*-cyclododecatriene (VII) and the corresponding *all*-*trans*-isomer VIII. Without mentioning the conditions, this

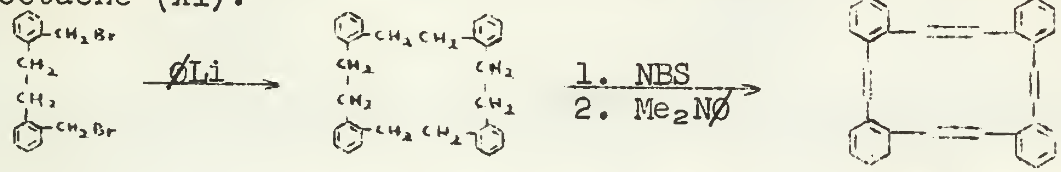
3 $CH_2=CH-CH=CH_2$



VII VIII

author stated that the triene is readily converted into the corresponding tetra- and pentaenes, but that it is much more difficult to introduce a sixth double bond without alteration of the carbon skeleton. Nevertheless an unspecified amount of a compound of composition $C_{12}H_{12}$ was isolated, which was found to contain a deep orange component sensitive to air and heat. No further details of this aspect of his study have been reported.

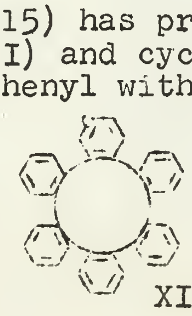
In 1953 Bergmann and Pelchowicz (14) treated 2,2'-bis-(bromomethyl)-dibenzyl (IX) with phenyl lithium and obtained 1,2,5,6,9,10,13,14-tetrabenzocyclohexadeca-1,5,9,13-tetraene, X, which was treated successively with N-bromosuccinimide and dimethylaniline to give *all-trans*-1,2,5,6,9,10,13,14-tetrabenzocylcohexadeca-1,3,5,7,9,11,13,15-octaene (XI).

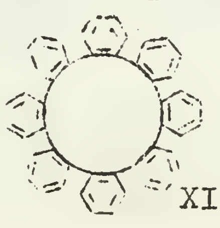


IX X XI

The strong infrared band at 955 cm.$^{-1}$ was taken as evidence that the double bonds have *trans* configuration. XI is a colorless crystal line solid melting at 267°. A model indicates the C_{16}-ring may achieve a puckered, strainless configuration.

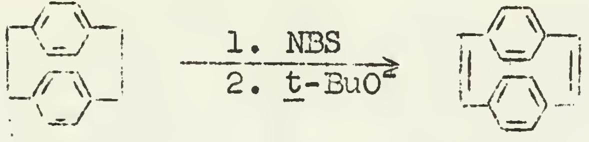
Wittig (15) has prepared the perbenzo derivatives of cyclododecahexaene (XII) and cyclohexadecaoctaene (XIII) by treatment of 2,2'-dilithium biphenyl with cobaltous chloride. These structures were


XII


XIII

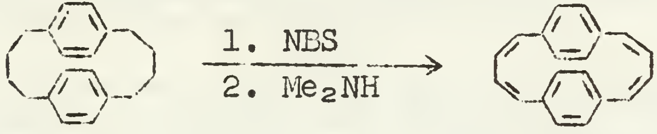
indicated by molecular weight measurements and the absence of aromat monosubstitution bands in the infrared. Models show the rings to b puckered, resulting in a rather compact molecular architecture. Supporting this observation is the fact that these compounds sublim about 50° below their melting points. Their ultraviolet spectra are similar to that of tetraphenylene, which is thought to be non-planar, and differ from that of the planar triphenylene.

Dewhirst and Cram (16) have prepared [2.2]paracyclophane diolefin (XV) from [2.2] paracyclophane (XIV) by successive treatment with N-bromosuccinimide and potassium t-butoxide. The perpendicula relation between the benzene rings and the unsaturated side chains in XV represents an extreme case of steric inhibition of resonance. Evidence for steric inhibition is found in the lack of significant difference in ultraviolet spectra of XIV and XV.

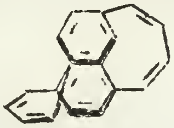


XIV XV

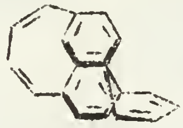
The same authors (17) were likewise able to prepare 1,2,3,4,11,12,13,14-dehydro [4.4] paracyclophane (XVII) from [4.4] paracyclophane (XVI). It is believed that XVII, in which conformation the eight bridging carbon atoms lie in a plane perpendicular to the benzene rings, possesses some bond angle strain. This strain can be relieved by rotation of one of the benzene rings by 60° about an axis passing through the center of both benzene rings. Conformer XVIIa and XVIIb result, depending on whether the direction of rotation is counterclockwise or clockwise. The two conformers are seen to be non-superimposable mirror images. It will be interesting to see if the energy barrier between XVIIa and XVIIb is sufficient to permit resolution.



XVI XVII

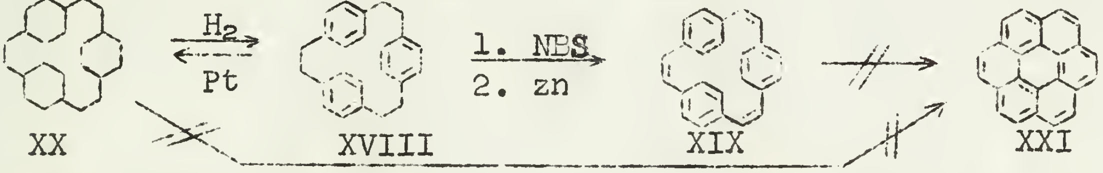


XVIIa



XVIIb

Cram and Dewhirst (17) have also prepared the triene XIX of [2.2.2] paracyclophane by successive treatment of [2.2.2] paracyclophane (XVIII) with N-bromosuccinimide and zinc. Treatment of XIX with dehydrogenating agents or with Lewis acids did not result in the formation of coronene (XXI). Full reduction of XVIII, followed by treatment with dehydrogenating agents, again gave no coronene, but instead XVIII was regenerated. Models show that only two of the three benzene rings in XIX can approach coplanarity. It is interesting to note that XIX might tautomerize to XXII, whose peripheral



XX XVIII XIX XXI

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

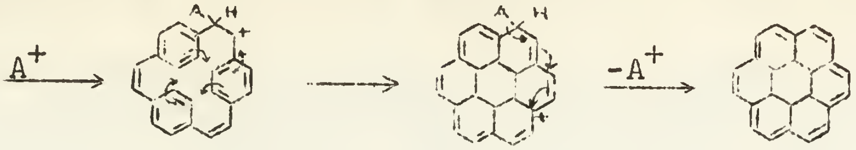
[illegible]

[illegible]

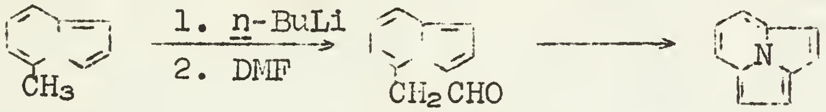
[illegible]

system of double bonds is shown by models to be fairly planar. Attempts to convert XIX to XXII using light or acids as catalysts failed, even though a plausible path for their interconversion was available.

XIX



It was noted earlier that repulsion of hydrogen atoms is responsible for nonplanarity in some conjugated macrocycles. Boekelheide and Windgassen (18) in effect replaced these hydrogen atoms with a single, centrally situated nitrogen atom. They prepared cycl [3,2,2] azine (XXV) by treatment of 5-methylpyrrocoline (XXIII) with n-butyl lithium followed by dimethylformamide, the resulting aldehyde XXIV cyclizing to XXV. In contrast to the starting material,



XXIII XXIV XXV

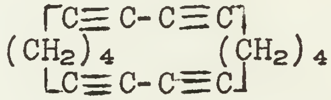
cyclazine is unusually stable to air, light, and heat, and the basicity of the nitrogen atom has been lost. The ultraviolet spectrum of XXV is unaffected by addition of acid.

In 1956, Sondheimer and Amiel (19) announced a promising approach toward synthesis of conjugated macrocycles, that of oxidative coupling of terminal diacetylenes. They treated octa-1,7-diyne (XXVI) with cuprous chloride and ammonium chloride in aqueous ethano at 55°, while passing air through the reaction mixture. Isolated were three products, the linear "dimer" XXVII in 40% yield, the linear "tetramer" XXVIII in 20% yield, and the cyclic "dimer" XXIX in 10% yield. The structure of XXIX was established by its ultra-

$HC{\equiv}C(CH_2)_4C{\equiv}CH \longrightarrow H{+}C{\equiv}C(CH_2)_4C{\equiv}C{+}_nH$

XXVI

XXVII, n=2
XXVIII, n=4



$$\begin{array}{ccc} \ulcorner C{\equiv}C-C{\equiv}C \urcorner \\ (CH_2)_4 \qquad (CH_2)_4 \\ \llcorner C{\equiv}C-C{\equiv}C \lrcorner \end{array}$$

XXIX

violet spectrum, which shows the absorption at 227, 239, and 254 mu characteristic of 1,3-diynes, and by its infrared absorption at 2240 and 2154 cm^{-1} (characteristic of disubstituted 1,3-diynes), and lack of absorption at 2100 and 3300 cm^{-1} ($-C{\equiv}C-H$ stretching bands). Ethanolic silver nitrate was without effect. Full hydrogenation furnished the known cyclohexadecane.

Oxidative coupling of terminal acetylenes, the Glaser reaction, has been of some general synthetic importance since not only acetyle ic hydrocarbons (20) but also alcohols (21), amines (22), nitro compounds (23), carboxylic acids (24) and esters (25) can undergo coupling. Baxendale and Westcott (26) have been the only workers to investigate the mechanism of this reaction. They showed cupric ion to be the oxidizing agent. Using the stoichiometric amount of cupric ion in an aqueous medium buffered to pH 6 (to avoid inhibition of the reaction by the liberated protons), they noted that the linear "dimer" formed rapidly in 50% yield, with the remainder of the acetylene converted into insoluble cuprous acetylide:

$$4\ RC{\equiv}CH + 2\ Cu^{+2} \longrightarrow RC{\equiv}CC{\equiv}CR + 2\ RC{\equiv}CCu + 4\ H^+$$

The latter is then slowly oxidized to coupling product by air or other oxidizing agent. The overall reaction is therefore

$$2\ RC{\equiv}CH \ +\ 2\ Cu^{+2} \longrightarrow RC{\equiv}CC{\equiv}CR \ +\ 2\ H^{+} \ +\ 2\ Cu^{+}$$

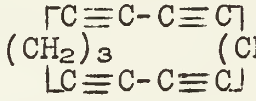
Eglinton and Galbraith (27) have found that coupling takes place in homogeneous solution, when anhydrous cupric acetate and methanol-pyridine solvent are employed. Recently Hay (28) reported that coupling can be effected in a manner of minutes at room temperature with air using a catalytic amount of an amine complex of a cuprous salt in an organic solvent. Sondheimer (29) has noted that solubility is important in determining the products of coupling reactions. Cyclic products larger than "dimers" will not form unless the reaction takes place in homogeneous solution. A complication which seems to have been largely ignored is the Straus reaction (30) in which copper acetylides couple to form vinyl acetylenes.

Continuing their investigation of coupling of various diynes, Sondheimer, Amiel, and Wolovsky (31) found that hepta-1,6-diyne (XXX) gave four products, separated by chromatography: (a) the first-eluted component, an unidentified chlorine-containing material; (b) the linear "dimer" XXXI, obtained in 26% yield; (c) the cyclic "dimer" XXXII, produced in 12% yield; and (d) the last-eluted substance, the linear "tetramer" (XXXIII) (18%). Models of XXXII indicate that

$$HC{\equiv}C(CH_2)_3C{\equiv}CH \longrightarrow H[C{\equiv}C(CH_2)_3C{\equiv}C]_nH$$

XXX

XXXI, n=2
XXXIII, n=4



$$\begin{matrix} \ulcorner C{\equiv}C{-}C{\equiv}C \urcorner \\ (CH_2)_3 \qquad\qquad (CH_2)_3 \\ \llcorner C{\equiv}C{-}C{\equiv}C \lrcorner \end{matrix}$$

XXXII

the linear diyne segments lie very close together. This feature of the molecule indicated by its explosive nature on heating, and by the displacement of the longest wavelength ultraviolet peak from 254 to 263 mu, attributed to transannular interaction of the chromophores

After Eglinton and Galbraith reported their method for coupling in homogeneous solution, Sondheimer <u>et al</u> (32) reinvestigated the coupling of various diynes. Hepta-1,6-diyne (XXX), for example, under the Eglinton-Galbraith conditions gave a complex mixture which was separated by chromatography. Two cyclic products were obtained in small yields, the cyclic trimer XXXIV in 3% yield and the cyclic tetramer XXXV in 4% yield. Cyclic products with higher molecular weight were isolated but remained unidentified. In like manner, octa-1,7-diyne, nona-1,8-diyne, and deca-1,9-diyne gave cyclic

$$HC{\equiv}C(CH_2)_3C{\equiv}CH \longrightarrow \boxed{[C{\equiv}C(CH_2)_3C{\equiv}C]_n}$$

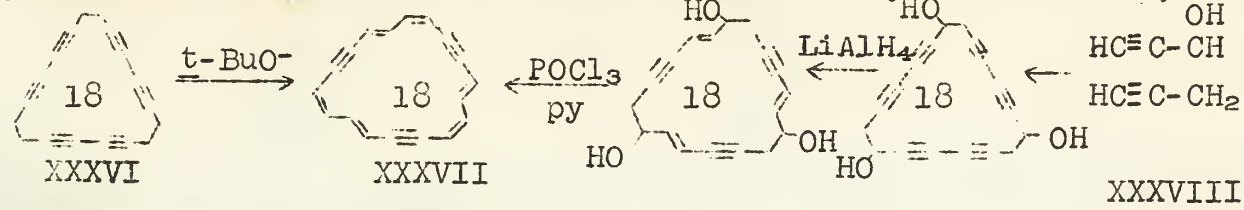
XXX

XXXIV, n=3
XXXV, n=4

dimers, trimers, tetramers, pentamers, and higher cyclic polyacetylenes in yields of 2-14%. Full hydrogenation gave cycloparaffins containing up to 54 carbon atoms, and some even higher analogs whose identity has not been fully established. All the cyclic polyacetylenes are colorless crystalline substances with melting points ranging from 81-218°. On exposure to air and light they gradually form yellow or brown insoluble polymers. They may be kept indefinitely in benzene solution in the dark.

Cyclooctadeca-1,3,7,9,13,15-hexayne (XXXVI), prepared in 6% yield by oxidation of 1,5-hexadiyne, undergoes prototropic rearrangement with potassium <u>t</u>-butoxide in <u>t</u>-butanol at 90° giving the fully conjugated, unstrained planar cyclooctadeca-1,7,13-(<u>cis</u>)-triene-3,9,

15-(trans)-triene-5,11,17-triyne (XXXVII) in 50% yield (33). Evidence for this structure is its reduction to cyclooctadecane, its ultraviolet spectrum ($\lambda_{max}^{isooctane}$ 245(18,800), 254(14,700), 322 (98,000), 334(160,000), 365(8700), 385(11,700), 400(15,200) and 434(1080); $\lambda_{max}^{benzene}$ 329(95,000), 342(155,000), 391(12,000), 407 (15,200) and 441(1100)), and its alternative production from 1,5-hexadiyne-3-ol (XXXVIII) by successive oxidative coupling, reduction with lithium aluminum hydride, and dehydration with phosphorous oxychloride-pyridine (34). Compound XXXVII contains 18 pi-electrons in conjugation, and if Hückel's Rule is applicable this macrocycle could be expected to exhibit reasonable stability. Some indications of its stability are its method of formation in 50% yield, its decomposition point at 200°, and the fact that it can be kept for several days in air with little change. Partial hydrogenation of XXXVII over Lindlar catalyst gave the fully conjugated cyclooctadecanonaene $(C_{18}H_{18})$ (XXXIX) in 30% yield. XXXIX is brown-red as crystals and yellow-green in benzene solution; $\lambda_{max}^{benzene}$ 378(297,000), 415(8700), and 456(28,400). The linear nonaene analog, $CH_3-(CH=CH)_9-CH_3$, has its highest wavelength maximum at 456 mu (benzene), and hence all the double bonds in XXXIX appear to form one chromophoric system. Sondheimer concluded that XXXIX was relatively planar, and therefore trans addition of hydrogen across the triple bonds in XXXVII must have occurred (since cis addition would have given a non-planar nonaene). Unpublished preliminary x-ray examination indicates that XXXIX is a near-planar molecule approximating to a centrosymmetric configuration (35). Compound XXXIX is strikingly more stable than its acyclic analog, which decomposes very rapidly at room temperature (36). It sublimes at 120° (0.5 mm.) and appears to remain unchanged up to 230°, at which point a non-reversible color change takes place, giving yellow needles. Compound XXXIX gradually decomposes on standing in air over the course of several weeks.



XXXVI XXXVII XXXVIII

XXXIX

Calculations by Gouterman and Wagiere (37) indicate that the bond lengths in XXXIX are not all equal; an alternation of about 0.1 A was found to give better agreement with the three ultraviolet transitions at 378, 415, and 456 mu. Very recently Coulson and Golebiewski (38) published calculations which show XXXIX cannot possibly be planar, as a result of steric forces. The most likely deformation is that in which the six inner hydrogen atoms are displaced ±0.9 A out of the plane.

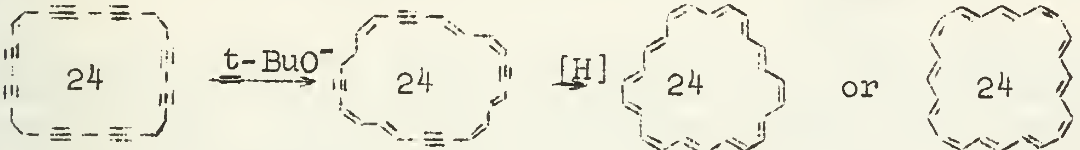
An interesting transannular reaction has been discovered as a side reaction accompanying the isomerization of XXXVI to XXXVII (39). Besides the 50% yield of XXXVII, about 7% of triphenylene (IV) was detected. The triphenylene probably arose from a nonplanar form of XXXVII, in which the carbon atoms 6/11, 12/17, and 18/5 are close enough to cause bond formation. That the planar XXXVII is not an intermediate in this reaction was shown by the fact that it gave no

IV when treated with potassium t-butoxide. This isomerization brin

XXXVIIa IV

to mind the work of Prelog (12) in which cyclooctadecane was dehydrogenated to triphenylene.

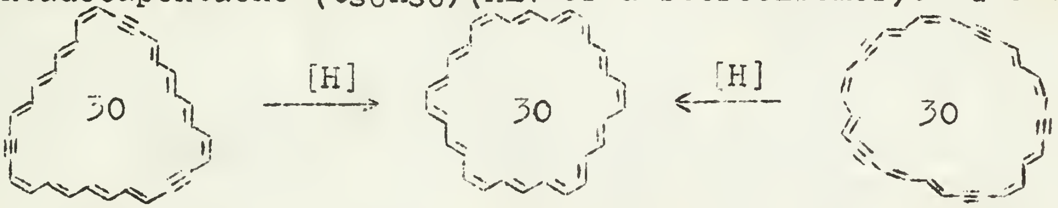
Cyclotetracosadodecaene ($C_{24}H_{24}$) (XLII) has been prepared by Sondheimer (40) by treatment of the cyclic tetramer XL of 1,5-hexadiyne with potassium t-butoxide to give the tetrayne XLI ($\lambda_{max}^{benzene}$ 333(120,000), 350(208,000), with absorption up to 600 mu), which upon partial hydrogenation over Lindlar catalyst gave 15% of XLII. Crystals of XLII are very dark blue and decompose on heating;



XL XLI XLIIa XLIIb

$\lambda_{max}^{benzene}$ 360(183,000), 375(195,000), 530(1720), with absorption up to 750 mu. The ultraviolet spectrum and color indicate that all 12 double bonds are part of one chromophoric system, and since XLIIa is more nearly planar than XLIIb, XLIIa was felt to be the more likely isomer. (Formation of XLIIa from XLI would require trans addition of hydrogen to the 4 triple bonds in XLI, plus isomerization of one cis double bond to a trans double bond.) XLII can not be converted to a more stable isomer by treatment with iodine in boiling benzene. It is far less stable than cyclooctadecanonaene (XXXIX): on standing in air for 24 hours it is 90% destroyed, and in benzene solution after 12 days it is 80% destroyed. Compound XLII has 24 pi-electrons and therefore cannot comply with Huckel's Rule.

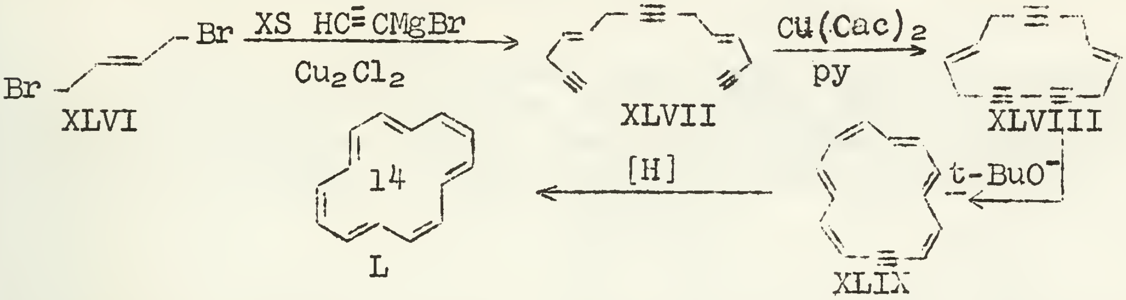
Sondheimer et al (41) have also prepared the 30-carbon conjugated pentayne XLIII (or a stereoisomer) and triyne XLIV (or a stereoisomer) by appropriate oxidation and rearrangement reactions. The orange-red crystals of XLIII decompose on heating; $\lambda_{max}^{benzene}$ (principal bands) 310(38000), 320(35,500), 383(101,000), and 400(122,000). The dark brown-violet XLIV decomposes on heating; $\lambda_{max}^{benzene}$ 323(47,00 and 406(108,000). Both XLIII and XLIV are reasonably stable and can be kept with little change in air for 24 hours or for several weeks in solution. Hydrogenation of XLIII and XLIV over Lindlar catalyst gives 5% and 10% respectively of the fully conjugated cyclotriacontadecapentaene ($C_{30}H_{30}$)(XLV or a stereoisomer). The brown-



XLIV XLV XLIII

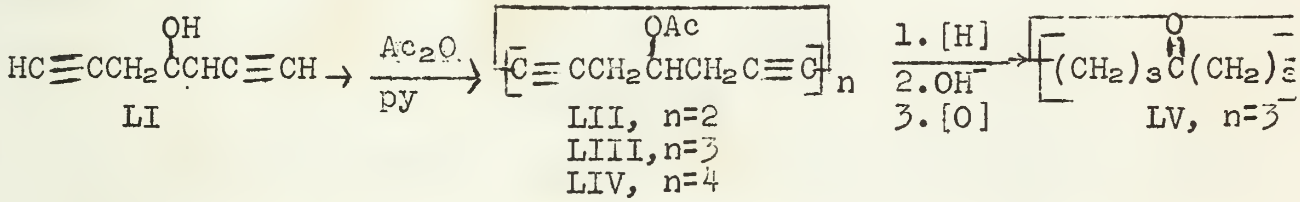
red crystals of XLV decompose on heating; $\lambda_{max}^{benzene}$ 331(43,000) and 432(140,000). Although XLV contains 4n+2 pi-electrons, it is quite unstable, being destroyed in air after several hours or on attempted isomerization with iodine in boiling benzene. It also gradually decomposes in dilute solution.

The nonplanar cyclotetradecaheptaene ($C_{14}H_{14}$) (L or a stereoisomer) has very recently been obtained (42) by treating trans-1,4-dibromo-2-butene (XLVI) with excess ethynylmagnesium bromide and cuprous chloride, followed by coupling under Eglinton-Galbraith conditions to XLVIII, isomerization to XLIX (or a steroisomer) with t-butoxide, and hydrogenation over Lindlar catalyst. Compound L crystallizes as dark-brown needles, m.p. 135°, $\lambda_{max}^{isooctane}$ 314(69,000 and 374(5700). After standing for one day in air, L is completely



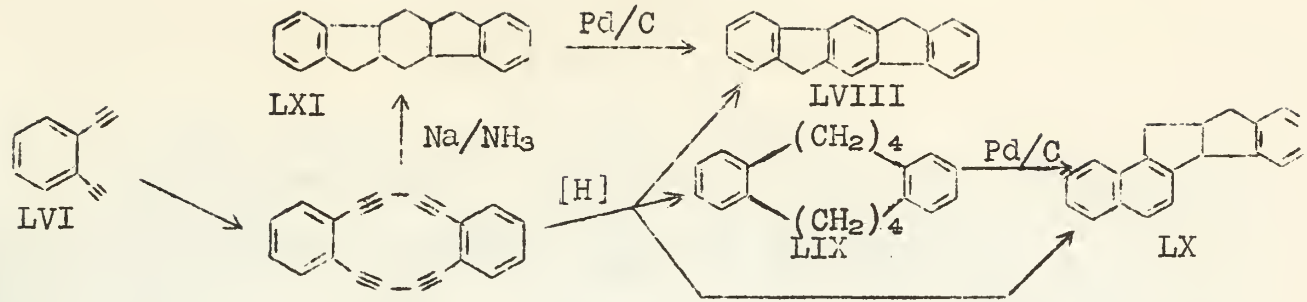
destroyed; after two weeks in solution it is 45% decomposed. Curiously, XLIX (of which two isomers were isolated) is stable for several weeks. It is also interesting to note that whereas the conjugated cyclopolyolefins containing 18,24, and 30 carbon atoms (which presumably are relatively planar) are more strongly adsorbed on alumina than the dehydro compounds from which they were derived, the nonplanar C_{14} homolog is less strongly adsorbed than its precursor.

Sondheimer and Gaoni (29) have studied the oxidative coupling of hepta-1,6-diyne-4-ol (LI). Obtained in 2.5% yield after acetylation was the cyclic dimer which, similar to its deoxy analog, exploded on heating and possessed an abnormal ultraviolet spectrum. The cyclic trimer was also obtained in 2-3% yield as evidenced by hydrogenation, saponification, and oxidation to the trione LV. Lastly, 1.5% of the cyclic tetramer LIV was obtained as a mixture of stereoisomers.



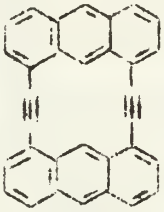
$$\underset{\text{LI}}{\mathrm{HC{\equiv}CCH_2\overset{OH}{C}CHC{\equiv}CH}} \xrightarrow[\text{py}]{Ac_2O} \underset{\substack{\text{LII, n=2}\\ \text{LIII, n=3}\\ \text{LIV, n=4}}}{\left[\mathrm{C{\equiv}CCH_2\overset{OAc}{C}HCH_2C{\equiv}C}\right]_n} \xrightarrow[\substack{2.\ OH^-\\ 3.\ [O]}]{1.\ [H]} \underset{\text{LV, n=3}}{\left[\mathrm{(CH_2)_3\overset{O}{\overset{\|}{C}}(CH_2)_3}\right]}$$

In 1957 Eglinton and Galbraith (43) coupled o-diethynylbenzene (LVI) and obtained a 40% yield of what they believed was the cyclic trimer, partly because models showed it to be strainless. However the product exhibited some unusual characteristics: it decomposed explosively on heating, its ultraviolet spectrum was unusual, and catalytic hydrogenation yielded a mixture of hydroaromatic substances, indicative of a transannular reaction. Later studies (44) demonstrated that the product was actually the highly strained cyclic dimer LVII. Molecular weight measurements indicated the dimeric structure. Absorption of hydrogen took place rapidly over palladium/charcoal but stopped when only 68% of the theoretical uptake for 4 triple bonds had been achieved. Isolated were 3% of 5,11-dihydroindeno-[1,2-b]-fluorene (LVIII), 50% of the expected saturated product LIX, and 38% of LX. LX was the sole product of dehydrogenation of LIX. Sodium-ammonia reduction of LVII gave a mixture of isomers of LXI plus some LIX and LX. The high degree of strain present in LVII has been vividly demonstrated by an x-ray study (45) which reveals the presence of "bowed diacetylenic chains."



LVII

A cyclic tetra-acetylene containing anthracene nuclei, LXII, has been prepared by Akiyama and Nakagawa (46) by oxidative couplin of the appropriate diyne. The orange crystals of LVII are stable in air, and change to black crystals when heated to 370°.



LXII

Bergelson, Molotkovsky and Shemyakin (47), incidental to a stud of diacetylenic macrocyclic lactones, have found what they believe to be transannular interaction between carbonyl and diyne groups. The carbonyl stretching frequency of the lactone LXIII (1724 cm^{-1}) differs from that of the corresponding open-chain ester LXIV (1740 cm^{-1}). Since the molecule does not appear strained, this shift indicates a possible transannular interaction.

$\overline{\text{—}C\equiv C(CH_2)_8CO_2(CH_2)_2C\equiv C\text{—}}$

LXIII

$HC\equiv C(CH_2)_8CO_2(CH_2)_2C\equiv CH$

LXIV

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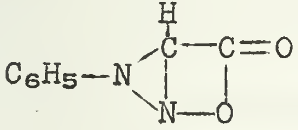
THE CHEMISTRY OF THE SYDNONES

Reported by R. P. Johnson January 5, 1961

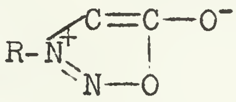
INTRODUCTION

Since the discovery, in 1935, of the "meso-ionic" compound, N-phenylsydnone, and its subsequent recognition as such, considerable interest has been aroused in the structure and properties of these unusual heterocycles. Reviews (1,2,3) concerning meso-ionic compounds have been published, of which only one is readily accessible, that by Baker and Ollis (1). This seminar will attempt to summarize the chemistry of the sydnones, with particular emphasis on the developments of the past three years.

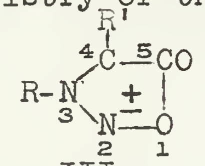
Inspection of the composition and properties of N-phenylsydnone led its discoverers at the University of Sydney (4) to postulate the bicyclic, covalent structure I. Baker and Ollis (5), however, pointed out the unsuitability of this formula. These authors regarded the sydnones as resonance hybrids of twelve dipolar and tetrapolar forms (e.g., II) to be represented as III. It may be noted that the planar five-membered ring possesses seven π-electrons available for delocalization and, like tropone, should be able to attain the "aromatic sextet" in the ring by donation of the seventh π-electron onto the exocyclic oxygen atom. This reasoning led to adoption (6) of formula IV to emphasize the aromatic character of the sydnone nucleus, in close analogy to tropone. The present author prefers the more vague designation III which makes no inferences as to the degree of aromatic character in the ring or the bond order of the exocyclic carbon-oxygen link, controversial points to be discussed later, and will therefore employ this representation in presenting the chemistry of these compounds.



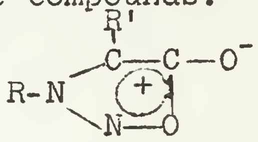
I



II



III



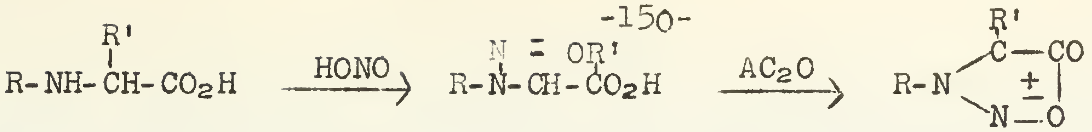
IV

According to the systematic nomenclature for betaines, recommended by Katritzky (7) for these systems, N-phenylsydnone (III, R is C_6H_5-; R' is -H) would be "anhydro-5-hydroxy-3-phenyl-1-oxa-2,3-diazolinium hydroxide." However, the trivial nomenclature based on the unknown parent sydnone (III, R=R'= -H) is usually employed for the sydnones, while the systematic nomenclature is used in describing the other meso-ionic compounds.

Baker and Ollis have suggested "that a compound may appropriately be called 'meso-ionic' if it is a five- or possibly a six-membered heterocyclic compound which cannot be represented satisfactorily by any one covalent or polar structure and possesses a sextet of electrons in association with all the atoms comprising the ring" (1). This definition and the use of the term itself have been attacked (8) on the grounds that it separates compounds otherwise very similar chemically into different classes on the arbitrary basis that a given structure is satisfactory or unsatisfactory, but usage of the term has been retained.

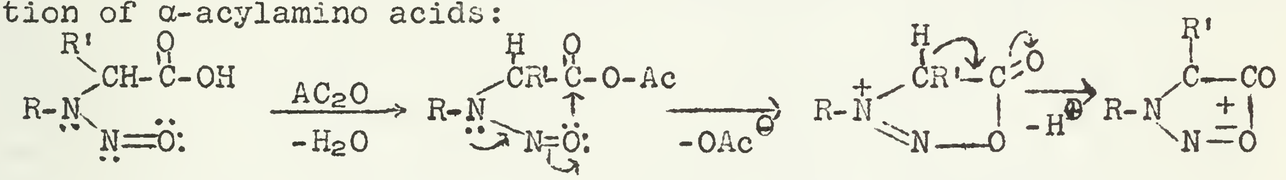
PREPARATION

The sydnones are generally prepared from the properly substituted glycines in a two-step synthesis:



The glycines can be prepared from an amine and the α-halo acid (9), from a halide and the α-amino acid (10), by catalytic reduction of a mixture of the amine with ethyl glyoxalate and subsequent saponification (11), via a Strecker-type reaction of the amine with glycolonitrile and subsequent hydrolysis (12), or by reaction of the amine and potassium cyanide with an aldehyde in the presence of sodium bisulfite (13) with subsequent conversion of the nitrile to the glycine. Nitrosation is accomplished, usually at 0°C, with nitrous acid generated in situ, when the amine is sufficiently basic (10).

Cyclization is generally carried out in acetic anhydride solution, at room temperature in a few days or more quickly at elevated temperatures. Trifluoroacetic anhydride or thionyl chloride may also be used, in anhydrous organic solvents at low temperatures. The dehydration is believed (14) to proceed through a mixed anhydride, e.g., V, in close analogy to the formation of oxazolones by dehydration of α-acylamino acids:



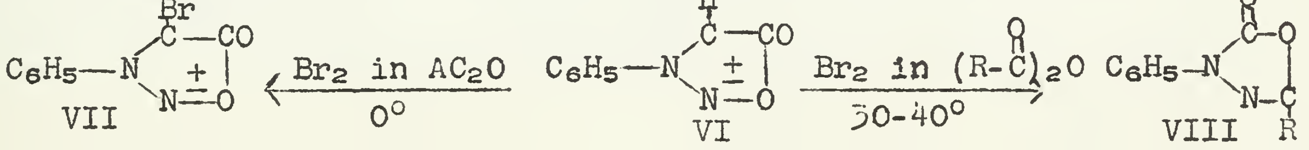
A recent innovation, appearing in the patent literature, eliminates isolation of the nitroso-compound. Thus, treatment of the aqueous nitrosation solution with organic or inorganic acid halides (15) or with carbodiimides (15,16) gives a precipitate of the sparingly-soluble sydnone. The mechanism postulated is analogous to the one above.

C-HALOGEN DERIVATIVES

The carbon atom in position 4 of the sydnone ring undergoes electrophilic substitution with surprising ease in a variety of reactions. Most work in this field to date has involved N-phenylsydnone, but the reactivity of the C-4 position appears to be a general phenomenon.

N-phenylsydnone (VI) is converted in good yield to 3-phenyl-4-bromo-sydnone (VII) upon treatment with N-bromosuccinimide, N-bromophthalimide, N-bromoacetamide or molecular bromine under a variety of conditions (17). Bromination occurs readily, even at 0°C. Similarly, the chloro-analog is obtained by treatment with chlorine in solution. No substitution on the phenyl-ring of VI has been observed.

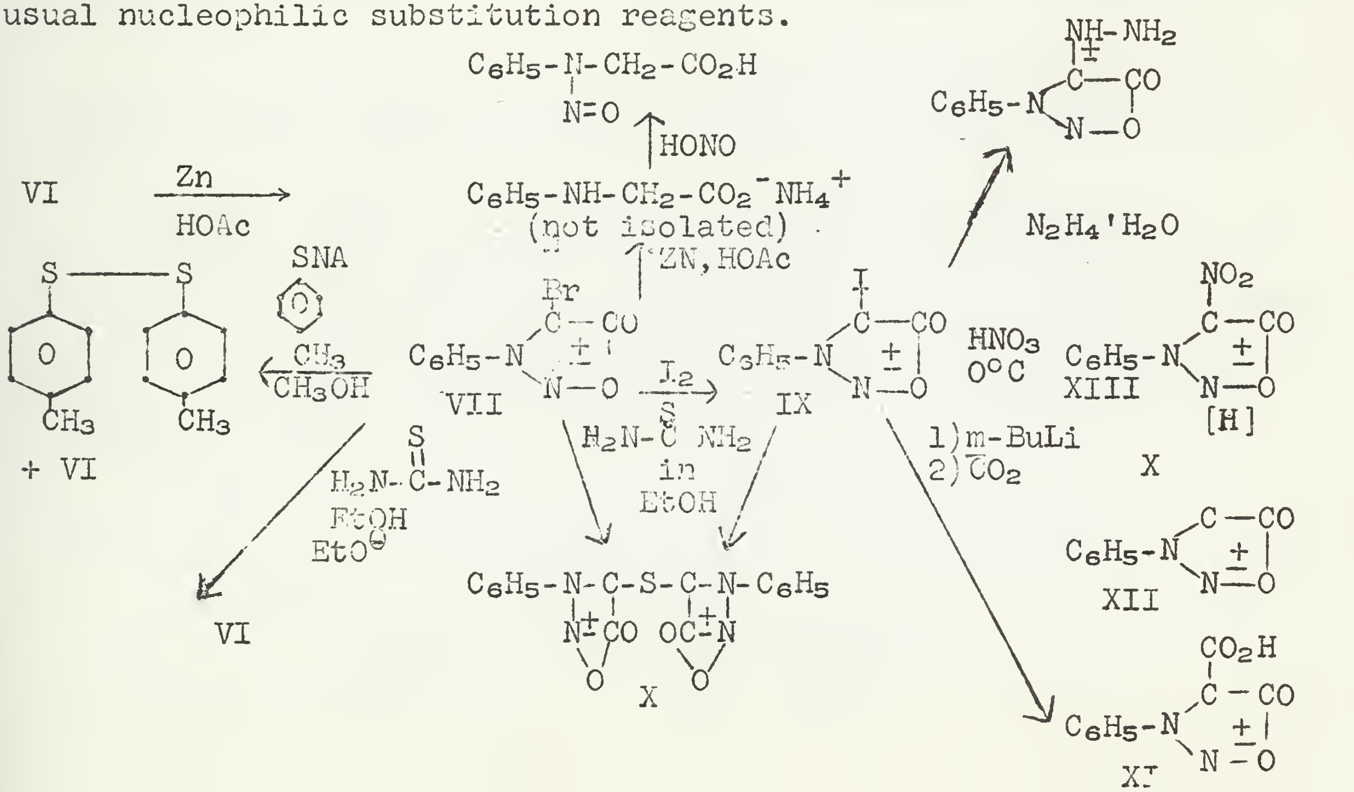
An interesting observation was noted in treatment of VI with bromine in the absence of a base to trap the HBr formed. At slightly elevated temperatures, in carboxylic acid anhydrides as solvents carbon dioxide is evolved and crystalline products are obtained whose structures were shown to be VIII, where R is methyl, ethyl and n-propyl (18). No effort was made to show that HBr alone could effect this transformation.

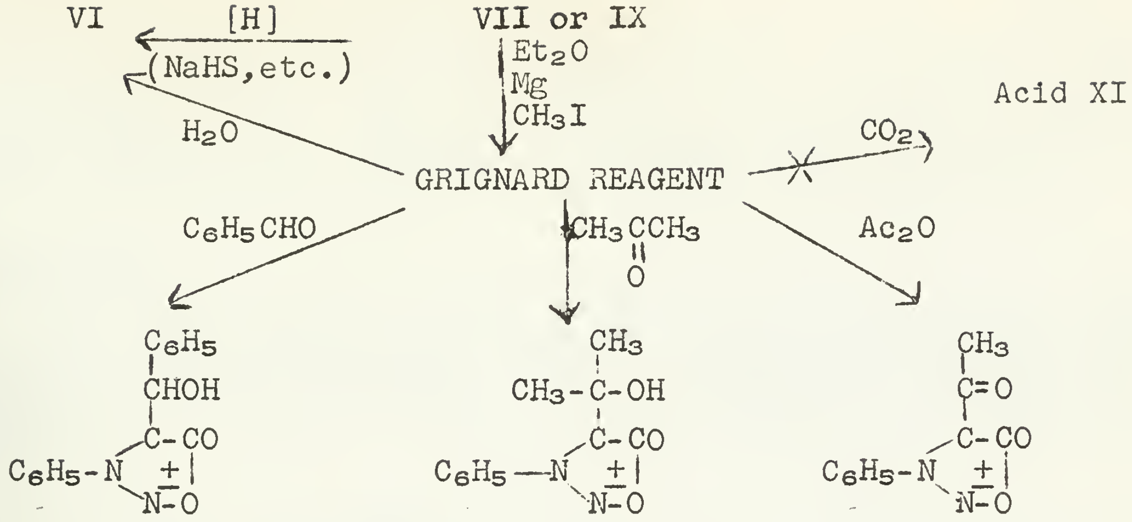


In dilute acetonitrile solution, N-phenylsydnone forms a 1:1 complex with iodine, detectable by a slight shift of the carbonyl absorption peak in the infra-red spectrum (19). These authors claim that the complex forms through the carbonyl oxygen atom, but no attempt to exclude the possibility that a ring nitrogen atom is involved has been made. An early attempt (20) to prepare the C-4 iodo derivative (IX) by treatment of VII with potassium iodide in ethanol yielded only N-phenyl-sydnone and elemental iodine. The C-iodo compound was later prepared (21) from the bromo-derivative under the action of iodine. The halo compounds VII and IX can be reduced to the unsubstituted compound by reaction with sodium hydrosulfide, sodium sulfide, or sodium p-thiocresolate in methanolic solution. More vigorous reduction of VII with zinc and acetic acid yields the same product as similar reduction of VI (22), ammonium anilinoacetate. Reaction of VII or IX with thiourea in ethanol produces the bis-sydnone-thio-ether X, but VII on treatment with thiourea in the presence of ethoxide ion, yields only the reduction product VI.

Formation of the Grignard reagent requires the use of a small amount of methyl iodide to initiate the reaction. The Grignard reagent undergoes the standard carbonyl addition reactions, but attempts to prepare the carboxylic acid XI in this way failed. Previous attempts via several routes also were not successful. The synthesis of XI was finally accomplished (23) by carbonation of the lithium reagent obtained upon interaction of VII with n-butyllithium. This acid undergoes the usual reactions, including conversion to the azide. Attempts to prepare the amino-sydnone XII in a Curtius reaction on this azide and by reduction of the nitro compound (XIII) have failed, leading at least one author (23) to question the stability of this amine.

No reaction, except partial decomposition, occurred (20) when VII was treated with silver nitrate, sodium nitrite, sodium phenoxide, acetyl nitrate, guanidine, sodium iodide or potassium cyanide. This demonstrates the inertness of this and other sydnones toward the usual nucleophilic substitution reagents.





OTHER ELECTROPHILIC SUBSTITUTION REACTIONS

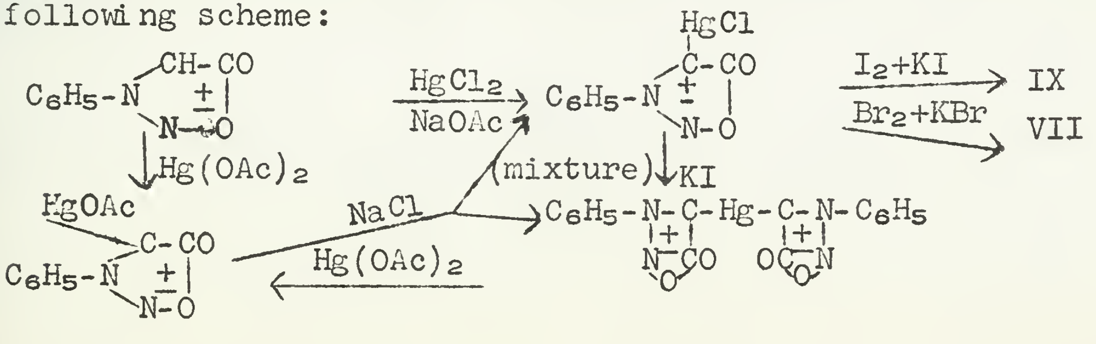
N-Phenylsydnone undergoes nitration in good yield at the C-4 position in concentrated nitric-sulfuric acid mixtures at -5 to -10°C (14,24). Similarly, a series of sydnones has been sulfonated with dioxane-sulfur trioxide in dichloroethane solution at 20-40°C (9). Yields, as barium salts of the C-4 sulfonic acids, approaches ninety percent of theoretical.

C-Acetylation of 3-phenylsydnone and 3-ethylsydnone was successful only upon heating the sydnone with acetic anhydride in the presence of boron trifluoride-ether complex. Other Friedel-Crafts conditions failed (25).

The same authors demonstrated that the C-4 unsubstituted sydnones 3-phenylsydnone and ethylene-bis-3-sydnone undergo deuterium exchange. The latter compound, in a D_2O-C_2H_5OD-D_2SO_4 mixture heated to 100°C for ten hours, had one-third of its C-4 hydrogens replaced by deuterium.

One further indication of the extreme reactivity of the C-4 position is the recent successful formylation of an unidentified sydnone with N-methylformanilide and phosphorus oxychloride (12).

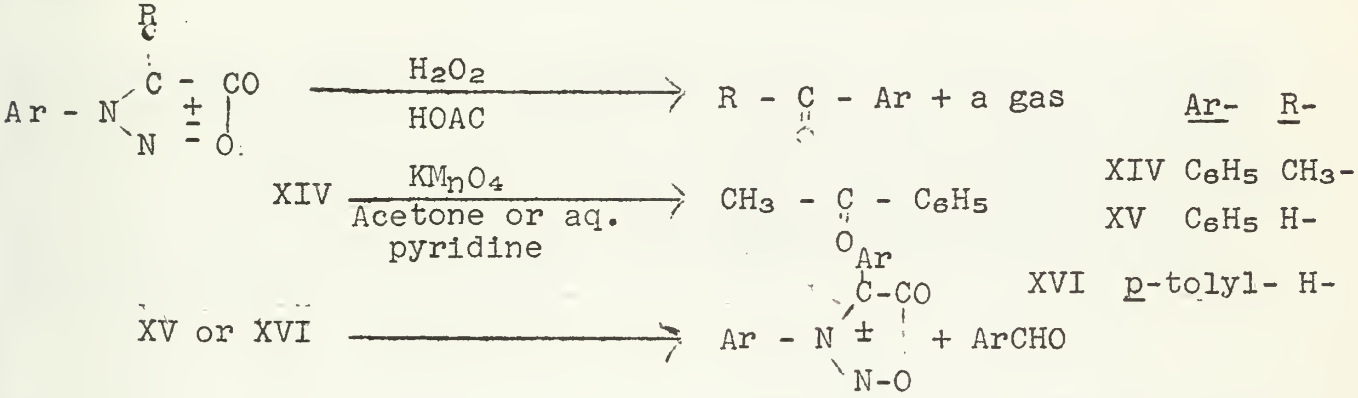
Another reaction characteristic of aromatic compounds is mercuration. Thus, aromatic hydrocarbons are mercurated by treatment with mercuric chloride at 90-160°C for one or more hours. Thiophene is a particularly reactive example of an easily mercurated compound; advantage is taken of this property for its separation from benzene (26). Mercuration of N-phenylsydnone has been accomplished by two independent groups (9,27), as summarized in the following scheme:



The reaction appears to be general, as Tien and Hunsberger have carried out a similar scheme with N-(3-pyridyl) sydnone (12,28). It should be emphasized that the ease of mercuration in the sydnone series is comparable to that of thiophene. The conversion of C-chloromercuri-N-(3-pyridyl) sydnone (XX) to the corresponding mercuri-<u>bis</u>-sydnone (XXl) was effected in high yield at room temperature in pyridine solution, a procedure which fails to convert other chloromercuri compounds to the mercury diaryls (12).

OXIDATION

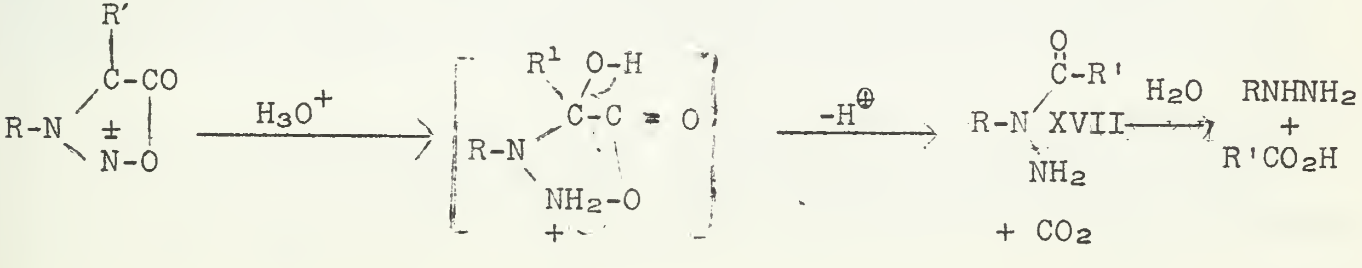
Investigating the aromatic character of the sydnones, Hashimoto and Ohta (29) attempted the oxidation of some 4-methylsydnones to the corresponding carboxylic acids. Insufficient evidence is available to permit a mechanistic explanation of the products at this time:



HYDROLYSIS

Most sydnones are stable in boiling water, and, indeed, this is a common recrystallization medium. Heating with aqueous alkali, however, causes cleavage of the "lactone-type" bond with regeneration of the substituted N-nitroso-amino acid, along with a small amount of 3,4-bond cleavage to give, in the case of N-phenylsydnone, sodium glyoxalate and phenylhydrazine (30). The 4-halosydnones give predominantly cleavage of both the 2,3- and the 3,4-bonds to yield an amine, sodium nitrite and sodium oxalate (31). Reaction of N-phenylsydnone with hot benzylamine yields the benzylamide of N-nitroso-N-phenylglycine, but aniline has no effect, even at 125° C (14).

The sydnones undergo an interesting reaction when heated with aqueous mineral acid, giving a hydrazine, a carboxylic acid and carbon dioxide. This has been shown to be a general reaction, and has been applied to the synthesis of alkyl- (32, 33 and previous references listed therein), aryl-(32), and hetero-aryl-hydrazines (34). The easiest route to the α-acylhydrazines (XVII) involves reaction of a sydnone in benzene solution with one mole of water and hydrogen chloride or bromide (35). Thus a partial mechanism has been postulated (1):



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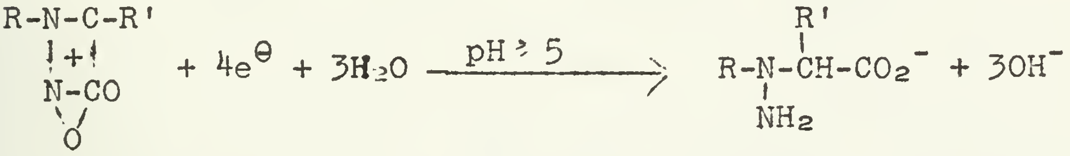
REDUCTION

N-Phenylsydnone resists catalytic hydrogenation except in the presence of highly active catalysts. It may be reduced slowly to the ammonium salt of N-phenylglycine with hydrogen and Adams' platinum oxide catalyst (36). As noted above, reduction to the same product can be accomplished with zinc and aqueous acetic acid (22).

Polarographic reduction in acidic solution yields the same product *via* a six-electron reduction. In alkaline media, however, a pH-independent four-electron reduction occurs:



On this basis, Zuman (37) concludes that the N-O bond is the most easily polarizable at the moment of reaction (but not necessarily in the ground state). Comparison of the half-wave potentials of 3- and 4-substituted sydnones showed that the polar and/or inductive effects of groups in these positions are easily transmitted to the N-O bond being reduced. Thus, for example, the 3-arylsydnones exhibited half-wave potentials which could be accomodated in a modified Hammett relationship:

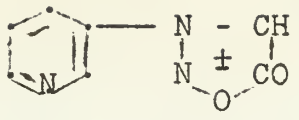
$$(E_{\frac{1}{2}}) - (E_{\frac{1}{2}})_0 = \rho_\pi$$

The value of ρ_π, the susceptibility of the N-O bond reduction to substituents on the aryl group as measured in this way, was +0.17, indicating that electron-withdrawing groups facilitate the reduction. Since these effects are so easily transmitted across the sydnone ring, Zuman concludes that the π-electron system in sydnones is highly mobile, just as in other aromatic compounds, rather than being localized.

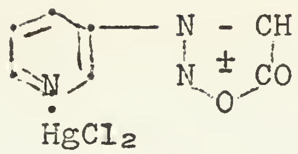
N-(3-PYRIDYL)SYDNONE

In attempting to extend the hydrazine-*via*-sydnone synthesis to the hetero-aromatic series, Tien and Hunsberger prepared N-(3-pyridyl)sydnone, XVIII (38). The surprising discovery was made that this substance is phototropic; *i.e.*, exposure to bright sunlight turns the colorless crystals to a deep blue. This reverts to the colorless form quickly on heating to 80°C, or more slowly on standing at room temperature in the dark. The colorless sydnone can be prepared without special precautions, indicating that in acetic anhydride solution it is stable. The infra-red spectra of the two forms are identical. Electron spin resonance studies show that the blue form interacts with air, forming an unknown radical, as it turns colorless (39). It should be noted that the minimum energy required to bring about the transformation is approximately 70 kcal. (4300 Å), sufficiently high to rupture some bonds.

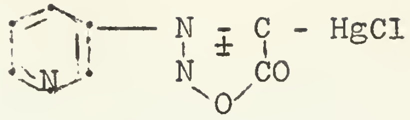
The mercurated derivatives of this sydnone (XIX,XX,XXI) did not exhibit this phenomenon (12), nor did the substituted compounds (XXII through XXV) listed below. The N-(3-pyridyl)sydnone, upon acid hydrolysis, yielded 3-pyridylhydrazine, isolated as the oxalate salt (XXVI) (34).



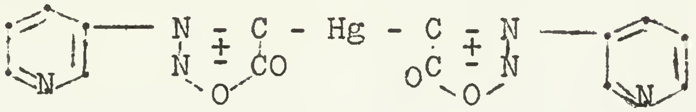
XVIII (38)



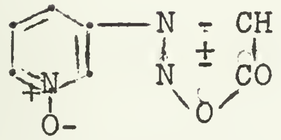
XIX (12)



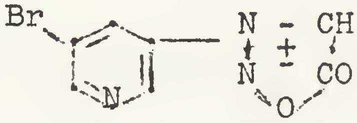
XX (12)



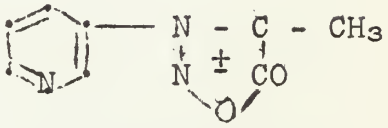
XXI (12)



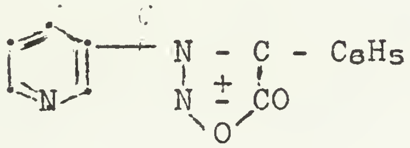
XXII (40)



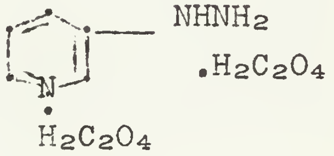
XXIII (40)



XXIV (41)



XXV (41)



XXVI

BIOLOGICAL ACTIVITY

The sydnones have been found to be effective acaricidal and ovicidal agents (15,16), active even against those mites which have become resistant to the other commonly used insecticides.

Attempts to demonstrate physiological activity in XVIII and its mercurated derivatives have been unsuccessful to date (12). A series of 3-methyl-4-substituted sydnones (C-H, C-isobutyl, C-isopropyl, C-benzyl) was prepared to investigate possible amino acid antagonism (42). None, however, showed activity in the tests conducted.

DISCUSSION

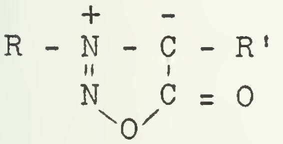
The sydnone nucleus has thus been proven susceptible to an entire series of electrophilic substitution reactions characteristic of aromatic compounds. Dipole moment studies (summarized in reference 1) show that the dipole of the sydnone structure has its negative pole directed toward the carbonyl oxygen atom. The polarographic studies of Zuman (37) demonstrate the mobility of the π-electron system. Infrared spectral studies (9,32) indicate that the characteristic absorption of C-4 unsubstituted sydnones at approximately 3100 cm $^{-1}$ is due to a C-4-hydrogen stretching vibration. The position of this band agrees well with representation IV, *i.e.*, considering the sydnone ring as an electron-poor aromatic system, to be compared with nitrobenzene at 3079 cm.$^{-1}$ (43a). This very briefly summarizes the evidence in favor of formula IV and the aromatic character of the sydnone nucleus.

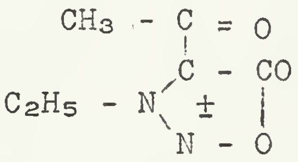
A notable contradiction to these arguments has been pointed out by Earl (30), who argues the resonance energy of the sydnone ring should be great enough to present a barrier to disruption of the ring, if the sydnones are truly aromatic. Since hydrolytic and oxidative cleavage occurs with relative ease, he discounts the aromaticity of the system. This argument, however, assumes that the transition state in these reactions has lost the resonance stabilization of the sydnone system, a condition which may not be true.

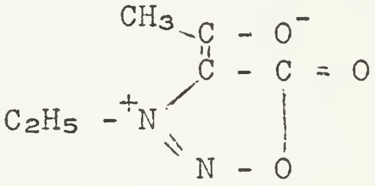
The bulk of the experimental evidence, then, appears to confirm the aromatic character of the sydnone nucleus. Even if aromaticity is granted, however, there remain serious objections to the use of formula IV to represent the structure of the sydnone system. As the Soviet workers have pointed out (9), the published spectra of several sydnones exhibit a clear and very intense absorption band corresponding to the carbonyl stretching frequency. The position of this band, although it varies from 1718 to 1770 cm.$^{-1}$, is commonly about 1740 cm.$^{-1}$, thus characterizing the carbonyl group as comparatively weakly polarized and similar to the carbonyl in α, β-unsaturated lactones (at 1750 cm.$^{-1}$ - see 43 b). Sydnone formula IV fails to successfully represent the relatively high multiplicity of the carbon-oxygen bond, which exceeds that of amides, aromatic ketones, and similar compounds. Comparisons with the carbonyl absorption shift from cycloheptanone at 1699 cm.$^{-1}$ to tropone at 1638 cm.$^{-1}$ (43b,12) illustrates the failure of the postulated analogy between tropone and the sydnones.

The fact that the halo-sydnones do not undergo nucleophilic substitution reactions, and the extreme reactivity of the C-4 position toward electrophilic substitution argue against a formulation such as IV with its positive charge on the ring atoms, at least for illustrating initial attack in such reactions and suggest a major contribution by structures such as XXVII.

The strong tendency of the sydnone ring to donate electron density to the C-4 position and its substituents in the ground state has been substantiated in infra-red spectral studies (25) on 3-ethyl-4-acetyl-sydnone (XXVIII). Two carbonyl bands appear - one at 1740 cm.$^{-1}$ attributed to the sydnone ring carbonyl, and one at 1635 cm.$^{-1}$ attributed to the acetyl carbonyl grouping. The position of the latter indicates considerable polarization, presumably due to a "large contribution" to the hybrid by structures such as XXIX.


XXVII


XXVIII


XXIX

The symbolism of structure III satisfactorily represents the resonance hybrid, immediately draws one's attention as differing from a saturated heterocyclic ring, and avoids assignment of an integral bond multiplicity to the carbonyl link. Therefore, this author believes III is to be preferred at this time over the more explicit, seemingly less correct representation IV, contrary to present practice by most workers.

OTHER MESO-IONIC COMPOUNDS

The reader interested in non-sydnone meso-ionic systems is urged to see references (1) and (44) through (50), which represent a general survey of this field, but are outside the scope of this seminar.

ACKNOWLEDGEMENTS

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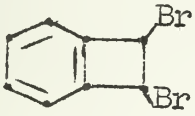
THE CHEMISTRY OF BENZOCYCLOBUTENE AND ITS DERIVATIVES

Reported by R. R. Haynes January 12, 1961

This report concerns systems in which a cyclobutane ring is fused on to an aromatic system, but excludes those generally classified as 1,2-diphenylenes. A very short general review of the subject was given by Cava (1) in the spring of 1959; the present review deals principally with material published since that time.

In 1910, Finkelstein (2) studied the product of the reaction of α,α,α',α'-tetrabromo-o-xylene with NaI in boiling EtOH. The substance was oxidized to phthalic acid when treated with HNO_3, and it regenerated the tetrabromoxylene when heated in a sealed tube with Br_2. The product, $C_8H_6Br_2$, was assigned structure I, 1,2-dibromobenzocyclobutene.

This field of organic chemistry then lay dormant for the next 46 years, although during this time, comment was made by Baker (3) that there was doubt about the stability of benzocyclobutene II because of the considerable strain upon the rings with no compensating added resonance.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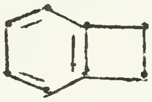
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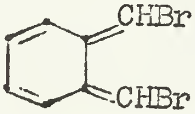
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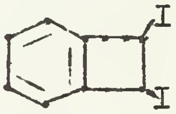
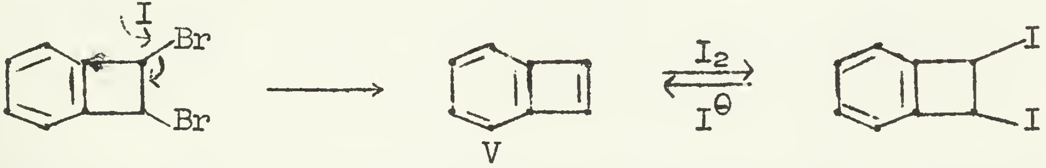

IV

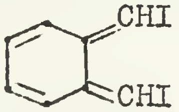
In 1956, Cava and Napier (4a,b) repeated Finkelstrin's work, and probed further into the reactions and structure of the dibromo-compound.

The quinonoid structure III was eliminated since the dibromocompound failed to react with refluxing Br_2 or with maleic anhydride. It was discovered that if α,α,α',α'-tetrabromo-o-xylene was allowed to react with an excess of NaI in boiling ethanol for a period of 2 days, or if the dibromo compound was allowed to react under the same conditions for 8 days, a diiodo-compound, $C_8H_6I_2$, assigned structure IV, was formed. Cava and Napier (5) utilized this diiodo compound to prepare, for the first time, benzocyclobutene II. When hydrogenated over Pd/C at room temperature, the diiodo compound yielded a volatile hydrocarbon, C_8H_8, that boiled at 150°, possessed a mass spectrograph peak at 104 m/e, an IR band at 10.05μ characteristic of a cycloalkane ring, and an UV spectrum similar to that of indane. It is of interest to note that although the tetrabromoxylene reacts with NaI to give both the dibromo and the diiodo compounds, no 1-bromo-2-iodo compound was found. Since the dibromo compound I was completely stable to boiling ethanol, and was also recovered unchanged after two days reaction with ethanolic KOAc, it was concluded that it was inert to S_N1 and S_N2 type reactions. The likely remaining path of reaction is the attack on the bromide by I^-. This type of reaction, that of a vicinal dibromide with I^- is well known, and it occurs with the formation of an olefin and I_2. In the usual case, where the bromine atoms can assume a completely transoid configuration to each other, maximum overlap is achieved in the transition state for the elimination, and the reaction proceeds smoothly. If on the other hand, steric factors prevent the complete coplanarity of the bromine atoms the reaction will be more sluggish. From steric considerations, it is assumed that of the two possible cis and trans

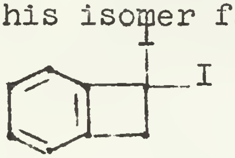
geometrical isomers of I, the trans is the more stable, since the cis would possess very great repulsion due to the inflexibility of the cyclobutane ring. However, because of this inflexibility, the two trans bromine atoms would be prevented from assuming a position even approaching coplanarity with the carbon atoms bearing them in the transition state for their elimination by I^-. From this consideration, it is not surprising that this reaction required several days to go to completion. But the most curious thing about the reaction is that the olefin, benzocyclobutadiene V, is not the major product, but rather the diiodide IV. The authors conclude that the diene V is formed but that its double bond is so reactive it easily undergoes addition of I_2.



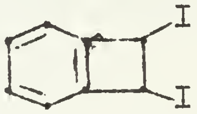
Jensen and Coleman (6) ran a product study of the reaction yielding the diiodo compound, and separated two isomeric $C_8H_6I_2$ compounds, one (91.6%) melting at 63°, and the other (8.4%) melting at 150°. The trans structure was assigned to the lower melting solid on the basis of dipole moment measurements, and on the probable instability that would be expected in the cis compound. The other isomer could have structure VI, VII, or VIII, since they would all be oxidized to phthalic acid. However, this isomer failed to add halogen at room temperature or to react with maleic anhydride when heated in benzene for 15 hrs. From this latter treatment some of the lower melting isomer was recovered. On the basis of this evidence, the higher melting isomer was assigned the cis structure. The equilibration of the two isomers was studied in refluxing ethanol-NaI (light absent), and ethanol solution with exposure to light. The composition of the equilibrated mixture was shown to be 9% and 6% cis, respectively. These equilibrations probably do not proceed via a carbonium ion, since only a negligible amount of ether was formed during a 12 day run. A possible mechanism was suggested whereby the isomerization proceeds through benzocyclobutadiene V. This would further suggest that the two compounds are cis-trans isomers. The interconversion by light, occurring at very low illumination, suggests a chain process involving the iodine atom.



VI



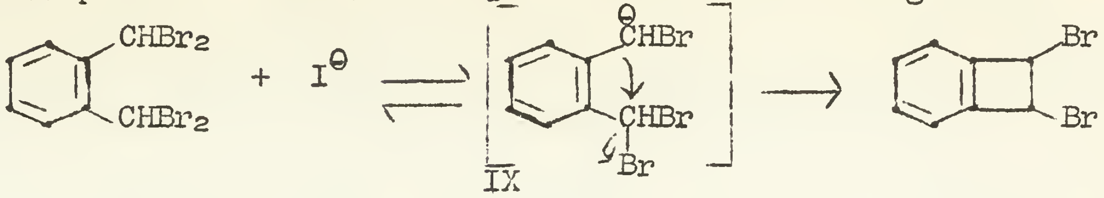
VII



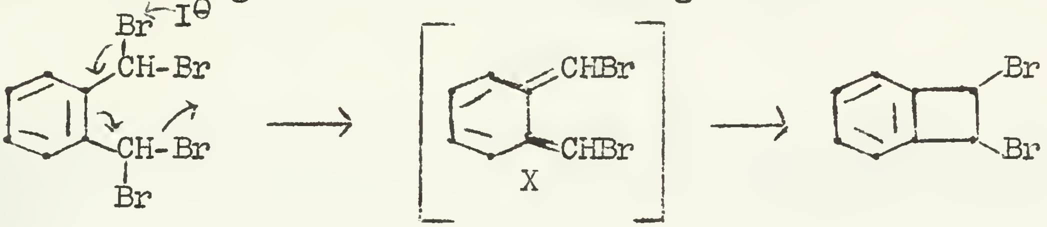
VIII

Two mechanisms for the conversion of tetrabromo-*o*-xylene to dibromobenzocyclobutene have been postulated. Jensen and Coleman (6) proposed the formation of the carbanion IX which displaces the Br^- from the opposite and very close carbon atom. This process must be concerted to a large extent or else the base could abstract a proton from the solvent (EtOH). Such a mechanism would give predominately the trans isomer. Unlike the diiodo compound, the

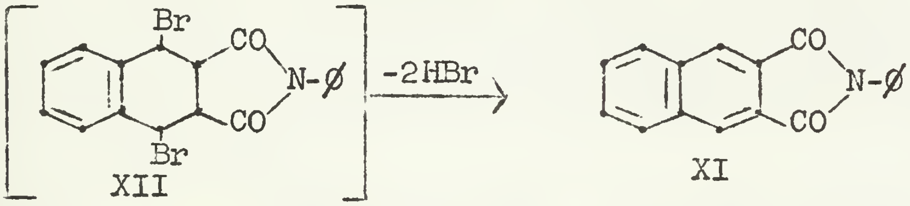
dibromo compound has never been found in the cis configuration



Cava and Napier (5) postulated a quinodimethane intermediate X which then undergoes intramolecular ring closure.

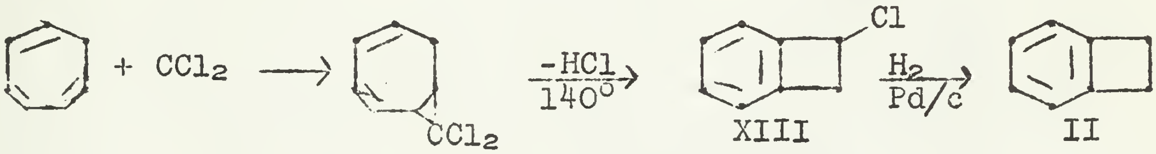


The proof of the latter mechanism was shown when Cava, Deana, and Muth (7) trapped the quinodimethane intermediate by menas of N-phenyl maleimide. When tetrabromo-o-xylene and NaI were warmed in DMF at 60° for 24 hours in the presence of N-phenylmaleimide, none of the dibromobenzocyclobutene or the analogous diiodo compounds were formed. The sole product isolated was N-phenyl, 2, 3-naphthalimide XI. This product was thought to arise from the loss of two moles of HBr from the Diels-Alder adduct XII. The possibility of this adduct arising from the reaction of 1, 2, dibromobenzocyclobutene was excluded on the groundsthat the dibromo compound did not give an adduct under the same reaction conditions for 6 hours.



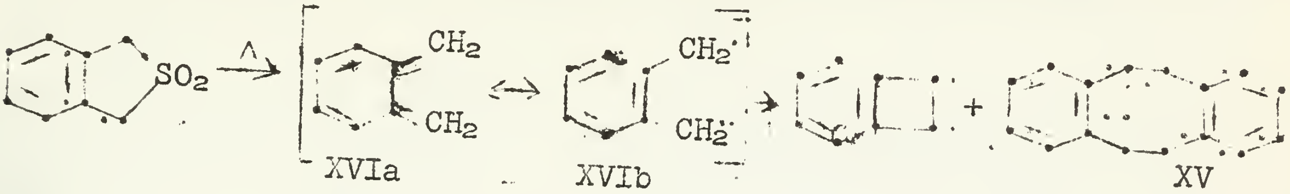
PREPARATION OF BENZOCYCLOBUTENE AND ITS DERIVATIVES

The first successful preparation of benzocyclobutene by hydrogenation of the diiodocompound was soon followed by other reports on ways to obtain the C_8H_8 hydrocarbon. Bickell and TerBorg (8) in attempting to prepare chlorocyclooctatetrene from the reaction of dichlorocarbene with cycloheptatriene obtained, instead, chlorobenzocyclobutene XIII, which could be hydrogenated to the hydrocarbon II.

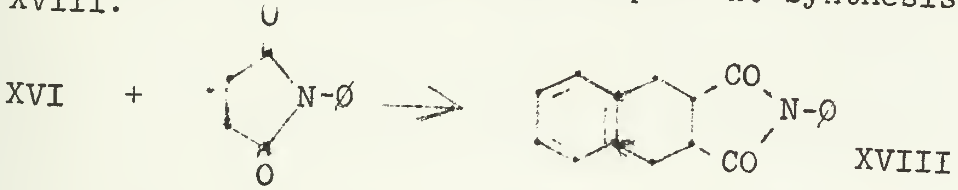


Cava and Deana (9) prepared benzocyclobutene II by pyrolysis of the sulfone XIV. The sulfone was obtained by peracid oxidation of the sulfide which was prepared by the action of Na_2S on α,α'-dibromo-o-xylene. Pyrolysis gave a 16% yield of a volatile liquid containing benzocyclobutene and o-xylene (4:1) when heated in the molten state. 1,2,5,6-Dibenzocyclooctadiene (4%) was isolated from a polymeric residue. The three products were postulated as arising from the very reactive o-quinodimethane XVI. This intermediate could give rise to benzocyclobutene by intramolecular cyclization, the diene XV by dimerization, and o-xylene by abstraction of hydrogen from

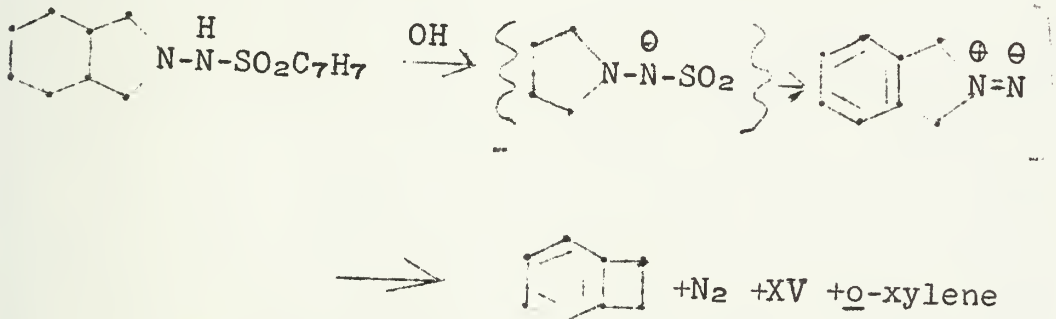
unreacted sulfone. The yield of the desired product increased little when the pyrolysis was effected in boiling diethyl phthalate, but the yield of the symmetrical benzocyclooctatriene XV rose to 48% Carrying out the pyrolysis at 770° on a Nichrome heating coil at low N_2 pressure resulted in the isolation of benzocyclobutene in 67% yield.



The proof of the intermediate XVI was shown by trapping it in reaction with N-phenylmaleimide to give the Diels-Alder adduct XVII. This adduct was prepared by an independent synthesis for comparison to XVIII.



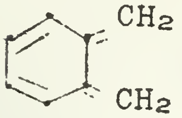
The quinodimethane type structure XVIa has received some attention from Roberts, Streitweiser, and Regan (10). They have calculated a free valence of 0.96 at the terminal methylene groups, a bond order of 1.78 for the exocylic double bond, and a delocalization energy of 1.95β for the molecule. Such a high free valence suggests that this substance should dimerize and /or polymerize readily. The action of base on N-(p-toluenesulfonamido-) dihydroisoindole XVIII was used by Baker, McOmie, and Preston (11) to prepare benzocyclobutene. o- Xylene and 1,2,5,6-dibenzocyclooctadiene XV were the side products.

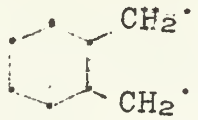


Further application of the pyrolysis of sulfones was used by Cava and Shirley (12) to prepare naphtho(b)cyclobuteneXIX. The sulfone precursor of the hydrocarbon was prepared by starting with 2,3-bis-(bromomethyl)-naphthalene, and treating it with aqueous Na_2S followed by oxidation to the sulfone with peracetic acid. Thehydrocarbon XIX melted at 86.5° and possessed an UV absorption very similar to 2,3-dimethylnaphthalene. The sulfone was pyrolyzed in boiling diethyl phthalate resulting in a 60% yield. This yield is

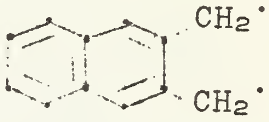
in sharp contrast to the very low yield of benzocyclobutene from

its sulfone precursor under the same conditions. The authors rationalize this by saying that of the intermediates XVIb and XXIb, the latter would be expected to be of lower energy content relative to its polyene resonance form XXIa than is the case in the benzene series (XVIa and XVIb). In other words, the diradical XXIb is less stabilized by its polyene resonance form XXIa than in the benzene case. As a result of this higher degree of diradical character,

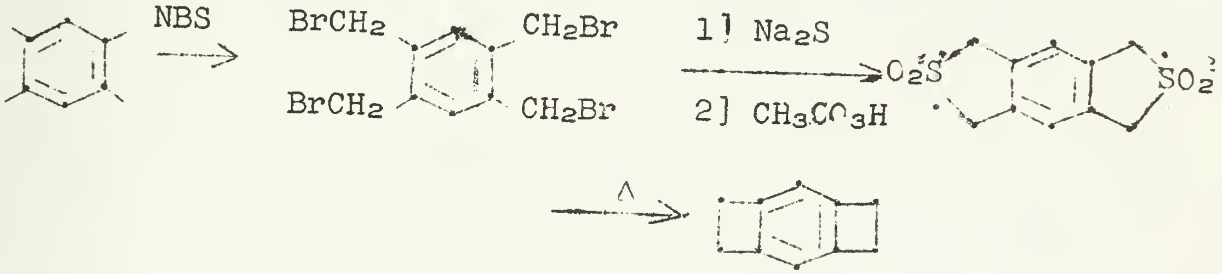

XVIa


XVIb


XXIa


XXIb

it undergoes a more rapid intramolecular ring closure under conditions where the benzene analog is long-lived enough to undergo mostly dimerization to XV. However, the intermediate XXIa was stable enough to be trapped by a dienophile scavenger in the same manner as XVIa. One of the most interesting compounds prepared in this series is benzo (1,2:4,5) dicyclobutene XXII. Cava, Deana, and Muth (13) prepared this compound from durene according to the scheme given below.

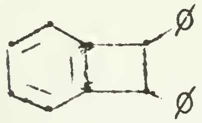


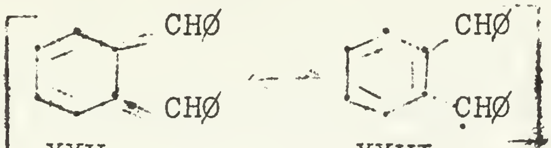
XXII

The pyrolysis was achieved by passage through a Nichrome coil heated to red heat. The volatile hyrocarbon $C_{10}H_{10}$ isolated in a 40% yield, melted at 101°, and was oxidized to pyromellitic acid when treated with permanganate. A comparison of the UV spectrum of durene with the dicyclo compound shows a bathochromic shift of 10mu,and a 10 fold increase in the extinction coefficient for the latter. This may well be due to the increase in strain present in the compound. Jensen and Coleman (14) prepared 1,2-diphenylbenzocyclobutene XXIV by the action of NaI on α,α'-dibromo-α,α'-diphenyl-o-xylene and by the action of base on α-bromo-α,α'-diphenyl-o-xylene. XXIII melts at 94-95° and has an IR band at 10.0μ which is characteristic of a cycloalkane ring. Its molar extinction coefficient in the UV spectrum are in agreement with the sum of those of two toluene molecules and a benzocyclobutene molecule. This evidence suggests that the major species in solution is XXIV and not XXV or XXVI. One of the interesting things about the diphenyl derivative is its high reactivity toward a number of reagents under conditions that benzocyclobutene is inert. With a molar amount of maleic anhydride in CCl_4 at room temperature, a nearly quantitative yield of the Diels-Alder adduct is formed within 24 hours. Treatment of XXIV with SO_2 for 15 min. in refluxing CCl_4, or for 23 hours at room temperature, gives a nearly quantitative yield of the sulfone XXVII. This sulfone when decomposed yielded chiefly 9-phenyl 9,10-dihydroanthracene. XXVIII. The diphenyl compound was hydrogenated over Pd/C at room temperature to o-dibenzylbenzene. The authors conclude from these data that there is an equilibrum in solution at room termperature between XXIV,XXV, and XXVI. However,

the low degree of activity of an ethanolic, water, basic, and H_2O - oxygen solutions of XXIV is not consistent with the high degree of activity expected from compounds with structures of the type XXV and XXVI.

Therefore, the authors do not exclude reaction directly with XXIV. For example, maleic anhydried could react with the diphenyl compound by a four - center type mechanism. No further work has been published to prove or disprove either concept. Blomquist and Meinwald (15)

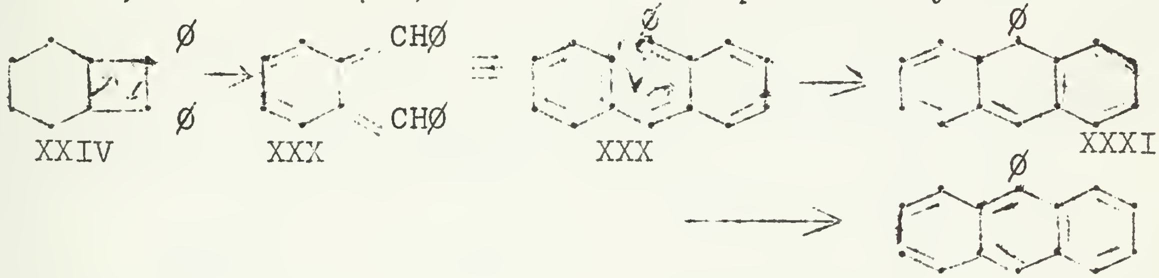

XXIV



XXV XXVI

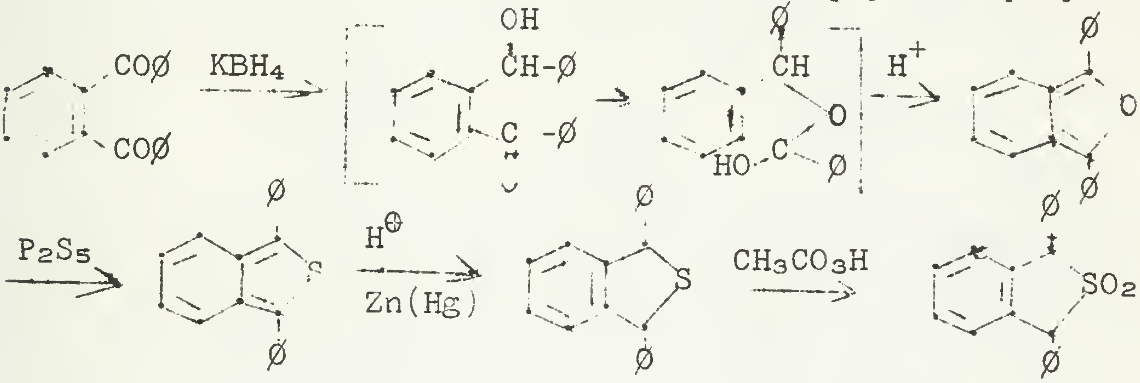
XXIX

attempted preparation of 1, 2-diphenyl-benzocyclobutene XXIV by a dehydrogenation-decarboxylation reaction on a stereoisomeric mixture of the dicarboxylic acid XXIX. However, a mixture of two hydrocarbons shown to be 9-phenylanthracene and o-dibenzylbenzene proved to be the only products formed. It is thought that at the temperature required for the hydrogenation - decarboxlyation ($300-350^\circ$), the cyclobutane ring in diphenylcyclobutene would open up to the diphenyl derivative of quinonedimethane XXX. This structure could then cyclize readily to the dihydroanthracene XXXI, which under the reaction conditions, could further dehydrogenate to 9-phenylanthracene. Cava, Mitchell, and Deana (16) have also attempted the synthesis of the



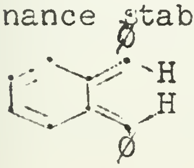
XXIV XXX XXX XXXI

hydrocarbon XXIV by pyrolsis of the sulfone XXXII. Its preparation is shown below. This sulfone had differnet physical properties than

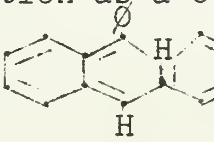


XXXII

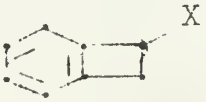
the sulfone XXVII Jensen (14) prepared. The authors feel that the sulfone XXXII is probably the trans compound, because the sulfide precursor is derived from a metal-acid reduction, a process that favors the more thermodynamically stable product. The sulfone XXVII is probably the cis compound, since SO_2 might be expected to add in a concerted manner to the quinodimethan structure XXV or at least take part in a transistion state resembling XXV. Of the possible cis and trans structures that can be drawn for XXV, only XXVa, which could give the cis sulfone, fulfills the steric requirements for full resonance stabilization as a coplanar structure.



XXVa



XXVb

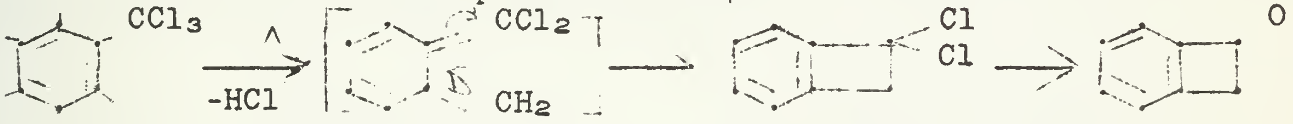


XXXIII

a x=Br
b x=Cl
c x=OH

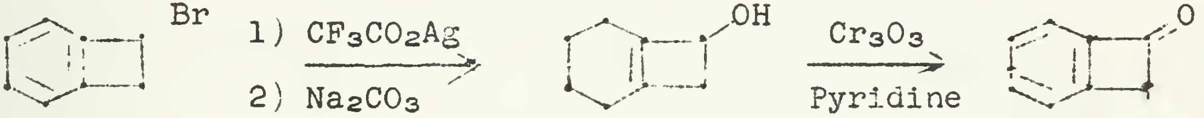
Mild thermal isomerization of XXVa to XXVb would lead to a structure with less overlap stabilization, and a more favorable conformation for ring closure to XXXI. However, when the trans sulfone was pyrolyxed in boiling diethyl phthalate, a 94% yield of 9-phenyl,9,10-dihydroanthracene XXXI was obtained. This product was explained in the same manner as in the preceding work of Blomquist (15). The authors trapped the quinodimethane type intermediate with 1,4-naphthoquinone. However, it should be stated that since Jensen was able to bring about reaction of diphenylbenzocyclobutene with SO_2 to form the Diels-Alder adduct, that such might well be the case here.

1-Bromobenzocyclobutene XXXIIIa can be prepared by the reaction of N-bromosuccinimide on the hydrocarbon; however, the dibromo compound has not been found to form upon further reaction (5). The monochloro compound XXXIIIb has been reported by Ter Borg (8). Hart and Fish (17) discovered that when trichloromethylpentamethylbenzene is heated at, or above its melting point, one mole of HCl per mole of compound is liberated, and a crystalline compound, $C_{12}H_{14}Cl_{29}$ melting at 73-74°, is formed. This substance gave an immediate precipitate with $AgNO_3$, and work up of this reaction mixture yielded a ketone XXXV, which could also be obtained by hydrolysis of the dichloro compount with aqueous acetone. A yield of 89% was obtained in the overall reaction making it an excellent means of preparing benzocyclobutenes. There was also obtained an analogous compound from mesitylene. A deuterium exchange experiment was conducted on the ketone XXX, and it was found that the receovered product contained considerable C-D absorption at 4.48μ.

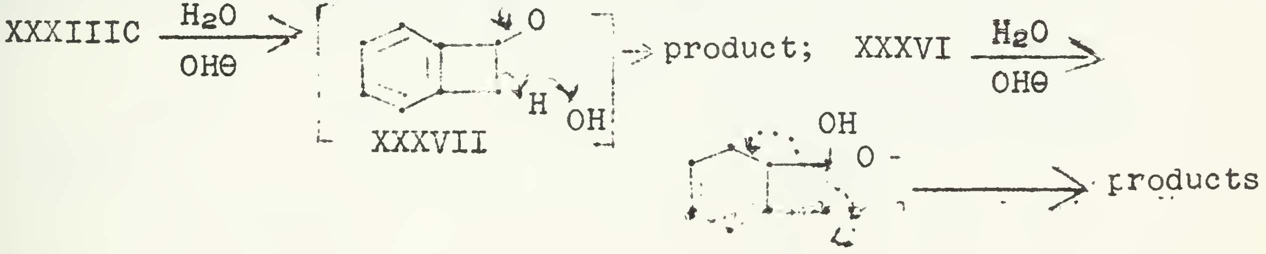


XXXIV XXXV

Cava and Muth (18) have prepared the alcohol XXXIIIc, and from it the ketone XXXVI by chromic oxide oxidation. The alcohol proved to be stable to acid, but reacted readily with base to form o-tolualdehyde in 72% yield, the driving force for the reaction being the relief of strain in the ring system. It is thought that the reaction proceeds through cleavage of the alkoxide XXXVII. The ketone showed the same type of stability, and it reacted with base to yield both o-toluic acid and phenylacetic acid in equal amounts. Here, the alkoxide intermediate XXXVIII cleave indiscriminately at either side of the carbonyl. The IR carbonyl band of the ketone is of interest



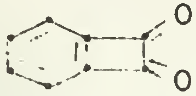
XXXIIC XXXVI



XXXVII XXXVIII

as there are present two closely spaced carbonyl bands at 5.640 and 5.695μμ Although the authors give no explanation for this phenomena, it is felt that this is an example of Fermi resonance (19,20). The diketone XXXIX has been prepared in 75% yield by Cava and Napier (21) by reacting 1,2-diiodobenzocyclobutene with aqueous $AgNO_3$ for eight

days followed by treatment of the dinitrate with Et_3N. The diketone was oxidized to phthalic acid and could be converted to phthalaldehydic acid by action of base. Cava and Pohl (22) have studied further reactions of the diketone, and by means of a Wittig reagent prepared 1,2-dicarbomethoxymethylene-benzocyclobutene XXXX and the corresponding keto-methylene compound XXXXI. The dicarbomethoxy compound failed to undergo reaction with tetracyanoethylene. The Wolff rearrangement



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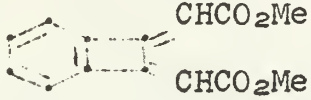

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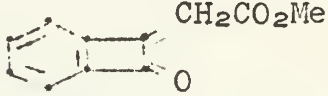
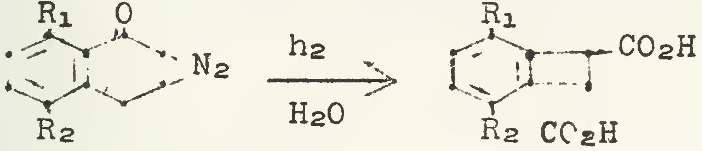
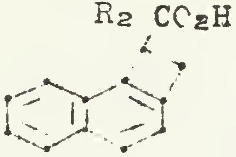


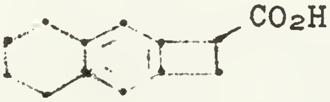
XXXXI

has been utilized for the preparation of other benzocyclobutene derivatives (23,24,25). From this reaction, Cava and co-workers prepared the series XXXXIIa,b,c., and Horner, the benzocyclobutene derivatives shown below. Electrophilic substitution, in the form of nitration, on

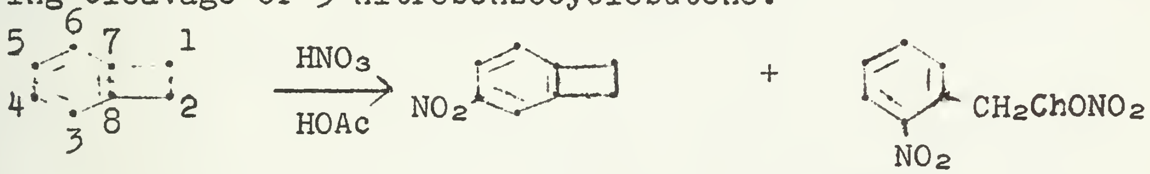


XXXXII a) $R_1=R_2=Me$
b) $R_1=R_2=H$
c) $R_1=Cl; R_2=Me$





benzocyclobutene has been studied by Horner (26). The products of the reaction were shown to be 4-nitrobenzocyclobutene XXXXIII and β - (2-nitrophenyl-)ethyl nitrate XXXXIV, the latter compound arising from ring cleavage of 3-nitrobenzocyclobutene.



XXXXIII

XXXXIV

A more quantitative examination of the reactivity of benzocyclobutene towards electrophilic substitution has been reported by Jensen and Maciel (27). To test the possible effects of bond compression on the rate of substitution in the benzene nucleus of benzocyclobutene, the authors conducted a kinetic study of benzoylation of a series of compounds similar to benzocyclobutene. This reaction was shown to be very sensitive, as the introduction of a methyl group into the benzene nucleus increased the reaction rate by a factor of 132. The compounds selected as standards were o-xylene, indane, and tetralin. With the standard compounds, the reaction went to at least 90% completion, but the benzocyclobutene reaction went only to 50%, and then the reaction fell off rapidly with the solution turning progressively blacker. The initial relative rates are given in table I

TABLE I

ArH	Relative Initial Rate
Benzene	1/1700
Toluene	1/13
o-Xylene	1
Benzocyclobutene	2.8
Indane	1.9
Tetralin	2.3

Two possible reasons are given for benzocyclobutene reacting at a normal rate. One is that the resonance stability of the compound is uneffected by the bond compression present, the second, that there is a decrease in the stability of benzocyclobutene as a result of bond

compression, but there is an equal degress of instability present in the transition state.

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SEMINAR TOPICS

II Semester 1960-1961

SALT EFFECTS IN UNIMOLECULAR SOLVOLYSIS REACTIONS

Reported by C. F. Heins February 13, 1961

The first signigicant investigation of salt effects in unimolecular reactions was made by Bateman, Church, Hughes, Ingold and Taher in 1940 (1). They studied the effects of LiCl, LiBr and NaN_3 on the solvolysis of tertiary butyl (2) and benzhydryl halides (3-5) in aqueous acetone, and observed two distinct phenomena. The first was a rate enhancement, which was ascribed to salt increasing the ionic strength of the solution. They reasoned that the transition state in these reactions was a dipole, stabilized by an atmosphere of solvent molecules. Adding an ionic species to the medium would provide a better environment for the solvation of this transition state. On the basis of this model, equation (1), relating rate of solvolysis to ionic strength and dielectric constant of the solution was derived.

$$(1) \quad \log k_t = \log k_t^{o} + \frac{0.912 \times 10^{18} \ \sigma\mu}{D^2 \ T^2}$$

k_t^{o} = rate in absence of salt
σ = z^2d, a measure of the charge separation in the transition state.
μ = ionic strength
D = dielectic constant

Equation (1) was tested by comparing σ values obtained by substituting experimental values in this equation, with σ values calculated from the defining equation of this parameter, (2) $\sigma - z^2d$; Z is the amount of charge transfer from carbon to the leaving group in the transition state (z is considered to be 0.5 in this case) and d is the distance of charge separation in the transition state. Table I lists σ values obtained in these two ways.

TABLE I

RX	σ(1)	σ(2)	RX	σ(1)	σ(2)
t-BuBr	0.74	0.65	$(C_6H_5)_2CHBr$	1.74	-
$(C_6H_5)_2CHCl$	1.61	-	$(MeC_6H_4)_2CHCl$	2.73	-

Larger σ values in the case of benzhydryl halides were explained by assuming considerable delocalization of the positive charge; a p-methyl group should greatly aid this process.

A second observed effect was a common-ion rate depression. For example, in the hydrolysis of p,p'-dimethylbenzhydryl chloride in 85% acetone, the reaction proceeded in the presence of 0.0555 M. NaCl at a rate roughly half that in the absence of salts; when 0.05 M. LiBr was used the rate was increased by a factor of 1.36. (5) This decrease in the rate of solvolysis was explained by proposing that the rate-determining ionization was reversible and the addition of a common ion increased the reversal of this step.

$$(3) \quad RX \rightleftharpoons X^- + R^+ \xrightarrow{SOH} ROS + H^+$$

It was proposed that all the experimental observations could be explained fairly well both quantitatively and qualitatively in terms of these two phenomena.

It is now clear that this theory was inadequately tested. The semilogarithmic relationship between rate and salt concentration predicted by equation (1) for uni-unimolecular salts was verified for a single case only, that of the effect of two concentrations of NaN_3

on the hydrolysis of p-tertiary butyl benzhydryl chloride in 90% acetone. Although here a fairly good fit was obtained, in many cases a linear relation between rate and salt concentration gives a much better correlation (22,37). The effects of too few salts were measured. Had $LiClO_4$ been employed during the solvolysis of tertiary butyl chloride in 90% acetone, it would have been found that this salt accelerates the reaction only half as much as either LiCl or LiBr (10). The possibility of there being specific salt effects, shown to be of importance in many instances (6,7,8), was not taken into account.

In 1942, Lucas and Hammett observed that in the hydrolysis of tertiary butyl nitrate in 80% dioxane, different salts exhibited a striking degree of specificity on the rate (6). 0.1 M NaCl caused a 10% increase, 0.1 M $NaClO_4$ a 16% increase, and 0.1 M. NaOH caused a decrease in the rate of solvolysis by more than 4%.

TABLE II

Effect of 0.1 M. salt on the rate of solvolysis of tertiary butyl nitrate.

t,°C.	% dioxane in solvent	Solute	% change in specific rate	association of anions with water. (in order of decreasing association.) (11)
10	60	NaOH	- 4.28	OH
25	75	NaCl	10.30	Cl
25	75	KNO_3	16.12	Br
10	60	$NaClO_4$	16.48	NO_3
25	75	$HClO_4$	36.62	ClO_4
25	75	$NaClO_4$	37.21	

These considerable variations were explained by suggesting that different salts affected the water activity of the solvent to different extents. When a salt is added whose anion is capable of associating with a considerable number of water molecules, the medium can become "dehydrated" to such an extent that hydrolysis of the alkyl nitrate occurs more slowly. Table II also lists the association of anions with water in decreasing order (11). It can be seen there is an inverse relation between rate enhancement and ability to associate with water for these salts. Hydroxide, which has a strong affinity for water, acts as an effective drying agent on the solvent.

A different interpretation of these results was made by Benfey, Hughes and Ingold (12). They studied the solvolysis of tertiary butyl bromide in 80% ethanol and 60% dioxane in the presence of sodium hydroxide, as well as the methanolysis of benzhydryl chloride in anhydrous methanol in the presence of sodium methoxide. In the presence of these salts the solvolysis was considerably more retarded than in the presence of other non common-ion salts.

TABLE II

Substrate	(salt)	$10^5 k_1$	% change
$(C_6H_5)_2CHCl$	in dry MeOH at 15°		
0.094	none	25.2	-
0.101	NaOMe (0.113)	25.1	0
0.094	NaBr (0.100)	30.6	+21
0.095	NaI (0.100)	31.0	+23
......			
t-BuBr in 80%	EtOH at 25°		
0.097	none	35.8	-
0.100	NaOH (0.105)	36.1	+1
.....			

Substrate	(salt)		% change
t-BuBr in 60%	dioxane at 10°		
0.103	none	28.9	-
0.106	NaOH (0.104)	28.7	-1

It was pointed out that with anhydrous methanol a "drying effect' could not occur, hence in this case Hammett's explanation is not applicable. The authors proposed that the decrease in rate is due to a lyrate ion (that is, a hydroxide or alkoxide ion) removing a proton from the solvation shell of the transition state. The proton defect that is generated impairs more strongly the solvation of the forming halide than it aids the solvation of the developing carbonium ion.

This "lyrate ion" theory has been criticised recently by Swain(13) In the hydrolysis of triphenyl-methyl fluoride in 50% aqueous acetone, he found that the rate, as measured by acid titration, is increased by the addition of sodium perchlorate but decreased by the addition of sodium chloride. This decrease cannot be due to the formation of triphenylmethyl chloride, since the latter compound is hydrolyzed much faster than the fluoride in 50% acetone even in the presence of 0.5 M. NaCl. It is obvious that the retardation cannot be due to lyrate ions, since none have been added. Swain proposes that association between salt and water, in a manner analogous to that proposed earlier by Hammett, accounts for the rate reduction. Swain also suggests that in the solvolysis of benzhydryl chloride in absolute methanol that was carried out by Ingold and coworkers (12), the decrease in rate that was observed upon the addition of sodium methoxide could result from association between alkoxide and alcohol; that is, there could be an activity coefficient effect stabilizing reactants (including solvent) with respect to transition state.

Taft has been able to measure the effects of salts on the activity coefficients of tertiary butyl chloride and the transition state for its hydrolysis in aqueous solution. (7,14)

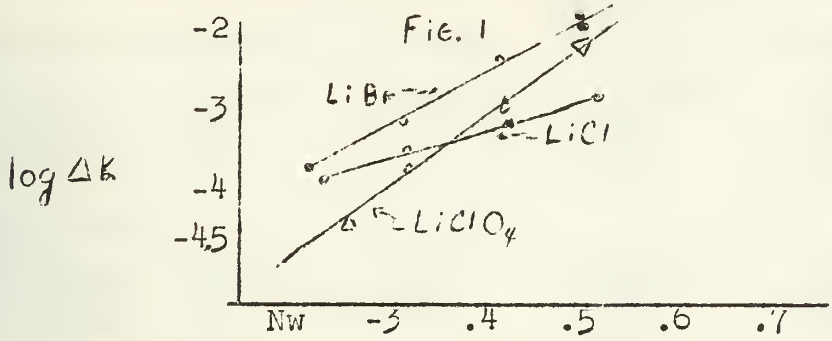
For tertiary butyl chloride, a salting pattern typical for non-electrolytes was observed. Increasing both cation and anion size of the salt increases solubility of the non-electrolyte (7). This same type of behavior has been observed in the case of benzene (15).

Electrolyte effects on the transition state were quite unusual. The activity coefficients showed a remarkable degree of independence of the cation employed. Large cations promoted very little salting in. The anions exhibited substantial effects on the activity coefficients, but the order was not the usual one for ordinary non-electrolytes. The high degree of specificity exhibited by various salts indicated that the ion atmosphere model of Hughes and coworkers does not deal even qualitatively with the salt effects observed for the transition state of this reaction.

The salt effects on the conventional rate constant, k_c, for the solvolysis of tertiary butyl chloride can be determined by measuring the difference in the Setschenow parameters obtained for the ground state and transition state. It was found that salts exhibit a large degree of specificity on k_c, some considerably retarding the rate. It has been suggested that this retardation is due to a decrease in the ability of the water to solvate the chloride ion being formed in the transition state. Solvation of the anion of the added electrolyte interferes with the ordering of water molecules to such an extent that optimum orientation of the water about the incipient halide is no longer possible (7).

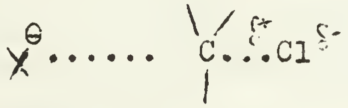
Spieth and Olson have made a study of electrolyte effects in the hydolysis of tertiary butyl chloride in aqueous acetone which indicate that there are specific salt effects which can vary considerably

depending upon the nature of the solvent (10). Using 0.1 N LiCl, LiBr and $LiClO_4$, they found that as the water content approaches zero chloride ion gives the largest accelerating effect. (In approximately 90% acetone, LiCl and LiBr roughly doubled the rate , $LiClO_4$ increased it by 50%). As the acetone content approaches zero, the order is inverted. This is seen in figure 1.



Graph relating log Δ k [$\Delta k = (k_1 - k_1^o)$] to Nw, mole fraction water, for the hydrolysis of t-BuCl in aqueous acetone.

Since at low water concentrations the salt effects parallel the basicity of the added anion ($Cl^- > Br^- > ClO_4^-$), it was suggested that the salt effect might in part be due to interactions between the anion of the salt and the alkyl halide, perhaps of the following nature:

(4)

$$X^{\ominus} \cdots\cdots \overset{\delta+}{C} \cdots Cl^{\delta-}$$

The anion could stabilize the charge-separated transition state or facilitate the departure of the chloride ion (10,38). As the water concentration increases, Cl^- would become more solvated that ClO_4^-; its activity would be reduced to a larger extent, resulting in the observed reversal.

Anion attack on the substrate in a manner similar to that proposed by Spieth and Olsen has been suggested by Winstein in his merged S_N2 - E_2 mechanism (16).

It has recently been reported that for the bimolecular reaction of n-butyl bromide with lithium halides in acetone, after correcting for the differences in dissociation of LiCl, LiBr and LiI the following anion order was observed for the rate of displacement (17).

Cl^- (18) > Br^- (4) > I^- (1)

As the solvent becomes more polar, the order is reversed. Here, also, the reversal has been attributed to the fact that in polar solvents Cl^- is more highly solvated than the other anions.

One feature of the work performed in 1940 by Ingold and his group on salt effects in aqueous acetone is that in many cases the salts were only partly dissociated. Nash and Monk, on the basis of conductivity data, determined the dissociation constants of bromide salts in 90% acetone (18).

TABLE IV
Dissociation constants x 10^3 of MBr in 90% acetone

Temp.	HBr	LiBr	KBr	$MgBr_2$
25°	6.3	12.0	13.0	0.31 (forward); 3.5 (reverse
30°	6.2			
35°	6.1			
50°	6.0	10*		*estimated

It was demonstrated, that in spite of the lack of complete salt dissociation, Ingold's model still appear to be valid in the cases he studied (18).

It has been observed that in the solvolysis of triphenylmethyl chloride in aqueous dioxane in the presence of azide ion, the ratio of alcohol to azide can be changed by the addition of salts (20). Increasing the salt concentration increases the fraction of alcohol formed.

TABLE V

75% Aq. dioxane (by vol.); $(Ph_3CCl) = 0.013$ M, $(NaN_3) = 0.039$ M

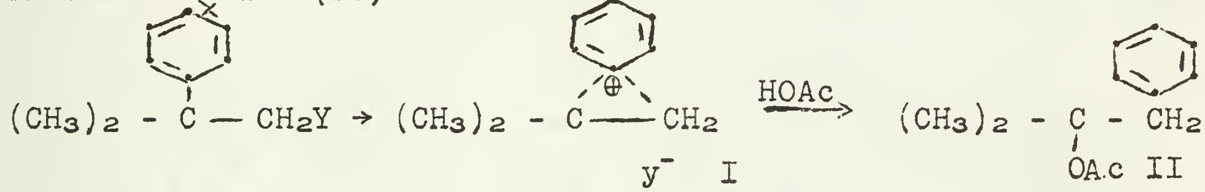
$LiClO_4$	0.00	0.0224	0.0448	0.0672	0.0892
% Ph_3COH	20.2	25.2	33.2	36.3	41.
% Ph_3CN_3	79.2	74.8	67.8	63.7	59.

$LiNO_3$	0.00	0.02	0.04	0.06	0.09
% Ph_3COH	20.2	23.4	28.0	32.1	38
% Ph_3CN_3	79.2	76.6	72.0	67.9	62

This order was explained in terms of an ionic strength effect. The addition of salt raises the ionic strength of the solution, stabilizing the ground state of the azide reaction (involving an ionic nucleophile) more than that of the hydrolysis (involving neutral water as the nucleophile).

Fainberg and Winstein studied the effects of a number of salts on the acetolysis of neophyl chloride, bromide, p-toluene-sulfonate, p-bromobenzenesulfonate and p-methoxyneophyl-p-toluenesulfonate in glacial acetic acid. (28)

(5)



In every case, even when the salt contained a common ion, an increase in rate was observed. A linear relation between rate and salt concentration was found to exist for salt concentrations up to 0.1 M.

$$k_t = k_t^o\,[1 + b(\text{salt})] \qquad (6)$$

k_t^o = rate constant in absence of salt

b = parameter specific for salt and reaction

Different salts exhibit a marked specificity, as can be seen in Table VII.

TABLE VII (22)

Effects of salts on the solvolysis of RX (R = neophyl) in acetic acid at 25°. ($k_t = k_t^o\,[1 + b\,(\text{salt})]$

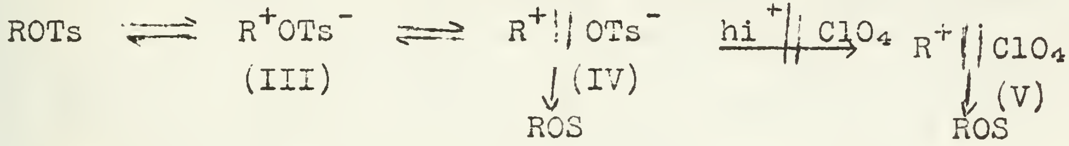
	b				
Salt	RCl	RBr	ROBs	ROTs	p-MeOROTs
HOTs	-	-	-	1.4	1.1
LiOAc	0.56	0.56	2	-	-
LiOTs	-	-	3.3	3.9	2.6
Diphenyl guanadinium (DPG) OAc	3.9	3.2	-	-	-
$LiClO_4$	7.6	6.4	11.6	15.0	12.2
DPG ClO_4	7.2	9.8	-	-	-

In those cases in which it was studied, the effects of two different salts were additive (22). In the acetolysis of neophyl halides, the effect of $LiClO_4$ and diphenylguanadinium perchlorate could be expressed by equation (7).

(7) $k_t = k_t^{\circ}\,[1 + b_1(\text{salt}) + b_2\,(\text{salt})]$

Neophyl compounds, for which there is no ion-pair return to starting materials, exhibit only these "normal", linear salt effects. In the solvolysis of compounds for which ion-pair return is of significance, for example, the acetolysis of 2-anisylethyl p-toluenesulfonate (23), another type of salt effect can occur. Here, the addition of $LiClO_4$ causes initially a very rapid rate increase which then levels off to a normal salt effect of the same magnitude as that observed in the acetolysis of neophyl compounds. It was proposed that this special salt effect is due to anion exchange between the added salt and the solvent-separated ion-pair (IV). (24,25)

(8)



$$\begin{array}{ccccccc} \text{ROTs} & \rightleftharpoons & \text{R}^+\text{OTs}^- & \rightleftharpoons & \text{R}^+||\text{OTs}^- & \xrightarrow{\text{hi}^+||\text{ClO}_4} & \text{R}^+||\text{ClO}_4 \\ & & (\text{III}) & & \downarrow(\text{IV}) & & \downarrow(\text{V}) \\ & & & & \text{ROS} & & \text{ROS} \end{array}$$

The very reactive alkyl perchlorate (V) formed would be converted rapidly into the acetolysis product, causing the observed rapid increase in the titrimetric rate constant.

Hughes and Ingold have criticised this interpretation of the special salt effect (26). They point out that in a medium of such low dielectric constant the salt will exist predominantly as ion pairs. They suggest that the effect observed at very low concentrations is probably due to dissociated perchlorate ions. This species, either in providing a better ion atmosphere or in catalyzing the reaction by direct attack on a substrate-solvent quadrupole (see below) would exhibit a more marked effect than the ion-pair on the rate.

This criticism fails to account for several facts, however. First, the rate is not proportional to the square root of the salt concentration, as would be predicted on the basis of incomplete dissociation (23). Second, it does not explain adequately why common ions are peculiarly unable to give this special salt effect (27). And finally, it does not account for the fact that the presence of a special salt effect depends upon the type of compound that is undergoing ionization. As has been pointed out, only compounds for which ion-pair return is significant exhibit this effect.

Salt effects of unusually large magnitude have been observed for the elimination of toluenesulfonic acid from p-methoxyneophyl p-toluenesulfonate in poorly ionizing solvents (9). In some solvents, a linear relationship between ionization and salt concentration exists; in others, such as diethyl ether and octanoic acid, the rate is more adequately expressed by equation (9).

(9) $k_t = k_t^{\circ}\,[\,1 + b(\text{salt}) + c(\text{salt})^{3/2}]$

Table VII lists a series of b values calculated for $LiClO_4$ and various solvents.

TABLE VII (9)

Effects of $LiClO_4$ on the ionization of p-MeOneophyl tosylate

Solvent	Temp.	b	Solvent	Temp.	b
AcOH	50	12.2	EtOAc	75	553
Ac_2O	75	47.1	THF	75	482
Me_2CO	75	47.0	Et_2O	50	2.98×10^5 $(c = 2.65 \times 10^6)$

A cause for these large salt effects has not yet been proposed.

Salt effects have been studied by Ingold and coworkers on the following reactions of trityl chloride in benzene: radio-chloride exchange with tetrabutylammonium chloride* (28), exchange with tetrabutylammonium azide (29), solvolysis with methanol (30) and solvolysis with benzyl alcohol (31). For the two anion exchange reactions, both initial rates, although considerably different ($k_1(N_3) = 5\ k_1\ (Cl^*)$), were found to be of zeroth order in salt in concentrations below 0.01 M; the addition of tetrabutylammonium perchlorate along with small amounts of ethanol slightly decreases the rate of product formation. For the methanolysis of trityl chloride, the rate (as measured by acid titration) is of varying order in methanol; the addition of tetrabutyl ammonium chloride severely decreases the rate; tetrabutylammonium perchlorate exhibits a rate-enhancing effect proportional to the square root of the salt concentration which is rapidly quenched by the addition of Bu_4NCl and other salts. The reaction with benzyl alcohol demonstrates salt effects similar to those observed in methanolysis.

To account for these results, the following mechanism for product formation was proposed (26).

$$\mathrm{RCl} \xrightleftharpoons[k_{-1}\ \text{fast}]{k_1\ \text{slow}} \mathrm{R^+Cl^-} \xrightleftharpoons[k_2\ \text{fast}]{k_2\ \text{fast}} \begin{pmatrix}\mathrm{R^+Cl^-}\\ \mathrm{M^+X^-}\end{pmatrix} \xrightleftharpoons[k_3\ \text{slow}]{k_3\ \text{slow}} \begin{pmatrix}\mathrm{R^+X^-}\\ \mathrm{M^+Cl^-}\end{pmatrix} \xrightleftharpoons[k_4\ \text{fast}]{k_4\ \text{fast}}$$

$$\mathrm{R^+X^-} \xrightleftharpoons[k_5\ \text{slow}]{k_5\ \text{fast}} \mathrm{RX} \qquad\qquad \text{VI} \qquad\qquad (10)$$

$$\mathrm{RCl} \xrightleftharpoons[\text{fast}]{\text{slow}} \mathrm{R^+Cl} \xrightleftharpoons[\text{fast}]{\text{fast}} \begin{pmatrix}\mathrm{R^+Cl^-}\\ \mathrm{HOR}\end{pmatrix} \xrightleftharpoons[\text{slow}]{\text{slow}} \underset{\text{VI}}{\begin{pmatrix}\mathrm{R^+OR^-}\\ \mathrm{H^+Cl^-}\end{pmatrix}} \xrightleftharpoons[\text{fast}]{\text{fast}} \mathrm{R^+OR^-} \xrightleftharpoons[\text{slow}]{\text{fast}} \mathrm{ROR}$$

The difference in rates of reaction of Bu_4NCl^* and Bu_4NN_3 is due to slightly different transition states in the slow third step. Catalysis by perchlorate, which is specific for alcoholysis, is considered to proceed by attack of the perchlorate anion on the quadrupole intermediate (VI). In the case of the anion exchange reactions, this would involve replacement of the salt anion by perchlorate, resulting in a quadrupole which could not collapse to products.

$$(11)\quad (\mathrm{R^+Cl^-})(\mathrm{M^+X^-}) + \mathrm{ClO_4^-} \rightarrow (\mathrm{R^+Cl^-})(\mathrm{M^+ClO_4^-}) + \mathrm{X^-}$$

Perchlorate attack on the alcoholytic quadrupole, on the other hand, would result in the replacement of the anion derived from trityl chloride. Ingold suggests the complex triple ion (VII) as a possible intermediate.

$$\underset{\text{VI}}{(\mathrm{R^+Cl^-})(\mathrm{HOR})} + \mathrm{ClO_4^{\ominus}} \rightarrow \mathrm{ClO_4^-R^+}\begin{pmatrix}\mathrm{Cl}\\ \mathrm{H}\\ \mathrm{OR}\end{pmatrix}^{-} \underset{\text{VII}}{\rightarrow} \mathrm{ROR} + \mathrm{HCl} + \mathrm{ClO_4^-}$$

Added Bu_4NCl turns ClO_4- out of the triple ion (VII), reverting it to the $(R^+Cl^-)(HOR)$ quadrupole.

Swain criticises this mechanism from both an experimental and a theoretical point of view. (32,33) Methanolysis of trityl chloride is very susceptible to hydrogen chloride catalysis, and the failure to complex hydrogen chloride formed by adding a tertiary amine (the reaction between amine and trityl chloride is shown to be negligible) invalidates the rate studies made. Moreover, a rate law based on Ingold's mechanism cannot explain his own results. Using steady state

assumptions for all intermediates, and assuming k_1, k_3, k_{-3}, and k_{-5} are small (equation 10) and all other rate constants large, Swain obtained the following rate equation.

$$(11)\quad \text{rate} = \frac{k_1k_2k_3k_4k_5(RCl)(M^+X^-)}{k_2k_3k_4k_5(M^+X^-) + k_{-1}k_{-2}k_4k_5 + k_{-1}k_{-2}k_{-3}\,k_4(M^+Cl^-)}$$

If the first term in the denominator is large compared to the other two terms so that rate becomes independent of the concentration of M^+X^-, the rate should also become independent of the nature of M^+X^-.

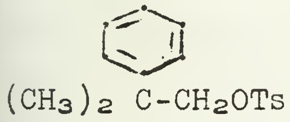
Grunwald has tried to express salt effects in terms of salt-induced changes of the medium. That is, salt changes the activity of the non electrolyte through changes of its solvent environment. He proposed that two effects are of importance: changes in internal pressure of the solution, and changes in the water-dioxane activity ratio.

From solubility measurements of naphthalene and 1-naphthoic acid in 50% dioxand in the presence of various salts, a salt-non-electrolyte interaction coefficient, K_{34}, was defined as

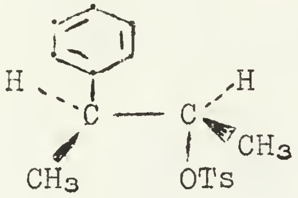
$$(12)\quad K_{34} = \log \delta_3/m_4$$

where δ is the activity coefficient and m the concentration. The subscripts 3 and 4 refer to non-electrolyte and salt, respectively. On the basis of his model Grunwald was able to derive an equation which accounted for several interesting empirical observations made regarding K_{34}. First, the values of this coefficient are specific for different salts. Second, a salting order exists; in 50% dioxane there is a linear relationship between K_{34} values for naphthalene and naphthoic acid. Third, the salting order for simple inorganic salts in 50% dioxane is the reverse of that observed in pure water. And fourth, there appears to be a linear relationship between $dF_{4_m}^{\circ}/dZ_1$ and K_{34}, where $F_{4_m}^{\circ}$ is the partial molal free energy of the salt and Z_1 the mole fraction of water in solution.

This model was also able to account satisfactorily for salt effects observed in two reactions: the solvolysis of neophyl *p*-toluenesulfonate (VIII) and the racemization of 1-(+)-threo-3-phenyl-2-butyl *p*-toluenesulfonate (IX).



VIII



IX

In both, the relation between salt concentration and rate could be described by the empirical equation (13);

$$(13)\quad \log(k_1/k_1^{\circ}) = S\,m_4$$

S is a parameter dependent on the salt and the reaction, and m_4 the salt concentration. A linear relationship between S and dF_{4m}°/dZ_1, predicted from the model, was found to exist in both reactions for most inorganic salts. Deviations could be accounted for either by S_n2 displacement reactions by the added salt (for example, in the case of an excessively large acceleration in loss of optical activity of (IX) by NaI) or by some type of short-range interaction between salt and substrate (large organic salts such as $(C_6H_5)_4PCl$ gave a poor correlation).

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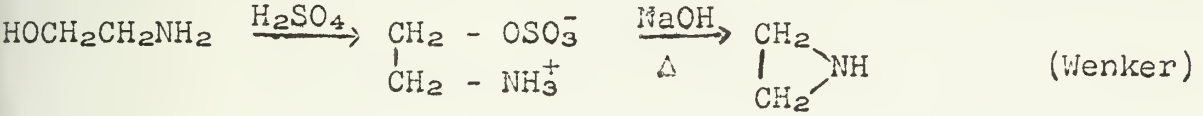
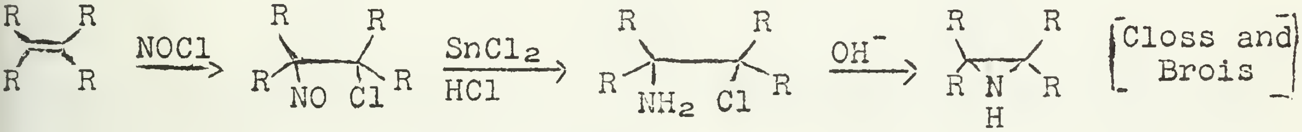
STUDIES OF THE RING CLEAVAGE OF ETHYLENIMINE

Reported by R. C. Slagel February 20, 1961

INTRODUCTION: The earliest paper mentioning ethylenimine (or aziridine) was published by Schreiner (1) in 1878. In this publication he refers to the compound, of then unknown structure, as "spermin". It was ten years later before this saturated heterocycle was synthesized by Gabriel (2) from 2-bromoethylamine and silver oxide or potassium hydroxide. However, Gabriel formulated the compound as vinylamine, $CH_2 = CHNH_2$, and it wasn't until 1899 that Marckwald (3,4) showed that the compound was actually a secondary amine in the form of a three membered ring.

Along with Gabriel's method, the most used synthesis of ethylenimine (EI) is that of Wenker (5) as shown. Tetraalkylaziridines have recently been synthesized in excellent yields (71-84%) by Closs and Brois (6).

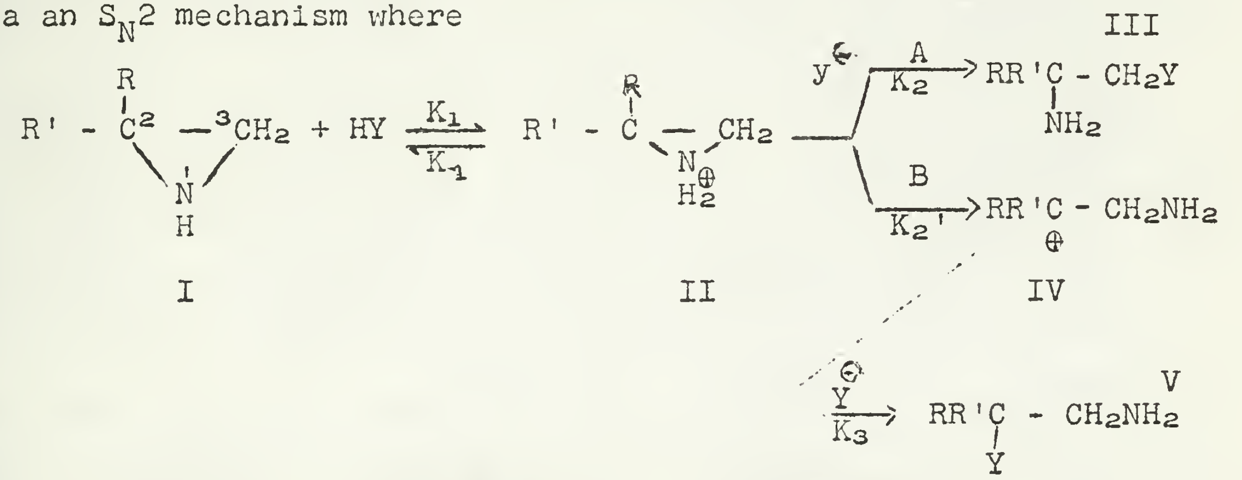




This seminar will deal with the ring cleavage reactions of EI and a few of its derivatives. There have been numerous patents released on reactions involving EI; however, due to lack of details and specific examples they will be excluded here. Also excluded will be the chemistry of EI ketones. These compounds have been investigated almost exclusively by Cromwell (7) and their ring opening reactions were reviewed in a previous seminar (15).

THE MECHANISMS OF RING OPENING REACTIONS: Most of the mechanistic studies have been carried out on unsymmetrical EI derivatives where two courses of cleavage are possible. Path A would be expected to proceed via an S_N2 mechanism where Y^- is a good nucleophile and path B via a carbonium ion or S_N1 mechanism. Cairns (8) has demonstrated that unsymmetrical EI's open at the secondary or tertiary carbon atom under hydrolytic conditions rather than at the primary carbon while Clapp (9) has shown that the strong nucleophile thiophenol causes cleavage at the primary carbon as would be expected for an S_N2 reaction.

Eq. 1



A. Reactions in Aqueous Solutions: In aqueous solution the imine, because of its fairly high basicity, can be assumed to be mainly in the

form of the imonium ion (II). Therefore, the rate determining step should be k_2 for path A and either k_2' or k_3 for path B.

Recent kinetic studies by Clapp and co-workers (10) have given excellent second order plots for the reaction of I ($R=R'=CH_3$) with the nucleophiles I-, Br-, SCN- and thiourea. These plots show the reaction to be first order in both reactants. Along with this they give two additional pieces of evidence for an S_N2 mechanism with such nucleophiles. They allowed EI, 2-ethylethylenimine (EEI) and 2, 2-dimethylethylenimine (DMEI) to react with various nucleophiles with the following results: (a) In all cases the products expected from an S_N2 mechanism were obtained--that is path A was followed. (b) The relative rates of ring opening were correlated using Swain's equation, $\log k/k_o = sn$ (11), and found to correspond to values of s which are normal for reactions with displacements as the rate determining step (see Table I). All the imines react at rates which reflect the nucleophilic character (see 11) of the nucleophile used, suggesting that all proceed by an S_N2 mechanism.

TABLE I

Imine	$k_o \times 10^8$	s
EI	1.54	0.87
EEI	0.658	0.91
DMEI	2.28	0.83

$$Cl^-,\ Br^-,\ SCN^-,\ I^-,\ \text{thiourea},\ S_2O_3^{=}\ \xrightarrow[\text{with imonium ion}]{\text{increasing rate}}$$

In the same article, Clapp describes an extensive study of the perchloric acid catalyzed hydrolysis of the three above-mentioned imines. The tertiary carbonium ion intermediate of DMEI would be expected to be more stable than the carbonium ion of either EI or EEI, and it is possible that bimolecular (A) as well as unimolecular (B) paths are important in these hydrolyses. If this is the case then the experimental first order (since solvent is reactant) rate constant would be composed of two terms, $k_{exp}=k_1 + k_2(H_2O)$. The authors were able to show the relative weights of S_N1 and S_N2 mechanisms by three methods. (a) By obtaining the rate constants over a temperature range, the activation thermodynamic quantities ΔH* and ΔS* were obtained. These values, as seen in Table II, indicate strongly a wide difference in mechanisms of hydrolysis. Especially noteworthy is the difference in the entropy of activation of DMEI from the others. This indicates a great predominance of S_N1 mechanism in DMEI hydrolysis. (b) A product study of these reactions was then made and, as seen in Table II, the S_N2 reaction predominates with EEI and the S_N1 with DMEI as would be expected. (c) The parameter o in Swain's equation corresponds to a second order rate constant. hus the evaluated k_o here should be close to that for a second order ydrolysis if it involves the same S_N2 mechanism as the other nucleohiles. By the deviation of $p(k_{exp}/H_2O)$ from pk_o, the amounts of S_N1 nd S_N2 character in this solvolysis reaction were estimated. It is fair conclusion, on the basis of the above results, to say that the

TABLE II

Imine	ΔH*, Kcal/mole	ΔS* e.u./mole	% Yield 1-amino alc.	% Yield 2-amino alc.
EI	23.0±0.6	-9.4±1.0	-------	--------
EEI	23.1±0.1	-10.0±0.5	22	61
DMEI	24.3±0.4	-1.9±1.0	80	20

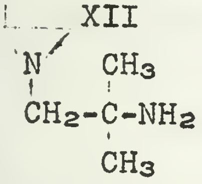
acid hydrolysis of DMEI is primarily S_N1 with a small S_N2 contribution while EEI proceeds primarily by S_N2 and EI probably exclusively by S_N2 (also see Table III on page 20). These results are consistent with the studies of Buist and Lucas (12).

Clapp and Schatz (13) have also shown that the reaction of DMEI in aqueous HCl gave 1-chloro-2-amino-methylpropane and 1-amino-2-methyl-2-propanol in varying ratios depending on temperature, concentration of acid, and imine to acid ratio (6N HCl gave 85-90% of former while 1N HCl at 100° gave 45% of former and 39% of latter). This effect of competing S_N1 and S_N2 reactions is in contrast to hydrolysis catalyzed by such acids as perchloric, picric and sulfuric where the conjugate base is a weak nucleophile and the mechanism, therefore, predominately S_N1 no matter what the concentration of the acid.

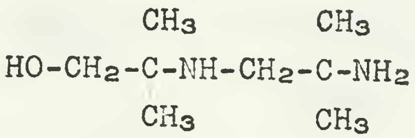
Another reaction of interest which is generally carried out in aqueous solution is polymerization. Three workers have provided nearly all the mechanistic work in this area--Kern(16), Jones (17,18), and Barb (19,20).

Dry EI has been observed to polymerize very slowly even at high emperature (19). However, addition of trace amounts of water increased he rate greatly and small amounts of acids to an even greater extent (16, 17, 19). Because of the violent reaction of bulk EI with acids, he reactions studied were carried out in aqueous solutions. It is teresting to note (16) that bases known to catalyze the polymeriation of ethylene oxide do not do so with EI. Also, inhibitors of ree radical vinyl polymerizations do not inhibit the polymerization f EI. These and other observations show that the polymerization of I is not a condensation type or a radical type, but an addition olymerization of polar nature. The ring opening was postulated as a odified Winstein-Buckles mechanism or S_N2 This was later confirmed t least for DMEI by a product study of the polymerization of DMEI in queous solution (18). The waxy polymer was obtained in 50% yield along th low yields of three intermediates, the dimer (XII), the hydroyzed dimer (XIII), and the trimer (XIV) (whose structures were conirmed by synthesis) showing that the ring opened at the primary C tom. Another piece of evidence for S_N2 ring opening is the fact that ptically active polymers were obtained from D and L-2-methyl EI atalyzed by Lewis acids such as BF_3 (59). The properties of these olymers indicate a high degree of retention, a fact consistent with n S_N2 propagation step.

XII

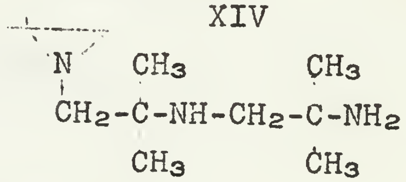


XIII



$$HO\text{-}CH_2\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{-}NH\text{-}CH_2\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{-}NH_2$$

XIV



Barb (19) describes the initiation and chain growth as follows: f it is assumed that basicities of imino nitrogens of monomer and olymer are similar, then in the early stages of the reaction most f the product will be dimer. Only as dimer concentration becomes ignificant will appreciable quantities of trimer, tetramer and higher olymers be formed. The mean degree of polymerization will rise until ll lower species disappear at the end. This has been confirmed by hromatographing the reaction mixture at various times. This phenomenon ccurs through a "transfer equilibrium" which entails proton transfer [illegible] of [illegible] (11) with a [illegible] of [illegible] products [illegible] and [illegible] [illegible]. These results are [illegible] ith the studies of [illegible] and [illegible] (11).

Clapp and Smith (11) have also shown that the reaction of [illegible] (12) with 1-[illegible] and [illegible] to [illegible] of [illegible] and [illegible] of [illegible] and [illegible] respectively, [illegible] here is a [illegible] of the [illegible].

[illegible] reaction of [illegible] that is [illegible] solution is [illegible]. Other [illegible] have [illegible] mechanisms [illegible] (11,14), [illegible] (17,18)).

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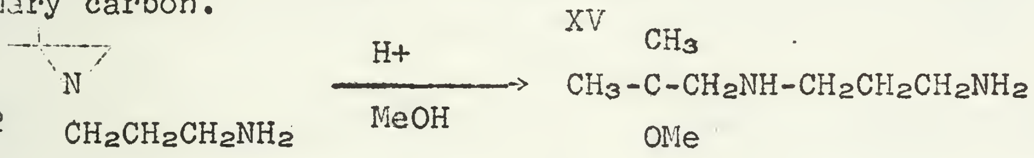
(I)	(II)	(III)
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]

[illegible] (13) [illegible] and [illegible] of [illegible] of the [illegible] of [illegible].

between monomer and polymer. Termination may occur by reaction with H_2O, the acid anion, or with a terminated chain (17).

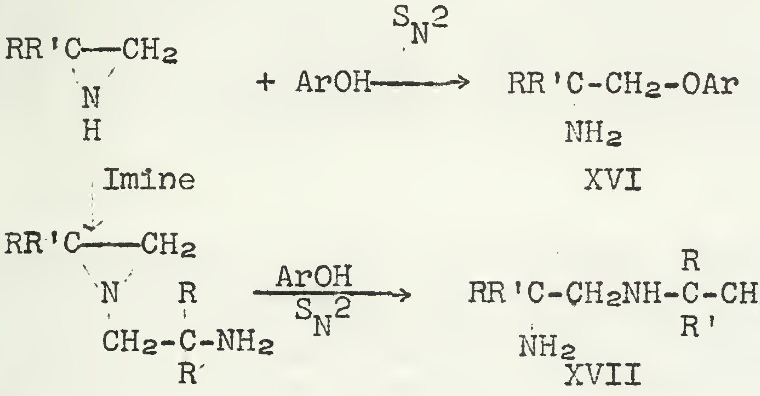
Two other items should be mentioned in passing. Benzoylation of poly EI introduces one benzoyl group per repeating unit indicating a linear polymer (20); secondly, many reagents capable of producing a tetravalent nitrogen, such as alkylating agents and Lewis acids (Cu and BF_3) as well as proton acids have been found to be effective catalysts in polymerizing EI (17).

B. Reactions in Non-aqueous Solutions: In non-aqueous solutions, the reaction course (Path A or B in eq.1) depends on the polarity of the solvent and the nucleophilic character of the reactant Y^-. Non-polar solvents would be expected to inhibit the formation of a carbonium ion intermediate (Path B) and thus enhance an S_N2 mechanism (Path A) while polar solvents would be expected to act similarly to water. Tarbell and Noble (21) treated 1-(3-aminopropyl)-2, 2-dimethylethylenimine (XV) with picric acid in methanol and observed an S_N1 reaction to take place as expected with no cleavage at the primary carbon.

Eq.2


On the other hand, Clapp, Powers and Schatz (22) obtained the product (68-98%) expected from an S_N2 reaction when treating EEI and DMEI with benzoic acids in dioxane as solvent. In a more polar medium such as water, one would expect some acid catalyzed hydrolysis (S_N1) to occur also.

In some cases the polarity of the solvent seems to make little difference. Thus in the reaction of various phenols with EEI and DMEI (23), the products XVI and XVII were formed in nearly equal amounts in several solvents of different polarity (pet, ether, $CHCl_3$, MeOH, EtOH).

Eq.3


Total yield of XVI + XVII is 60%; Ar=Ø

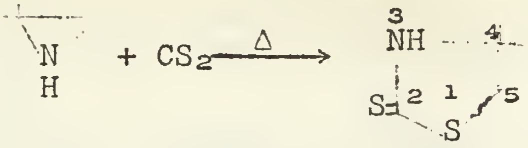
Polymer=30%

It is thought that the phenol is a strong enough acid to catalyze polymerization and a reactive enough nucleophile to cut off polymerization at the dimer stage.

In other cases no solvent was used at all and the reactants were heated together in a sealed tube. Thus, when EEI and DMEI were treated in this manner with primary and some secondary amines using ammonium chloride as a catalyst, cleavage occurred predominately at the primary carbon atom giving α, β-diamines in 55-68% yields indicating an S_N2 mechanism (24). The same C-N bond broke when DMEI was

heated with carbon disulfide (25) giving 4, 4-dimethyl-2-thiothiazolidone (XVIII) in 84% yield.

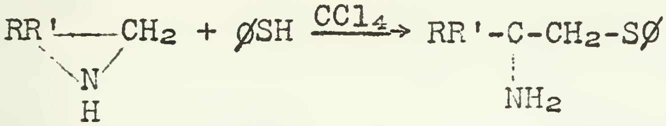
Eq.4



XVIII

Since non-polar solvents do not favor separation of charge, the equilibrium between species I and II in equation 1 would be expected to lie toward the left, possibly making this step rate-determining. Clapp and Meguerian (9) studied the reaction of DMEI

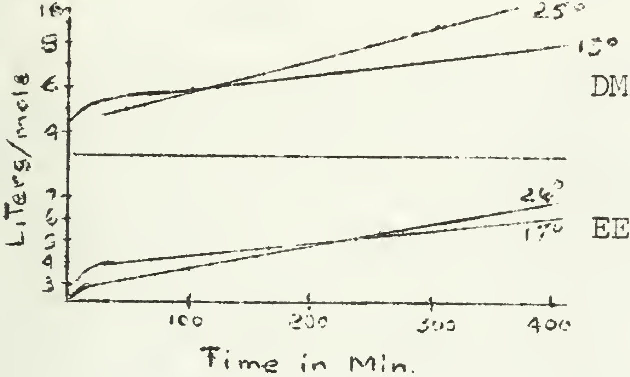
Eq.5



	% Yield
$R=R'=CH_3$	86
$R=Et;\ R'=H$	92

and EEI with thiophenol in CCl_4. The reaction (eq.5) definitely goes via an S_N2 mechanism. A second order rate plot gave a straight line for nearly the entire reaction. However, the initial rate, as seen in figure 1, was much faster. This was interpreted to mean that the intermediate imonium ion was formed rapidly at the beginning of the

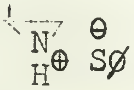
Fig 1.



Steady State rate eq.

$$-\frac{d[ØSH]}{dt} = \frac{k_1k_2[EI][ØSH]^2}{k_{-1}+k_2[ØSH]}$$

reaction until a "steady state" was reached. At this point a regular bimolecular reaction takes over. In order for this reaction to be second order after the steady state is reached, $k_{-1} \ll k_2(ØSH)$ and the rate then equals $k_1(EI)(ØSH)$. Thus the rate determining step is the formation of the intermediate which in this case is probably the ion pair instead of the free imonium ion (II).

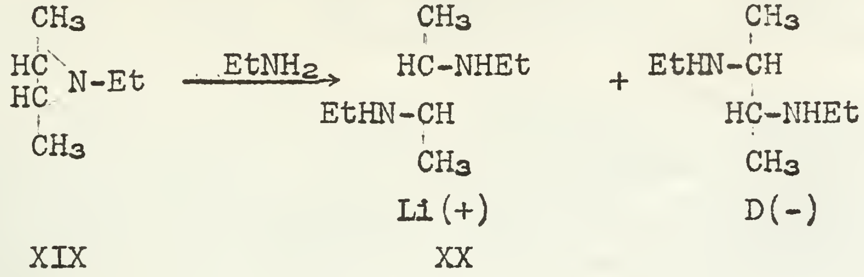


C. Stereochemistry: Most of the recent work on the stereochemistry of ring formation and opening has been produced by Lucas (26,27,28), Fanta (29) and Tanaka (30). They have found that the EI's are analogous to epoxides in that the opening and closing of the ring is accompanied by a Walden inversion for symmetrically substituted rings where an S_N2 mechanism is operative.

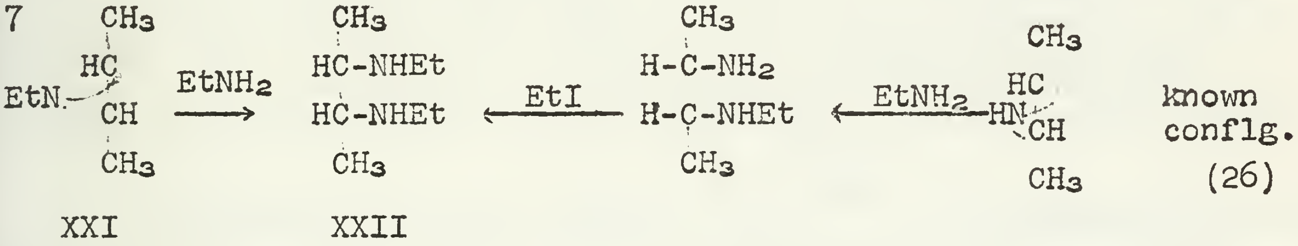
Lucas has treated cis and trans-2,3-iminobutanes with NH_3 (26), acetic acid (27) and ethylamine (28), obtaining nearly identical results. In the last case he treated cis-N-ethyl-2,3-iminobutane (XIX) with aqueous ethylamine to give inactive DL-threo-2,3-bis-(ethylamino) butane. The mixture was resolved with (-) dibenzoyl

tartaric acid and the structures of the isomers confirmed by relating them to D and L -2,3-diaminobutanes of known configuration (26). By treating the active trans imine (XXI) in the same fashion Lucas

Eq.6



Eq.7



obtained an inactive non-resolvable compound which was shown to be the expected meso-2,3-bis(ethylamino) butane (XXII) as seen in equation 7.

REACTIONS INVOLVING N,N-DIALKYL ETHYLENIMONIUM ION INTERMEDIATES: It was indicated strongly above that the active species of EI in displacement reactions is the imonium ion. A great deal of work on nitrogen mustards during the second world war has shown that the high reactivity of these compounds is due to the formation of EI ions as intermediates which, like ethylene oxides, are formed readily and react readily (due to ring strain and polar nature of C-N bond) furnishing paths for reactions that would otherwise proceed much more slowly.

All of the nitrogen mustards contain two or more β-chloroethyl groups (XXIII) and thus resemble mustard gas (XXIV) in structure as well as chemical properties. Bartlett (31), Hanby (33), Columbic (32), Cohen (34), Nickerson (35), Chapman (36) and Izumi (37) have all obtained kinetic data on the reactions of these compounds in

$R-N(CH_2CH_2Cl)_2$

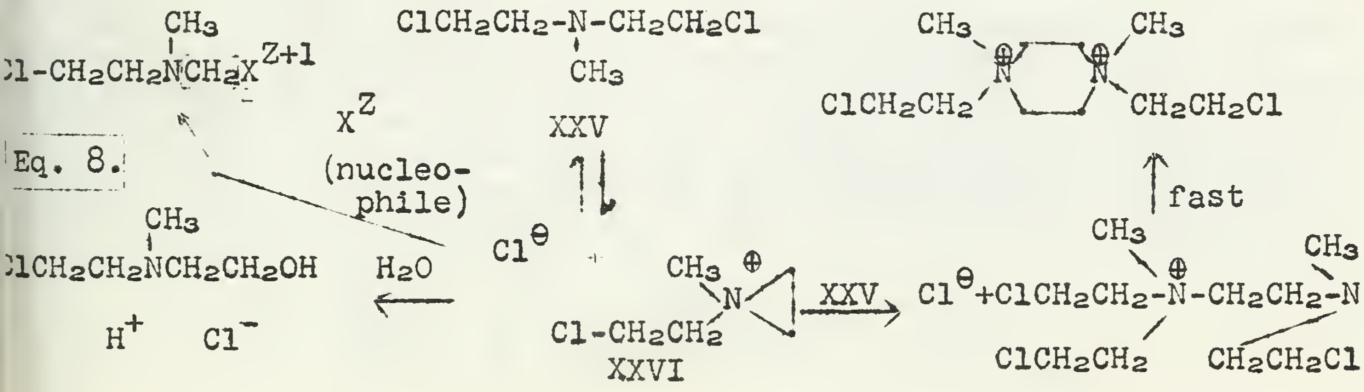
XXIII

$ClCH_2CH_2-S-CH_2CH_2Cl$

XXIV

solution and arrived at the identical conclusion that the imonium ion (XXVI) is an intermediate. This conclusion came from the observations

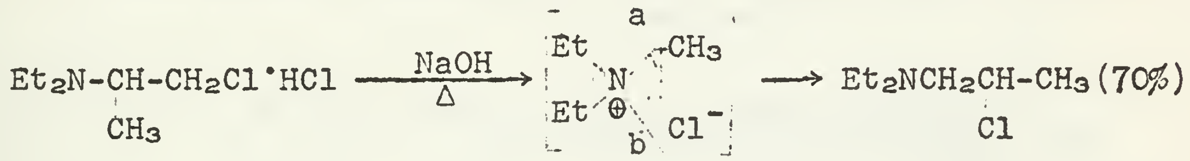
Eq. 8.



hat (a) Cl^- was released much more rapidly than H^+ at the beginning f the hydrolysis reaction indicating that the intermediate (imonium on) was collecting, (b) added Cl^- decreased the rate of reaction onsiderably, (c) S_2O_3 was quickly taken up by the intermediate, and d) several imonium salts were isolated, most of them as the picryl ulfonate.

This class of compounds is of great interest because of their harmacological action. Under physiological conditions (pH 7.5 at 37°) he nitrogen mustards cyclize to the imonium ion which, being a owerful alkylating agent, can then react with free amino, sulfhydryl, arboxyl and other susceptible groups in the biological system to ause adverse effects and eventually death (32,36,38,39).

Several rearrangements have been published which are postulated o involve an EI ion intermediate. Fuson and coworkers (40) found hat 1-diethylamino-2-chloropropane (XXVIII) was obtained by heating -diethylamino-1-chloropropane (XXVII) with sodium hydroxide. By con-rast, Ross (41) has converted XXVIII into 2-diethylaminopropanol cleavage at b. instead of a. as in former case) with sodium hydroxide n a water:acetone mixture at room temperature. The S_N2 attack would



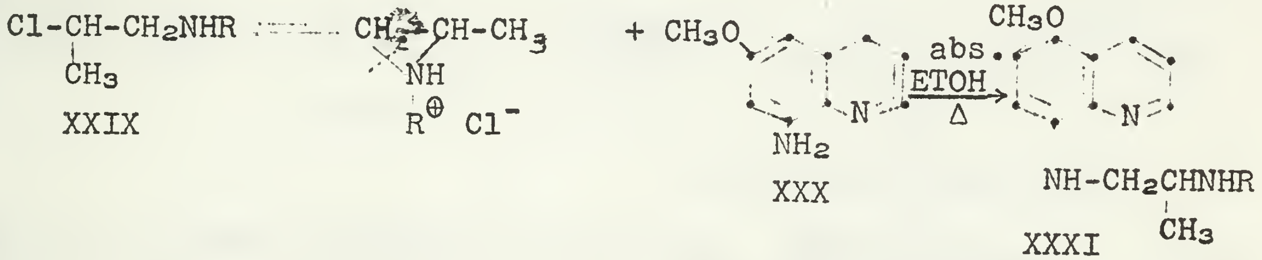
q.9

XXVII

XXVIII

e expected in the latter case in view of the nucleophilic strength of H^-. Also, it has been shown (13) that a higher temperature increases he importance of an S_N1 process when competing S_N1 and S_N2 paths are ossible, as in the former case, because of higher activation energy or S_N1. It should be noted, however, that the reaction in equation 9 ccurs with only heat(42).

In another case, Cope and coworkers (43) found that the desired roduct from treating an N-substituted-2-chloropropane(XXIX) with 6-ethoxy-8-amino quinoline (XXX) was not obtained but that the product as actually the rearranged isomer (XXXI). The cleavage occurred at he primary carbon as would be expected for reaction with the nucleohilic amine.



q.10

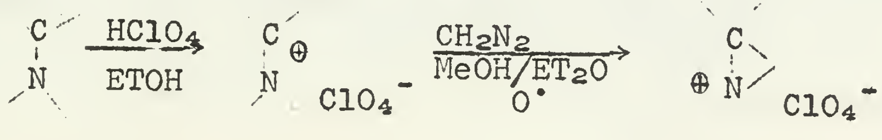
XXIX

XXX

XXXI

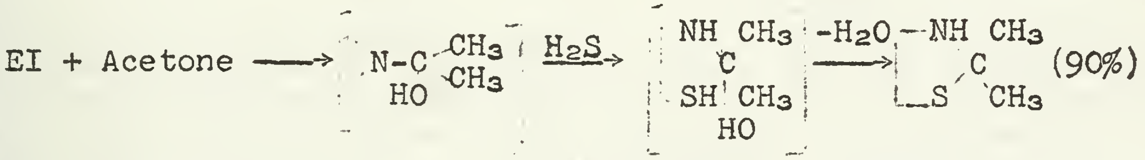
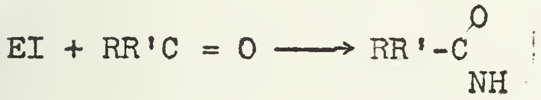
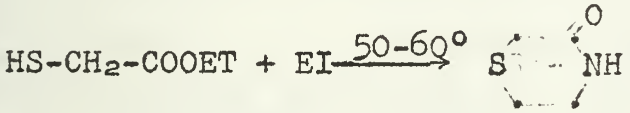
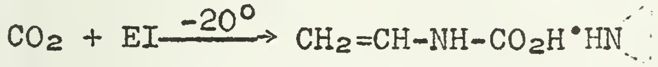
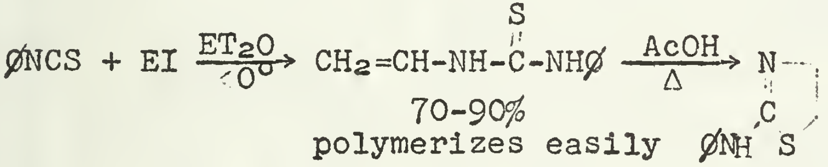
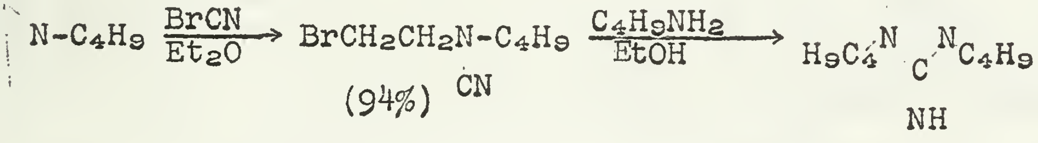
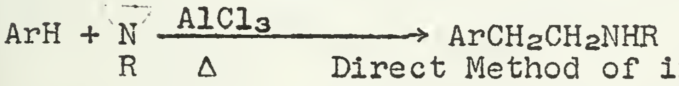
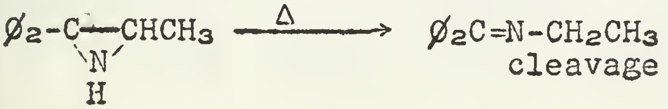
Before leaving this discussion it should be mentioned that a new ynthesis for EI salts has been discovered by Leonard and Jann (44) eading to easily handled compounds in excellent yields. Thus by treatg an enamine with perchloric acid, a ternary iminium perchlorate is btained, which is converted into the aziridinium compound with diazoethane. This synthesis now provides the possibility for the systemtic study of the chemistry of these three-membered ring compounds lly substituted on nitrogen.

1. 11



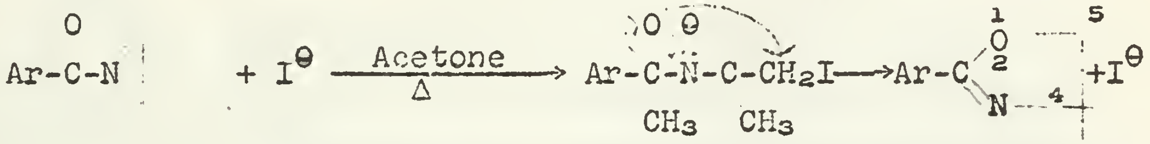
OTHER REACTIONS: Most of the reactions covered in this section have not been studied in detail mechanistically as have those given above. However, these reactions do have synthetic value and are, therefore, of interest. Many other examples may be found in Fruton's chapter in Elderfield's "Heterocyclic Compounds" (53).

TABLE IV

	REACTION	REF.
1.)	 2,2 dimethyl thiazolidine Good yields obtained with other ketones and aldehydes.	45
2.)	 R=H, R'=C_6H_{13} (95%); synthesis for ketones give poor yields.	46
3.)	 (65%) 3-keto-1,4 thiazane or thiomorpholone-3	45
4.)	 N-vinyl carbamic acid (quant. yield) Gives polymer at higher temperatures (17).	47
5.)	 70-90% polymerizes easily 2-anilino-Δ^2-thiazoline (50%)	48
6.)	 (94%) A cyclic guanidine (86%)	49
7.)	$RR'NH + EI \xrightarrow[\Delta]{AlCl_3 \text{ or } NH_4Cl} RR'NCH_2CH_2NH_2$ R+R'=Alkyl,aryl or H. (55-89%) General synthesis for α, β-diamines	24,50
8.)	 55-80% when Ar=Ø- Direct Method of introducing 2-amino group into benzene ring.	51
9.)	 (50-75%) Only case of cleavage at C-C bond.	52

N-Substituted carbonyl groups have a profound effect on the reactions of EI's. It was Gabriel (54) who first showed that 1-benzoylaziridine rearranged at its boiling point to 2-phenyloxazoline. Recently, Heine, Fetter and Nicholson (55) have shown that unsymmetrical EI's react in the same fashion when heated in acetone with a sodium iodide catalyst or in hexane with an $AlCl_3$ catalyst, giving excellent yields of 2-aryl-4,4-dimethyl-2-oxazolines (above 90%). The cleavage occurs at the primary carbon. However, if a sulfuric acid solution is used, cleavage occurs at the tertiary carbon and high yields of 2-aryl-5,5-dimethyl-2-oxazolines are obtained. Finally Fanta and co-workers (56,57,58) have demonstrated that pyrolysis of 1-acyl or 1-benzoyl aziridines proceeds via an elimination similar to that of Chugaev and Cope (ref.14,page 305)

Eq. 12.



CONCLUSION: The ring opening reactions of ethylenimine have been shown to be quite similar to those of epoxides on which there is an abundance of literature (ref. 53 p. 22; ref. 14 p. 106). Because of their highly reactive character, these compounds can be expected to occupy considerable interest in the future.

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TABLE III

$k_{exp}=k_2(H_2O)$ or $k_2=k_{exp}/(H_2O)$; then $k_o=k_2$ or $k_o=k_{exp}/(H_2O)$

ine	$k_{exp} \times 10^6$	$k_{exp}/(H_2O) \times 10^6$	$p(k_{exp}/H_2O)$	pk_o	pk_2 (est. from product study
EI	0.703	0.0127	7.898	7.812	7.898
EI	0.452	0.0083	8.083	8.182	8.216
EI	3.67	0.067	7.179	7.642	7.703

CORRELATION OF N.M.R. CHEMICAL SHIFTS WITH HAMMETT SUBSTITUENT CONSTAN

Reported by V. F. German February 27, 1961

Introduction

The Hammett substituent constant (σ) is frequently considered a measure of the change in electron density at the reaction site (1,2). Although the substituent constant is obtained from ionization constants of benzoic acids, replacement of the carboxyl group with a suitable probe which would allow determination of the electron density at the position previously occupied by the carboxyl group, should show to what extent the above consideration is correct. The n.m.r. shielding parameters of F_{19}, H_1, and C_{13}, which are substituted for the carboxyl group, should serve as a means of determining the changes of electron density produced by the substituent at the position previously occupied by the carboxyl group. It should be emphasized that while the substituent constant is a measure of the effect of the substituent on the free energy difference of two states (i.e., reactant and product, or reactant and transition state) the shielding parameter is a measure of the effect of the substituent only on the ground state.

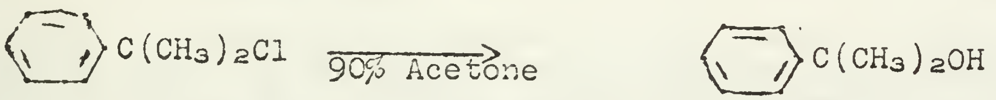
Hammett Sigma Constants

The substituent constant (σ) as defined by Hammett is

$$\log (K/K^{o}) \equiv \sigma \qquad [1]$$

where K^{o} = the ionization constant of benzoic acid
and K = the ionization constant of the substituted benzoic acid (1,2).

The general applicability of the Hammett equation indicates that the substituent constant is largely independent of the reacting side chain. In certain cases, however, the sigma constants are dependent on the type of reaction, and the conditions under which the reaction is run. The two extremes are represented by the ionization of phenols and the solvolysis of phenyldimethylcarbinyl chlorides. For these extremes dual sigma values have been defined. Resonance interactions of electron withdrawing substituents with the reaction center has led to the σ^- - scale of substituent constants for the ionization of phenols and the protonation of anilines (1). A similar interaction of electron donating substituents in electrophilic reactions has led to the σ^+ scale of substituent constants (3). The defining reaction is the solvolysis of phenyldimethylcarbinyl chloride in 90% aqueous acetone.



Values of sigma intermediate between the extremes of the σ^- and the normal Hammett σ and σ^+ and the normal Hammett σ are frequently observed. These intermediate values are probably the result of varying degrees of resonance interaction of the substituent with the reaction center. In addition to the dependence of the substituent constant on resonance interactions with the reaction site, substituent constants are dependent to some extent on solvent. However, the extent of this dependence is a characteristic of each substituent. It would seem doubtful that the Hammett sigma values (σ) could be correlated exactly with chemical shifts of F_{19}, H_1, or C_{13} in the aromatic series. However, a definite trend should exist.

Separation of the Hammett Sigma Values into Resonance and Inductive Components

Correlation of the flourine chemical shifts in substituted fluorobenzenes and hydrogen chemical shifts in substituted benzenes with Hammett substituent constants (σ) is usually quite poor and wide scattering of individual points results. Linear relationships between

chemical shifts and Taft's substituent constants are obtained when the appropriate sigmas are used. For a discussion of the dependence of chemical shifts on substituents a review of Taft's treatment of the Hammett substituent constant is necessary.

Inductive Sigma Constants (σ_I)

A general scale of inductive effects of substituents has been proposed by Taft (4). The defining reactions are the hydrolysis of aliphatic esters in acid and base. The value of sigma inductive (σ^*) is obtained from the following expression for the system RCO_2R':

$$\sigma^* = \frac{1}{2.48} [\log (K/K^o)_B - \log (K/Ko)_A] \qquad [2]$$

The standard of comparison is $R = CH_3$, $(K/K^o)_A$ and $(K/K^o)_B$ refer to acid and base hydrolysis rate constants respectively, and 1/2.48 is a factor which gives the sigma inductive constants a value comparable in magnitude to the Hammett sigma constants (σ). Similar studies were conducted on the effects of substituents on the ionization constant of bicyclo[2.2.2]octane-1-carboxylic acid (5). In both systems the effect of the substituent on the rate constant of hydrolysis or ionization is presumed to be principally inductive. The inductive constants of Taft are related to those from the bicyclooctane series by

$$\sigma' = 0.45\, \sigma^* \equiv \sigma_I \qquad [3]$$

A sigma inductive constant has been defined for the aromatic series (4,5). Cited as justification for the applicability of inductive constants from the aliphatic series to the aromatic series is the observation that complete steric inhibition of resonance gives Hammett sigma values (σ) which agree well with the aliphatic inductive sigmas.

Separation of inductive and resonance effects requires the following assumptions:

1. The substituent effect on free energy behaves approximately as the sum of inductive and resonance effects.

$$\log(k^m/k^o) = I + R^m \qquad [4]$$

$$\log(k^p/k^o) = I + R^p \qquad [5]$$

2. The resonance contribution from the meta position is proportional to the resonance contribution of the para position.

$$\alpha = R^m/R^p \qquad [6]$$

3. The inductive contribution from the meta position is approximately equal to the inductive contribution from the para position. Elimination of the resonance effect from equations [4] and [5] gives an expression independent of R and dependent on the variable parameter $\underline{\alpha}$.

$$I = \left(\frac{1}{1-\alpha}\right) [\log(k^m/k^o) - \alpha \log(k^p/k_o)] \qquad [7]$$

$$I = \sigma_I/\rho_I \qquad [8]$$

$$\rho_I = I/\sigma_I \qquad [9]$$

Taft and Lewis have arbitrarily assigned a value of 1/3 to α for substituents which do not interact abnormally with the reaction center (6,7). A value of 1/10 was assigned to $\underline{\alpha}$ for the cases in which resonance interactions occur. A statistical evaluation of $\underline{\alpha}$ by Roberts and Jaffe has shown that the values of $\underline{\alpha}$ for widely differing reactions range between 0.2 and 0.6 with the majority of values falling close to 0.4 (8).

A test of equation [7] is the adherence to a linear plot of I vs. σ_I. In the cases of extreme deviation of the Hammett substituent constant, equation [7] was found to apply within experimental error by

selection of 0.1 for the value of α for the deviating substituents. Evaluation of equation [7] is limited to those reaction series for which the necessary values of k^m and k^p are available.

Assuming the inductive contribution from the meta and para positions equal is not entirely justified. Inductive effects should be a function of the distance between the substituent and the reaction site. Cited as partial support for this equality are the Hammett sigma values obtained by Roberts and co-workers for the trimethylammonium ion (9). Although the effect of the $-N(CH_3)_3^+$ group may be principally inductive, resonance interactions of the reaction site with the ring are probably not negligible.

Resonance Parameters ($\bar{\sigma}_R$).

Evaluation of the resonance parameters was accomplished by rearrangement of equations [4] and [5] (6).

$$R^m = \log(k^m/k^o) - I \qquad [10]$$

$$R^p = \log(k^p/k^o) - I \qquad [11]$$

From the resonance contributions an effective resonance parameter is defined. Deviations from the Hammett equation which depend on reaction type and conditions are detected by deviation of the particular value of $\bar{\sigma}_R$ from its normal value.

$$\bar{\sigma}_R = \sigma_{Hammett} - \sigma_I \qquad [12]$$

$$\bar{\sigma}_R \equiv R/\rho_I \qquad [13]$$

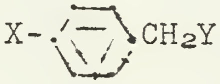
For the special case of $\rho_I = \rho$ equations [4] and [5] become the familiar Hammett equation.

$$\log(k/k^o) = R + I = \rho_I\ (\sigma_I + \bar{\sigma}_R)) = \sigma\rho \qquad [14]$$

As might be expected the resonance constants are highly dependent on reaction type and conditions (7). The inductive parameters are independent of reaction type and conditions. For a wide variety of reactions sigma inductive (σ_I) is constant to within ± 0.03 units.

Sigma Para Constants (σ^o_P)

A sigma constant has been defined for the para substituted benzyl system (10).



Y = reaction center, X = substituent.

The saponification of $ArCH_2CO_2Et$ in 88% aqueous EtOH was taken as the defining reaction. The Hammett reaction constant (ρ) for the saponification of $ArCO_2Et$ is 2.80. The methylene group between the ring and the reaction site decreases the effect of the substituent by a factor of approximately 1/2.80. By adopting the saponification reaction as the reference reaction the sigma values obtained for this reaction are directly comparable with the Hammett sigma para values (σ_P). The utility of the σ^o_P values is not confined to the $ArCH_2Y$ series. These substituent constants are applicable to reactions in which no direct resonance interation with the reaction center is possible. Also defined for this system are resonance constants.

$$R/\rho_I \equiv \sigma^o_R \qquad [15]$$

Evaluation of direct resonance interaction between the substituent and the reaction center is obtained in the following manner:

$$\Delta = \bar{\sigma}_R - \sigma^o_R \qquad [16]$$

The values are relatively independent of reaction type and conditions of the reaction for electron donating groups. However, this resonance

parameter is solvent dependent for electron withdrawing groups.

Correlation of Substituent Constants with Chemical Shifts in Substituted Fluorobenzenes.

Gutowsky and co-workers have reported that for substituted fluorobenzenes a general correlation between the chemical shifts and the Hammett substituent exists (12). Deviation of individual points from a strict linear relationship was often greater than experimental error particularly in the case of para substituents. A plot of the fluorine chemical shift vs. the Hammett sigma values showed that the points for the meta substituents and the para substituents did not fall around the same straight line. The relationships between the chemical shifts and substituent constants are given below:

$$\sigma_m = -1.69\ \delta_m \qquad [17]$$

$$\sigma_p = -0.560\ \delta_p - 0.271 \qquad [18]$$

A better correlation was obtained by Taft using sigma resonance and inductive constants (13). The data were correlated by the following relationships:

$$\delta_m = -0.583\sigma_I + 0.02 \qquad [19]$$

$$\delta_p = -0.583\sigma_I - 1.880\bar{\sigma}_R + 0.08 \qquad [20]$$

The value of sigma resonance constant is that obtained from the Hammett sigma constant minus the inductive contribution ($\bar{\sigma}_R=\sigma-\sigma_I$).

It is interesting to observe the absence of a resonance term in equation [19]. In Taft's separation of resonance and inductive effects a contribution of 1/3 R^p for the resonance contribution from the meta position was found necessary to explain experimental observations (6,7). The chemical shifts of the para substituted fluorobenzenes are functions of both inductive and resonance parameters; however, the sensitivity of the chemical shift to resonance contribution is approximately three times greater than to the inductive contribution. Dependence of chemical shifts of both meta and para substituted fluorobenzenes on the inductive parameter is equal and supports the equality of inductive effects in both positions.

Table I^e

Substituent	δ_p^F a,b	δ_m^F a b	σ_I b	δ_m^H c,d	δ_p^H c,d
H	0.00	0.00	0.00	0.00	0.00
NH_2	1.41	-0.02	0.10	0.13	0.40
OH	1.08	-0.09	0.25	0.37	0.37
F	0.68	-0.30	0.50	——	——
CI	0.32	-0.20	0.47	0.00	0.00
Br	0 25	-0.22	0.45	0.00	0.00
I	0.12	-0.26	0.38	0.17	0.10
CN	-0.94	-0.10	0.59	-0.30	-0.30
NO_2	-0.97	-0.33	0.63	-0.30	-0.42
CH_3	0 45	0.12	0.05	0.10	0.10

---

a) Chemical shifts with reference to fluorobenzene, CCl_4 solvent.
b) cf. reference 10.
c) Chemical shifts with reference to benzene, cyclohexane solvent.
d) cf. reference 15.
e) $\delta=(H_S-H_r/H_r) \times 10^5$ for fluorine chemical shifts.
$\delta=(H_S-H_r/H_r) \times 10^6$ for hydrogen chemical shifts.

Several features of Table I are of interest. The great difference in the absolute magnitude of the fluorine chemical shifts at the meta and para positions is noteworth, particularly when electron donating substituents are present. The shielding parameters of the meta substi-

tuents follow the order $CH_3 > H > NH_2 > OH > Br > NO_2$. The shielding parameters of the para substituted fluorobenzenes, however, follow the order $NH_2 > OH > F > CH_3 > H > NO_2$. The great difference between the shielding parameters of the meta and para substituents has been used by Taft as a test of this σ_R^o scale of resonance constants (10). The fluorine atom is not expected to exert a strongly polarizing effect on the benzene system. This is indicated by the small Hammett sigma constant (0.06) for the para fluoro group. Correlation is obtained by the following expression:

$$\delta_p - \delta_m = -2.97\,\sigma_R^o. \qquad [21]$$

Studies on polysubstituted fluorobenzenes have demonstrated that the chemical shift can be predicted by a simple summation of the chemical shifts produced by the individual substituents (12,13). Deviations of the observed chemical shifts from calculated ones occur frequently, but the deviations are usually small. Taft found the correlation between the chemical shift of meta substituted benzenes and the sigma inductive constant to be

$$\delta_m = -0.583\,(\Sigma\sigma_I) + 0.02. \qquad [22]$$

Correlation of the para substituted fluorobenzenes was less exact, particularly for the p-NO_2, CN, and $COCH_3$ groups. These substituents are thought to experience resonance interation with the fluorine atom. In the less ambiguous cases the chemical shift could be evaluated by

$$\delta = -0.583\,(\Sigma\sigma_I) - 1.880\,\bar{\sigma}_R + 0.08. \qquad [23]$$

Correlation of Hydrogen Chemical Shifts with Substituent Constants.

The use of hydrogen chemical shifts of the ring hydrogens in substituted benzenes as a measure of electron density at a particular carbon atom has several disadvantages. The chemical shifts of the ring hydrogens are seldom as large as the fluorine chemical shifts of substituted fluorobenzenes. Assignment of absorption bands to the various hydrogens is often questionable. Solvent effects play a more important role in the hydrogen chemical shifts than in the fluorobenzene system. However, by a judicious choice of the aromatic system for study many of these difficulties can be overcome.

The extreme limits of the hydrogen chemical shift which arise from substituent effects on a carbon atom in the aromatic system would probably occur in the cyclopentadienyl anion (I) and the cycloheptatriene cation (14).

I

II

Both systems approximate the benzene system, having 6 π electrons. The hydrogen atoms in both (I) and (II) are equivalent and give rise to one olefinic hydrogen peak. The hydrogen chemical shift of (II) relative to benzene is 1.84 ppm to lower field and in (I) the shift is 1.76 ppm to higher field. In the substituted benzenes the chemical shift would probably lie within these extremes with the exception of cases in which the ortho hydrogens interact abnormally with the substituent.

The initial study of the hydrogen chemical shift of mono substituted benzenes was conducted by Corio and Dailey (15). This system gives rise to an AB_2C_2 or AB_2X_2 type of spectra depending on the substituent (16-a). A five spin system is difficult to analyze and one of extreme complexity. In addition the work of Corio and Dailey was conducted at a radio frequency of 30 Mc. For this reason the fine splitting structure is absent from the spectra. In most spectra the most intense peak was assigned to the para hydrogen.

In all cases the difference in chemical shift between the meta and para hydrogens for mono substituted benzenes is less than the values for the similar flurobenzenes (See Table I). The chemical shift between para and meta hydrogens in nitrobenzene is 0.12 ppm. The fluorine chemical shift between para and meta nitrofluorobenzene is on the order of 7.0 ppm. The important facts are that for nitrobenzene both meta and para positions are deshielded with reference to the hydrogens of benzene and there is little difference between the chemical shifts in both positions. The same observations apply for the ortho-para directing substituents. All ring hydrogens are shifted to higher field with reference to the hydrogens of benzene. In the fluorobenzene series the fluorine chemical shift for the meta substituted member is often to a lower field than the unsubstituted fluorobenzene. However, the chemical shift in the para substituted benzene is to a higher field. An illustration of this point is the comparison of the hydrogen resonance spectra of aniline and the fluorine spectra of meta and para fluoroanilines. The hydrogen chemical shifts of the meta and para hydrogens are 0.13 ppm and 0.40 ppm to higher field. However, the chemical shift of the fluorine atom in meta and para fluoroaniline is 0.2 ppm to lower field for the meta compound and 14.1 ppm to higher field for the para compound.

The effect of the replacement of hydrogen atoms with chlorine is clearly demonstrated in the case of toluene. The ring hydrogens of toluene even at 56 Mc. give rise to a single peak (17). The absorption of the ring hydrogens is 0.1 ppm to higher field with reference to benzene. Addition of one chlorine to the methyl group lowers the chemical shift to zero (15). Further replacement of hydrogen by chlorine results in ring proton shifts to lower field. Corio and Dailey have indicated that the effect of the halogens is entirely inductive. However, in trichlorotoluene, even though the meta and para hydrogens are at lower field than the reference the meta hydrogen is more shielded (i.e., shifted to higher field) than is the para hydrogen. Either assignment of absorption bands to meta and para hydrogens is in error or resonance interaction of the trichloromethyl group with the ring occurs. Roberts and co-workers have suggested that the Hammett sigma para constant contains both an inductive and resonance term for the CF_3 group (18).

The ring hydrogens of toluene show a small but definite trend toward lower field as the hydrogens on the methyl group of toluene are replaced by methyl groups (19). The decrease in the chemical shift from methyl to the t-butyl group is not uniform but the trend definitely exists. Within experimental error the trend is independent of solvent. The chemical shifts observed in cyclohexane are almost identical to those observed in nitromethane.

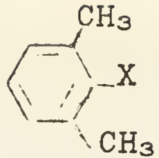
Taft has obtained correlation between the hydrogen chemical shifts of mono substituted benzenes and sigma inductive and resonance $(\bar{\sigma}_R^o)$ constants (10). The relation between the constants and the chemical shift is the following:

$$\delta_H = -0.040\,\sigma_I - 0.104\,\sigma_R^o - 0.002 \qquad [24]$$

The most intense peak is used for correlation. Partial justification for assigning the most intense peak to the para hydrogen is found in the similarity of the ratios of the inductive parameter to the resonance parameter of the chemical shifts of monosubstituted benzenes to the para substituted fluorobenzenes. In both cases the ratio is approximately 3.

An improved method of studying the effect of substituents on chemical shifts in the substituted benzenes is to block one or more positions of the reference compound. Two such systems have been investigated.

(III)



(IV)

System (III)is particularly suited for a study of the dependence of chemical shift on substituents. The system has been described as an A_2B_2 system which, when the chemical shifts between the meta and ortho hydrogens are large, approximates a simple four line spectrum (20). In cases where the chemical shifts are not large, coupling of the hydrogens ortho to the methyl group provides an additional means of identification without the difficulties encountered in the mono substituted benzenes. The effect of the methyl group is assumed to remain constant throughout the range of substituents. The 2,6-xylene system (IV) presents a more diffcultly analyzed spectrum (21). The spectrum is of the AB_2 type and consists of nine lines. Fraser has conducted an analysis of the spectra and has found general agreement with the results obtained by Corio and Dailey (15). However, assignment of the spectrum is more certain.

The 2,6-xylene-1-d showed the hydrogens ortho to the methyl groups shifted to higher field by 10.3 cps at 60 Mc. than the para hydrogens. It was assumed that this preferential shift remained constant throughout the series and the values for the chemical shift of the ortho hydrogens were corrected. For the 2,6-dimethylaniline and 2,6-dimethylanisole the values of the chemical shifts were corrected for steric inhibition of resonance.

The shifts in cycles/second of the meta and para hydrogens were found to be linear combinations of Taft's inductive and resonance constants for the substituents investigated. The relationships are given below:

$$\Delta\nu^1_m = 14.5 - 17\sigma_I - 10\bar{\sigma}_R \qquad [25]$$

$$\Delta\nu_p = 14.5 - 17\sigma_I - 46\bar{\sigma}_R \qquad [26]$$

The maximum error of the meta hydrogen shift was 2.4 cps for the bromoxylene The maximum error of the para hydrogen shift was 1.7 cps for the iodo xylene. The relationship for the meta substituent, unlike the meta substituted flurobenzenes, is a function of the resonance constant. However, the sensitivity of the chemical shift on the resonance constant is less than the sensitivity to the inductive parameter. The correlation for the para hydrogen shows good agreement with the correlation obtained by Taft (See equation [24]). The ratio of the resonance constant to the inductive constant is on the order of 3, which is the approximate value obtained by Taft.

A plot of $\Delta\nu_p$-$\Delta\nu^1_m$ vs. $\bar{\sigma}_R$ gave a good linear plot, indicating an equal dependence of both $\Delta\nu_p$ and $\Delta\nu^1_m$ on the inductive substituent constant. Exceptions were the substituents in which steric inhibition of resonance was possible (i.e., CO_2H, NO_2, OCH_3, $N(CH_3)_2$). These values were corrected by an amount suggest by ultra violet studies (22). The corrected values also showed considerable deviation. It has been suggested that n.m.r. studies such as these offer a more accurate means of determining steric inhibition of resonance than either ultra violet spectroscopy or chemical means.

Solvent effects have been shown to play an important role in the magnitude of the chemical shifts of the ring hydrogens of aromatic systems. This effect has been cited by several authors as a source of serious error in attempted correlation of chemical shift with substituent constants (21, 23, 24). Fig. 1 shows the positions of the resonance signals of the hydrogens ortho and para to the nitro group in nitrotoluene. Chloroform is the reference. It is seen that both ortho and para hydrogen signals vary from solvent to solvent. More impor-

tant is the fact that the internal chemical shift $(\nu_m - \nu_o)$ between the two types of hydrogen does not remain constant but varies from 35.9 cps in acetone to 72.2 cps in benzene. A preferential shift of the hydrogen meta to the nitro group is also observed. This preferential solvent interaction of the hydrogens meta to the nitro group might possibly arise because of steric hinderance to solvent interaction with the ortho hydrogens by the nitro group. However, both types of hydrogens of p-tert.-butyltoluene were shifted the same amount in benzene solvent relative to n-hexane. The same effect was observed when the solvent was acetone. This discredits preferential solvent interactions arising from steric effects alone. Para substituted alkyl benzenes containing electron donating substituents experience similar preferential solvent interactions. In these cases the hydrogens ortho to the substituent were shifted to higher field in benzene solution. This suggests that hydrogen chemical shifts are related to electron density at least in a qualitative manner. However, it is doubtful if a quantitative measure of the electron distribution can be obtained by hydrogen chemical shifts.

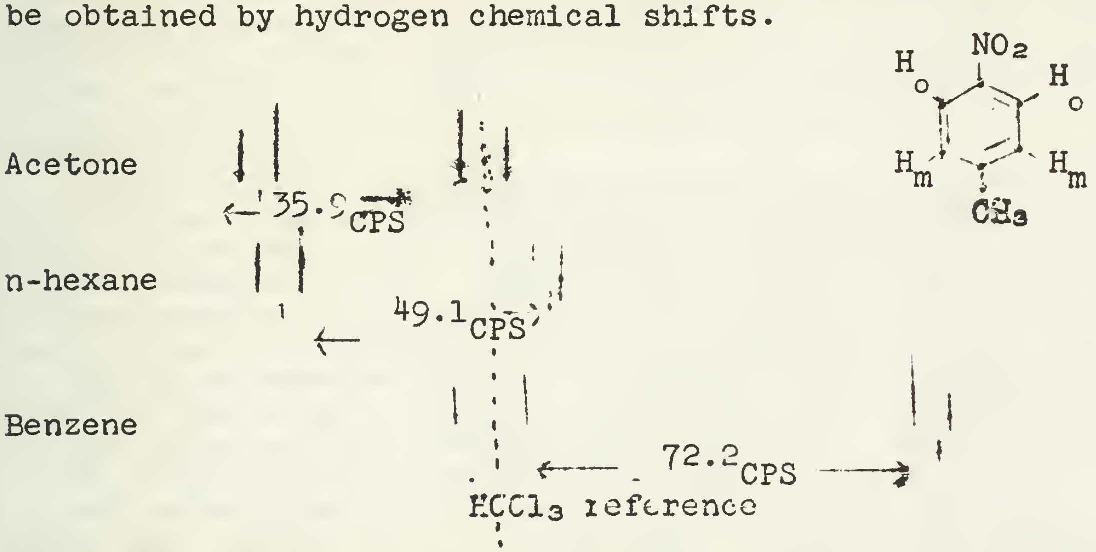


Fig. 1 Dependence of Internal Chemical Shift on Solvent

Correlation of 2-Substituted Propylenes with Substituent Constants.

Recent work indicates that the ionization constants of trans substituted acrylic acids follow a linear free energy relationship (26,27). The trans substituted 2-butenoic acids were also found to follow this relationship.

The 2-substituted propylenes are more suitable for n.m.r. investigation than are the substituted ethylenes. Analysis of the latter is complicated by the additional olefinic hydrogen. Assignment of τ values to the hydrogens cis and trans to the substituent was made according to the results of Jackman (28). Only in the case of the chloro substituent was no differential shielding observed. Jackman has assigned the olefinic hydrogen with the higher τ value to the position trans to the substituent in the compounds with the substituents CO_2CH_3, $COCH_3$, $CONH_2$, C_6H_5 and CHO. It is thought that the carbonyl group deshields the hydrogen cis to the substituent. However, there is doubt as to the correctness of the assignment.

Correlation was obtained by use of the Hammett sigma minus constant and τ. There is little deviation of individual points from the linear relationship. Assignment of the cis-trans configuration to the cyanoethylene is in doubt. However, the differential shielding is 0.04τ and either value lies close to the line. The hydrogen assigned cis to the substituent in the case of bromine has a higher value than does the trans hydrogen. It is interesting to note that in the plot of σ vs τ the linear relationship between σ and τ is obeyed reasonably well for the hydrogens assigned trans to the substituent. A similar plot for the cis hydrogens shows considerable scattering of

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individual points. The one exception is when bromine is the substituent. In this case the τ value assigned to the cis hydrogen correlates much better with the "trans" points than does the value assigned to the trans hydrogen.

Whipple and co-workers studied the same system and have reported no linear relation between any of the sigma values and τ (29). There is considerable disagreement between their data and those of Jackman and co-workers (28).

Long range deshielding effects such as these could explain the abnormally low shielding parameters of the ortho hydrogens in mono substituted benzenes. Preferential deshielding of the ortho hydrogens was observed in this system when the substituents were CO_2R, CHO, $COCH_3$, and NO_2 (15).

Correlation of C_{13} Chemical Shifts with Substituent Constants.

At first glance an isotope of carbon which has a magnetic moment would be an ideal system for study of the effects of substituents on shielding parameters. Unfortunately, the only stable isotope of carbon with a nuclear magnetic moment is C_{13} ($I= 1/2$) which has a natural abundance of 1.1% (16-b). The low abundance of the isotope and its long relaxation time make measurements of its resonance absorption difficult.

Lauterbur has measured the C_{13} chemical shifts of a number of substituted toluenes with the methyl carbon labeled with the C_{13} atom (25). In general, poor correlation of the chemical shifts and Hammett sigma constants exists. Application of Taft's resonance ($\bar{\sigma}_R$) and inductive constants showed better correlation but deviations of individual points were frequent. However, correlation was obtained between the fluorine chemical shifts for substituted fluorobenzenes and the chemical shifts of substituted toluenes. This treatment applied both for the meta and para substituted compounds. A plot of the chemical shift of meta substituted toluenes and the chemical shift of fluorine in meta substtitued fluorobenzens gave a negative slope. A positive slope was obtained for a similar plot of para substituted compounds.

As of yet, the errors associated with the C_{13} chemical shifts make correlations for this system questionable.

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Azo-*bis*-nitriles

Reported by J. J. Uebel March 6, 1961

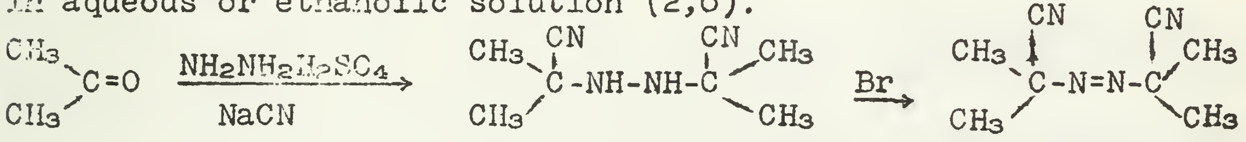
Introduction

The decomposition of azo-*bis*-nitriles is generally thought to be a simple homolytic cleavage of the carbon-nitrogen bonds to produce nitrogen and two radical fragments. The effects of solvent and other radicals in solution are slight; however, the inefficiency of these compounds in producing scavengable radicals and the effects of structural changes are noteworthy and have attracted considerable interest. Since these compounds can be conveniently decomposed by heat or light to yield radicals, they have found use as radical initiators.

The purpose of this seminar is to survey this little-reviewed field (3,4), briefly discussing the relation of structure to reactivity and the efficiency of these compounds in producing "free" radicals (41

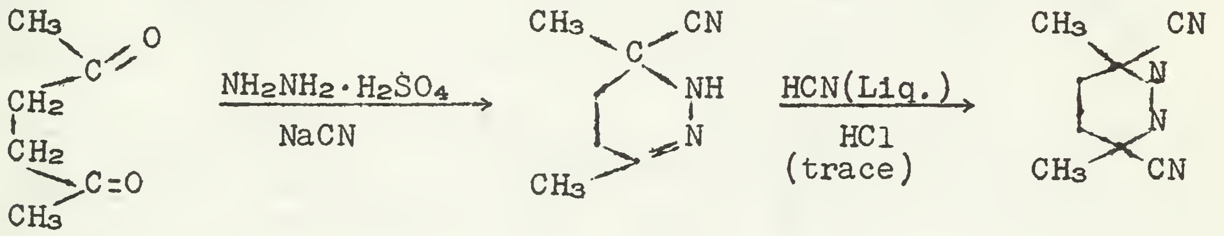
Synthesis

The general method of preparation usually consists of shaking a mixture of a reactive ketone with hydrazine sulfate and sodium or potassium cyanide in aqueous or aqueous-ethanolic solution to yield a hydrazo-*bis*-nitrile which can then generally be oxidized with bromin in aqueous or ethanolic solution (2,6).



a hydrazo-*bis*-nitrile α,α'-azo-*bis*-isobuter-nitrile AIBN

An alternate method, especially valuable for unreactive ketones, consists in preparing the azine for the corresponding ketone by reacti with 100% hydrazine followed by treatment with an excess of liquid HCN to which a slight amount of HCl is added for catalytic purposes (5 The resulting hydrazo-*bis*-nitrile, which normally precipitates out of solution, is then oxidized in the usual way.



acetonyl acetone 57.6% 83.5% (37)

Kinetic Measurements

Probably the most frequently employed method to determine the rate of decomposition of azo-*bis*-nitriles is through measuring the volume of nitrogen released as a function of time. Care must be taken to swee the system with nitrogen and to provide for stirring in the reaction vessel; otherwise, erratic measurements with long induction periods are observed (1,5,6,8,12,14).

Another method is to monitor the disappearance of a radical scavenger by spectrophotometric methods (7,8,34). This method does not necessarily yield the rate of decomposition of the azo-bis-nitril but rather the rate at which scavengable radicals are produced (19).

Closely related to this method are the product analysis and induction methods which are used to determine the efficiency or expected efficiency of an initiator in starting polymer chains. Labele initiators have been used to polymerize vinyl monomers. From the amount of activity in the isolated polymer, together with its molecular weight, and a knowledge of now much initiator has decomposed, one can calculate the average number of initiator fragments per chain and thus the efficiency. This method is subject to several sources of error. First there may be more than one initiator fragment per chain if the termination is by coupling of a growing chain with an initiator radical. There may also be less than one initiator per chain if the propagation steps involve a large amount of chain transfer. Finally, upon isolation of the polymer, it may break up into shorter chains which may be lost or cause a change in the measured molecular weight (20,35,36). The induction method essentially involves the measurement of the length of the induction periods produced by some scavenger in the oxidation of a compound initiated by various amounts of nitrile (33,10,8,34).

The rate of decomposition has also been followed by use of ultraviolet (8,11) and infrared spectroscopy (8,10,18,34) by monitoring the appropriate absorption peak.

Reactivity: Structural Effects

Azo-bis-nitriles when heated in solution or irradiated by u.v. light decompose with evolution of nitrogen. That radical fragments are also produced is supported by the facts that

1) the major products of the decomposition are substituted succinonitriles together with smaller amounts of typical radical products (10,15,16,23),
2) solvents have little effect on the rate of decomposition (1,6,14,38),
3) the compounds can be used to initiate the polymerization of such vinyl monomers as styrene, butadiene, and methyl methacrylate (6,20,21),
4) and the radicals have been trapped by various scavengers (12,17,18,22).

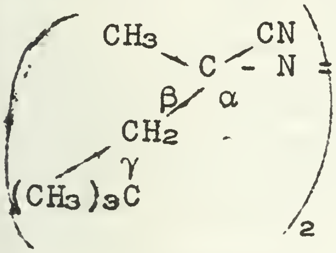
Mixtures of azo-bis-nitriles in solution have been shown to give rise to crossed products, thus showing that at least some of the radicals are "free" in solution and fairly stable (24).

Since changing the concentration of azo-bis-nitrile in solution does not change the rate of decomposition (14,6), one can rule out any induced decomposition as has been found in the decomposition of benzoyl peroxide for example (39). This of course is providing that the induced reaction is not first order in nitrile.

Overberger et al. have put considerable effort into determining a relation between the structure and the reactivity of azo-bis-nitriles. Normally differences in rates of decomposition are attributed to steric factors (5,6,24,26,27,30). For example, a series of compounds of the type

$$R(CH_3)C(CN)-N=N-C(CN)(CH_3)R$$

where R is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, and t-butyl were studied. All the rates were comparable with one another except i-butyl which was about ten times faster (56). A comparison of models of the i-butyl with those of the t-butyl show that steric interaction between the groups on the α-carbon, B-strain (5), is greater in the t-butyl case (25). This would indicate that in the absence of other effects the rate is not very sensitive to B-strain. Models also show that in order to have interaction between halves of a molecule, F-strain (25), one must substitute on the γ-carbon atom (5,26). This might explain why the iso-butyl case was slightly faster, and seems to be borne out in the following series of compounds (26).



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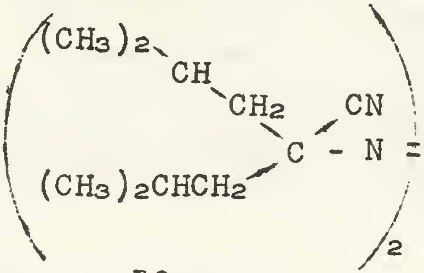

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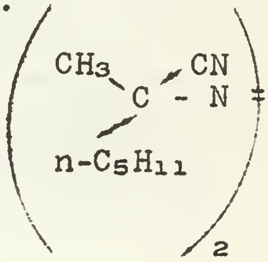

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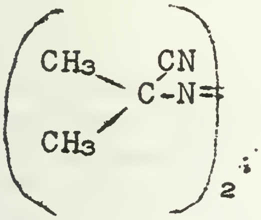

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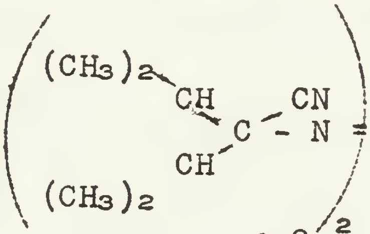

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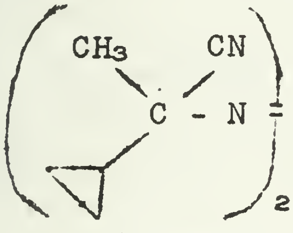
It seems strange to this observer that strain between halves of the molecule should be so much more important than strain between groups on the α-carbon atom. Models indicate that the strain between groups on the α-carbon would be greater, especially since these compounds appear to have a trans configuration (5).

Overberger has done a series of compounds where R is cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The results are summarized below.



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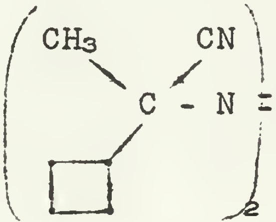

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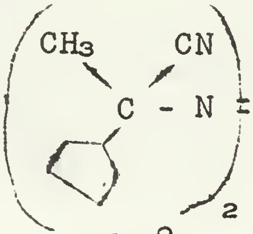

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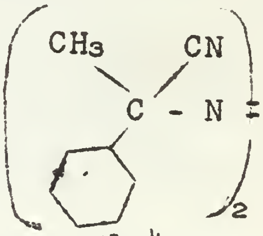

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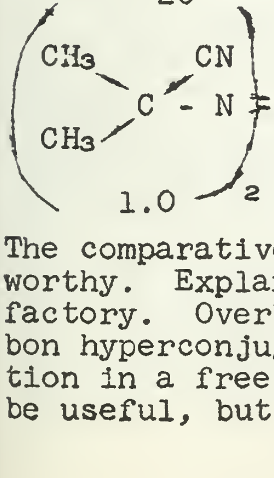
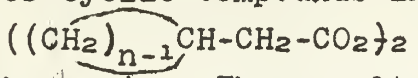


1.0

The comparatively fast rate of the methyl cyclopropyl case is noteworthy. Explanations involving B-strain, or F-strain are not satisfactory. Overberger explains the rate increase in terms of carbon-carbon hyperconjugation (5,27). This may be a case of carbon participation in a free radical reaction, and undoubtedly a product study would be useful, but unfortunately none has been done.

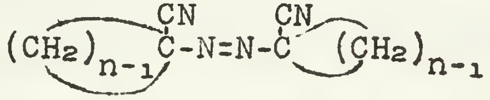
This brings to mind the work of Roberts and collaborators who have found extensive rearrangement in the solvolysis of cyclopropyl carbinyl and cyclobutyl derivatives (28). However, in the radical photochemical vapor-phase chlorination of cyclobutane and methyl cyclopropane they observed no rearrangements (28). Hart has recently studied a series of cyclic compounds in the diacylperoxide family,



$((CH_2)_{n-1}CH\text{-}CH_2\text{-}CO_2)_2$

analogous to Overberger's. The results showed that $C_3 > C_4 \sim C_5 \sim C_6$. However, rate measurements for the cyclopropyl case were very erratic, yielding rate constants ranging from about 2.7×10^{-4} to 1.3×10^{-2} sec.$^{-1}$. The lower values were obtained when the compound was washed well with base or water. It was, even at its slowest rate, about ten times faster than the other members of the series. A product study revealed no rearranged products, with cyclopropyl carbinyl cyclopropane acetate (cyclo-C_3H_5-CH_2-CO_2-CH_2-C_3H_5-cyclo) being produced in 85% yield (29). There is some doubt however, as to whether this is a radical reaction.

A series of compounds of the type



$(CH_2)_{n-1}\overset{CN}{C}\text{-}N{=}N\text{-}\overset{CN}{C}(CH_2)_{n-1}$

was decomposed by Overberger who felt that the relative rates would indicate something about the bond strain, and the steric strain due to compression of van der Waal's radii, I-strain (31), present in the ring (32). The strain between the two halves of the molecules was felt to be minimal since the rates of 1,1'-azocyano-2-methylcyclohexane and 1,1'-azocyanocyclohexane were nearly equal (32). Although this is not conclusive, nevertheless in view of his earlier work it seems reasonalbe. The rates are in the following order.

cyclo $C_8:C_{10}:C_7:C_5:C_6:C_4$ :: 1340:290:200:12:1.0:0.03

It is interesting to compare Overberger's results with those of other workers. For example, Brown and Gerstein (38), found in the solvolysis of 1-chloro-1-methylcycloalkanes that the order was $8 > 5 > 7 > 10 > 6 > 4$, and Prelog and Kobelt found in the dissociation of cyclalkanone cyanohydrins that the order was $10 > 9 > 8 > 7 > 5 > 6$ (37). It is improbable that solvent effects are a contributing factor in the decomposition of cyclic azo-bis-nitriles since the rate of decomposition has been shown to be practically independent of medium, i.e., the cycloheptyl case was done in both acetic acid and toluene with the rates being nearly equal (9,32). However solvent effects may be important in Brown and Gerstein's work, and might well account for some of the differences in the order of reactivity.

One can not help but wonder why I-strain should influence the rate so much while B-strain was found to have only a slight effect in the cases studied (5,6,26). Overberger's case for B-strain is not complete since the i-propyl--t-butyl and the di-t-butyl compounds have yet to be studied. Certainly in these compounds one would expect the steric interactions to be at a maximum, and therefore influence the rate where it might otherwise be unaffected.

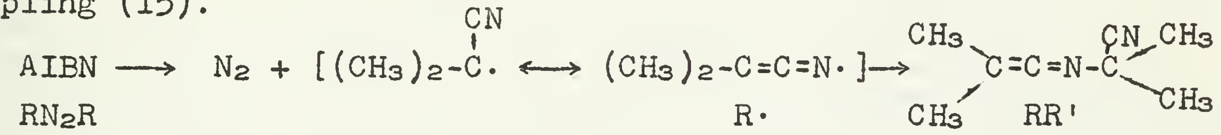
In those instances where the products have been determined, they appear to be mainly those which result from carbon-carbon coupling of the radical fragments, together with small amounts of disproportionation products. Hydrogen abstraction from solvent molecules does not appear to be important (6,21,23).

Efficiency in Radical Production

Much work has gone into determining the efficiency of azo-*bis*-nitriles, especially AIBN in initiating free radical polymerization, or in the production of radicals which may scavenged. The efficiency is generally defined as $^1/_2$ the ratio of the number of polymer chains initiated or the number of radicals which may be captured by a scavenger to the number of azo-*bis*-nitrile molecules destroyed.

Such scavengers as I_2, diphenylpicrylhydrazil (DPPH), and O_2 + 2,6-di-t-butyl-p-cresol (DBPC) have been frequently used to give an indication of the number of "kinetically free" radicals produced (8,17,33,34). For example Hammond measured the yield of tetramethylsuccinonitrile (TMSN) produced in the presence of varying concentrations of scavenger (n-butyl mercaptan). His results showed that the yield of TMSN initially decreased as the concentration of RSH was increased but then leveled off at higher concentrations. Hammond felt that this could be best explained in terms of a cage effect ie. recombination of radical pairs before they diffuse into solution (33).

Talat-Erben and co-workers have detected a reaction intermediate in the decomposition of AIBN in the u.v. and from derivatives concluded that it was a ketenimine formed by carbon-nitrogen radical coupling (15).



They proposed that this decomposes quantitatively via a non-radical path to TMSN (16). Their evidence was based on the fact that they failed to observe a deviation from the kinetic behavior expected from such a mechanism. However, there is reason to believe that their measurements were not sufficiently refined to detect a deviation (34). In addition this intermediate has been isolated and shown to initiate the autoxidation of cumene and the polymerization of styrene (10).

An interesting feature of the RR' decomposition is that it was quite a bit faster in styrene than in benzene (ie. the rate constant in benzene is 3.92×10^{-5} sec.$^{-1}$ while in styrene it was 6.22×10^{-5} sec.$^{-1}$ at 70° C.). The difference in the rate constants for the decomposition of AIBN on the other hand was only about 10%. The acceleration of RR' in styrene could be due to scavenging from the cage by a styrene molecule or else induced decomposition of the ketenimine (10).

Roy, *et al.* (12), have presented evidence in support of an accompanying non-radical reaction in the decomposition of AIBN. They photolyzed AIBN in toluene containing iodine. They found that the quantum yield of organic halide was proportional to the iodine concentration up to I_2 concentrations as high as 0.3M. They felt that I_2 was capable of reaction with germinate radical pairs. However, in the thermal decomposition it was found that the yeild of organic halide relative to the amount of decomposition was constant. The efficiency was calculated to be about 0.6 and remained constant for iodine concentrations ranging from 0.022 to 0.15 moles/liter. It was felt that the inefficiency was not due to a cage effect, recombination of germinate radical pairs before they defuse, but to some non-radical process, perhaps some type of a molecular rearrangement of AIBN to TMSN with the elimination of nitrogen.

On the other hand, Smith and Rosenberg found that the yeild of ketenimine from the photolysis of AIBN at room temperature was similar to that of the thermal decomposition at higher temperatures (40). If two processes were going on one might well expect the yields of ketenimine to be different, unless some coincidences have arisen so as to make the carbon-nitrogen bond formation in the photodecomposition equal to that in the thermal decomposition. If on the other hand one assumes an all radical mechanism for the decomposition, one can infer that the relative amounts of carbon-carbon and carbon-nitrogen recombination are the same inside or outside the solvent cage and that such reactions are practically independent of temperature. This is reasonable since radical coupling reactions have low activation energies.

Hammond and Trapp (38), in an effort to test between a reaction in a solvent cage or a non-radical path, felt that if they were to run the reaction in the presence of a good radical scavenger which could compete with cage recombination, they would alter the course of the reaction if it were radical, but if it were non-radical the scavenger would probably have little effect. Thus they decomposed AIBN in liquid bromine. They felt that they were observing the same reaction since the rate was only about two times that observed in ordinary solvents. Although no reaction products were identified it was shown that if TMSN were formed, it would be stable under the reaction conditions. It was shown later that TMSN is formed in solution even when a large excess of bromine was present (34).

The general scheme proposed by Hammond is given below (8,34).

$$(1)\quad RN_2R \xrightarrow{k_1} \overline{2R\cdot + N_2} \quad \text{(bar indicates solvent cage)}$$

$$(2)\quad \overline{2R\cdot + N_2} \xrightarrow{k_2'} RR + N_2$$

$$(3)\quad \overline{2R\cdot + N_2} \xrightarrow{k'_3} RR' + N_2$$

$$(4)\quad \overline{2R\cdot + N_2} \xrightarrow{k_4} 2R\cdot + N_2 \quad \text{("free" radicals)}$$

$$(5)\quad 2R\cdot \xrightarrow{k_2} RR$$

$$(6)\quad 2R\cdot \xrightarrow{k_3} RR'$$

$$(7)\quad \underline{RR}' \xrightarrow{k'_1} \overline{2R\cdot}$$

$$(8)\quad \overline{2R}\cdot \xrightarrow{k''_2} RR$$

$$(9)\quad \overline{2R}. \xrightarrow{k''_3} RR'$$

$$(10)\quad \overline{2R}\cdot \xrightarrow{k'_4} 2R\cdot$$

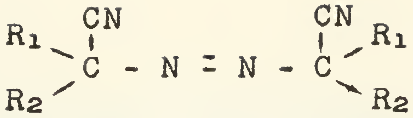
Evidence for this general scheme is provided by the following observations. Note that the rate constants k_2, k_3, k_2' and k_3' are those for primary and secondary recombination processes. The ratio $k_3/k_2 + k_3$ gives the relative amount of ketenimine formed outside the cage. This ratio is the same whether the source of the radicals is an azo-*bis*-nitrile (RN_2R) or a ketenimine (RR'). It was observed that this held true in both the AIBN and 1,1'-azocyanocyclohexane systems, thus indicating that the radicals are kinetically the same regardless of origin, as required by the scheme.

In both the 1,1'-azocyanocyclohexane and AIBN systems the ratios k_3/k_2+k_3 and $k_3'/k_2'+k_3'$ were comparable but not the same. For example with 1,1'-azocyclohexane k_3/k_2+k_3 is 0.68 and k_3'/k_2+k_3' is 0.57 at 100° C. The fact that they are similar in either system is taken to imply that the factors which determine the relative rates of formation of RR (a succinonitrile) and RR' (a ketenimine) in the cage are similar to those for coupling of free cyanoalkyl radicals. In addition in the 1,1'-azocyanocyclohexane system it was found that the ratios did not vary much with temperature. If we assumed two reaction paths this would require that the activation energies be about equal. This fits well with an all radical mechanism since such reactions would be expected to have low activation energies.

The efficiencies of RN_2R and RR' were comparable in each system, 0.6 and 0.4 in the 1,1'-azocyanocyclohexane system and 0.45 and 0.35 in the AIBN system respectively. Note that the efficiency of RR' in each system is smaller. If this is significant it might well be due to the fact that radicals derived from RN_2R are already separated by a molecule of nitrogen and thus can more easily diffuse (8,34).

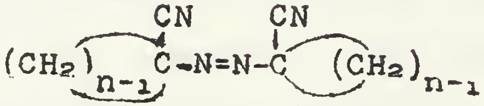
Rate Table

Compounds of the type:



R_1	R_2	$k_1 \times 10^4$ sec.$^{-1}$ corrected to 80.2°C.	E_a (kcal./ mole)	Source
CH_3	CH_3	1.66	34±3	6
C_2H_5	CH_3	0.86	31±3	6
n-C_3H_7	CH_3	1.70	31±3	6
i-C_3H_7	CH_3	1.02	32±4	6
n-C_4H_9	CH_3	1.58	....	6
i-C_4H_9	CH_3	7.10	29±4	6
cyclo-C_6H_{11}	CH_3	0.083	....	6
cyclo-C_3H_5	CH_3	33.0	28±1	5
		26.0 a	26±1	
i-C_4H_9	CH_3	10.0	29±2	5
		7.1 a	29±2	
t-C_4H_9	CH_3	0.77	35±1	5
		1.09 a	30±2	
		now corrected to 80.0° C.		
neo-C_5H_{11}	CH_3	158.13	27±1.5	26
		136.10 a	29±1.5	
n-C_5H_{11}	CH_3	1.63 .1	.....	26
i-C_4H_9	i-C_4H_9	49.5 2.5	.....	26
i-C_3H_7	i-C_3H_7	1.25 .04	.....	26
i-C_3H_7	C_3H_5	0.95 .05	.....	26
		corrected to 80.2° C.		
cyclo-C_3H_5	CH_3	33		5
cyclo-C_4H_7	CH_3	1.51		27
		1.51 a		
cyclo-C_5H_9	CH_3	1.30		27
		1.31 a		
cyclo-C_6H_{11}	CH_3	2.27		27

Compounds of the type:



n	k x 10^{-4} sec.$^{-1}$ (at 80.0° C.)	E_a	$\Delta F^{\ddagger}$	$\Delta S^{\ddagger}$	
4	.00173	32.1	31.6	1.3 eu.	32
5	.726	33.8	27.2	18.9	32
6	.062	35.4	29.0	17.8	32
7	12.22	37.5	25.4	6.1	32
8	83.5	35.9	23.8	5.9	32
10	18.45	28.0	25.0	8.5	32
(2-methyl-cyclohexyl)	.0743				32

a) dl and meso forms

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THE CHEMISTRY OF ADAMATANE

W. S. Chilton

March 9, 1961

Introduction

Adamatane (I) is a symmetric tricyclic hydrocarbon constituent of many petroleum crudes. (1,2).

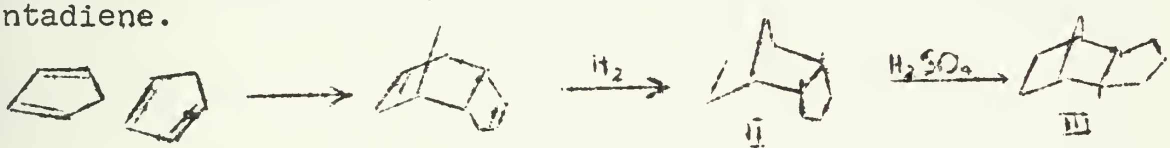
I

It has four identical bridgehead positions and six identical methylene bridges. Adamantane may be regarded as four fused cyclohexane rings all in the chair conformation, from which it is clear that all angles in the framework have the tetrahedral value. The carbon skeleton is rigid but free of angle strain, and all hydrogens are staggered as in the chair form of cyclohexane. The symmetry of the molecule is reflected in its high melting point. Some two hundred hydrocarbons with the formula $C_{10}H_{16}$ are known to melt below 80°C. (3). Adamantane has a melting point of 267°C. The high degree of symmetry is also responsible for the simplicity of its infra-red spectrum. (4). Aside from frequencies due to normal hydrocarbon vibrations, there are two additional bands due to skeletal vibrations at 966 and 1101 cm^{-1} which are found in all adamantane derivatives.

Adamantane was first isolated in 1933 from a Czechoslovak petroleum in minute quantities. (5). Although the discoverers proposed the correct sturcture based on the simplicity of its spectrum and its cubic crystal system, the hydrocarbon was not synthesized until 1941. (6). The synthesis of adamantane and heterocyclic adamantanes have been reviewed. (3,7). The difficulty of isolation from petroleum and the poor yield by synthetic methods hampered study of this interesting hydrocarbon until a novel synthesis from endo-trimethylenenorbornane (8) and a method of introducing functional groups (9) made it readily accessible to investigation.

Synthesis from Trimethylenenorbornane

Endo-trimethylenenorbornane is available from the catalytic hydrogenation of dicyclopentadiene, the Diels-Alder dimer of cyclopentadiene.



The endo to exo isomerization of (II) has been studied by several workers. Schleyer found that endotrimethylenenorbornane after twenty-four hours' equilibration at 100°C in 99.8% sulfuric acid yields a mixture of 99% exo-(III) and 1% endo-trimethylenenorbornane. (10). No traces of any other products were detected by gas chromatography. An attempt was made to synthesize pure exo-trimethylene norbornane in order to approach equilibrium from the other direction, but exo-trimethylene norbornane could not be prepared sufficiently free of endo isomer for this purpose. The endo to exo isomerization is probably initiated by anchimerically assisted hydride removal at C-2.

When trimethylene norbornane was equilibrated in the presence of the stronger Lewis acid, AlCl$_3$, the predominant product was exo-trimethylenenorbornane with a small amount of the endo isomer and a third, isomeric hydrocarbon which was identified as adamantane by infrared spectrum, mass spectral analysis, gas chromatography and mixed melting point. An optimium twenty percent yield of adamantane was obtained when endo-trimethylenenorbornane was treated with twenty mole percent AlBr$_3$ and sec. butylbromide for forty-eight hours at room temperature.

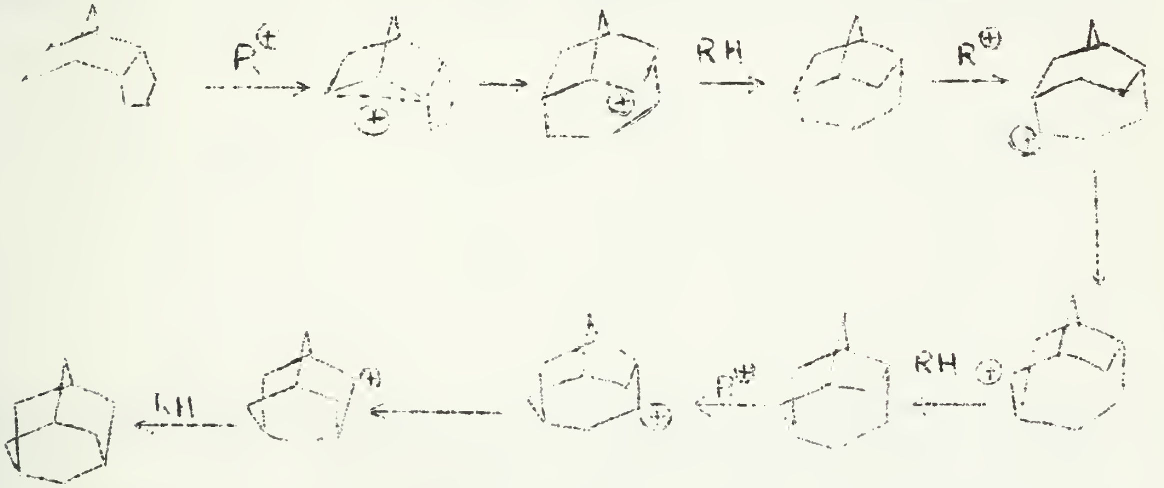
Conversion of endo-trimethylenenorbornane into the exo-isomer in the presence of aluminium chloride was rapid while further isomerization to adamantane was slow. No rearrangement of adamantane on heating in the presence of AlBr$_3$ or **AlCl$_3$** with or without solvent could be detected. Hydrogen-halogen exchange with endo-trimethylenenorbornane and t-butylchloride in the presence of AlCl$_3$ giave a low yield of endo-trimethylene-5-exo-norbornyl chloride (IV) and unreacted starting material only. (11).

IV

V

Under similar conditions exo-trimethylene-2-exo-norbornyl chloride (V) also failed to undergo rearrangement.

Relief of angle strain of the norbornyl system on rearrangement to adamantane provides a driving force for the reaction. The strain energy of norbornane due to CCC angle distortion is about 10 kcal. It is doubtful that equilibrium has been reached in runs starting from endo-trimethylenenorbornane which yield mixtures of 20-25% adamantane and 50-60% exo-trimethylenenorbornane since no reverse isomerization of adamantane is observed under similar conditions. A mechanism involving a 2,6 alkyl shift in the norbornane system (11)



followed by two ring enlarging alkyl shifts has been suggested. (10).

Introduction of Functional Groups

The introduction of functional groups into adamantane is of interest because of the possible limitations imposed on reaction transition states by the molecular rigidity. Radical hydroxylation of adamantane has been accomplised by ultra-violet irradiation of adamantane and peracetic acid in methylene chloride solvent. (11). The composition of the irradiated mixture was 62% adamantane, 24%

1-adamantanol and 7% 2-adamantanol.

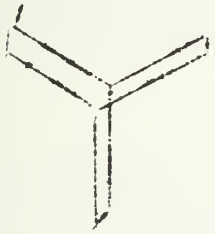
Halogenation is another method of introducing a functional group into adamantane. Bromination at 100°C yields 1-bromoadamantane, identified by its n.m.r. spectrum and its further bromination to the known 1,3 dibromoadamantane in the presence of boron tribromide. (12 13). Bromination in the presence of a large excess of bromine at 150°C without a catalyst gave only the mono bromo product. The bromination is accelerated by Lewis acid catalysts, $AlBr_3$, FeBr, or BBr_3, and is not promoted by light. (14). Introduction of the second bromine is more difficult, requiring a catalyst at 100°C. Introduction of a third and fourth bromine in a sealed tube at 150°C in the presence of $AlBr_3$ gives the symmetrically substituted 1,3,5,7 tetrabromoadamantane. Attack by bromine is specific at the tertiary carbon; no methylene substitution products are observed. The evidence suggests an ionic mechanism involving a carbonium ion at the bridgehead.

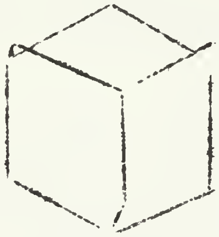
$$R\text{-}H + Br^{\oplus} \rightarrow R^{\oplus}\rightarrow HBr$$
$$R^{\oplus} + Br_2 \rightarrow RBr + Br^{\oplus}$$

Chlorination follows the same course. (15).

The ease of formation of a bridgehead carbonium ion has been demonstrated by the synthesis of adamantyl-1-carboxylic acid by direct carboxylation of adamantane with formic acid in concentrated sulfuric acid employing t-butyl chloride as a hydride acceptor. (16). An 80% yield of adamantyl-1-carboxylic acid is obtained with trimethyl acetic acid as a by-product. Increasing the amount of t-butyl carbonium ion does not give any dicarboxylic acid. Probably the combination of a bridgehead site and the inductive effect of the carboxyl group prevent introduction of a second carboxyl group.

Reactions of the bridgeheads of two other similar systems, bicyclo [2.2.1] heptane (VI) and bicyclo [2.2.2] octane (Vii) have been studied extensively. (22,31). No ionic halogenation of bicyclooctane or bicycloheptane is known, however bicyclooctane may be brominated or chlorinated at 30°C in carbon tetrachloride using ultraviolet light as initiator. (16). The chlorine radical attacks to give equal amounts of bridgehead 1-chloro-bicyclo [2.2.2] octane and 2-chlorobicyclo [2.2.2] octane. The tertiary hydrogen is about six times as reactive as secondary hydrogen, a reactivity ratio similar to that found for radical hydroxylation of adamantane. Radical halogenation attacks bicyclo [2.2.1] heptane primarily at the 2-position. No bridgehead halogenation is detected. (17).


VII


I


VI

Reactions at the Bridgehead

Adamantane undergoes a large number of reactions at the bridgehead.

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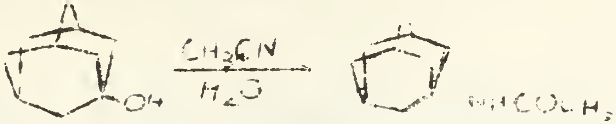
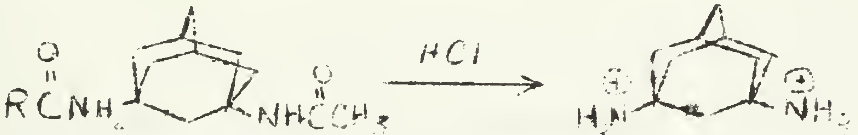
The first example of a Ritter reaction at a bridgehead has been carried out on 1-adamantanol. (12).



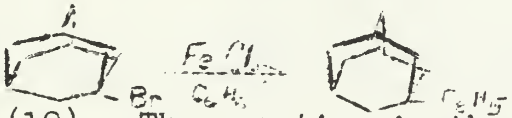
The 1,3-bis acetamido adamantane is obtained from 1,3-dibromo adamantane only in the presence of silver salts. (14).

The amide of 1-adamantane carboxylic acid undergoes the Hoffmann degradation as do the bridgehead carboxamides of bicyclooctane and bicycloheptane. (18,19). The product of the degradation in methanol is N-(adamantyl-1) methylurethane which undergoes basic hydrolysis to 1-amino adamantane. (20). On acid hydrolysis the urethane, toluene sulfonamide and acetamide cleave at the alkyl carbon-nitrogen bond to give 1-chloroadamantane. Amino adamantane itself is stable to refluxing hydrochloric acid. While acid hydrolysis of adamantyl urethane and acetamide involves the adamantyl carbonium ion, acid hydrolysis of 1,3 bis acetamido adamantane gives 1,3 diamino adamantane.

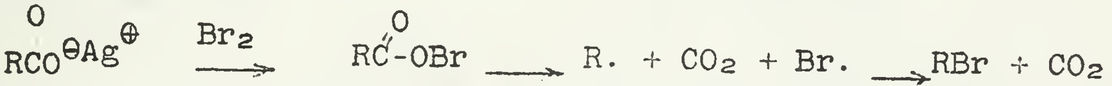


The anomalous course of the hydrolysis of the mono acetaamido adamantane is an indication of the stability of the bridgehead carbonium ion in adamantane. The normal course of hydrolysis of the bifunctional adamantane may be due to the inductive effect of the substituents. A Substituent effect is also noted in the reactivity of the bridgehead bromides which decreases in the order 1-bromo > 1,3,5 tribromo > 1,3,5,7 tetrabromo. (14). Tri- and tetra-bromo adamantane do not undergo the formic acid carboxylation or the Ritter reaction even in the presence of silver salts.

The reaction of 1-bromo adamantane with benzene in the presence of $FeCl_3$ is the only example of a Friedel-Crafts reaction with a bridgehead halide. (12). The reaction in the presence of sodium may be related. Bromo adamantane reacts with benzene and sodium at room temperature to give diadamantyl and phenyl adamantane. At 200° the sole product isolated is phenyl adamantane. (21).



The Hunsdiecker reaction appears to go easily at most bridgehead positions. (22). The generally accepted mechanism for this involves radical intermediates.



$$R\overset{O}{C}O^{\ominus}Ag^{\oplus} \xrightarrow{Br_2} R\overset{O}{C}\text{-}OBr \longrightarrow R\cdot + CO_2 + Br\cdot \longrightarrow RBr + CO_2$$

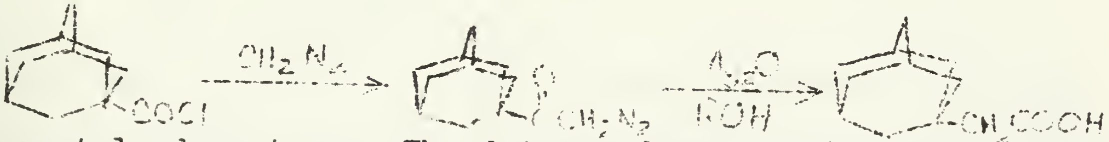
Adamantane-1,3-dicarboxylic acid gives a good yield of 1,3-dibromoadamantane.

Ring Enlargement

In an attempt to prepare adamantyl-1-acetic acid, 1-hydroxymethyladamantane, obtained on $LiAlH_4$ reduction of 1-carbethoxyadamantane, was treated with concentrated sulfuric acid and formic acid. The

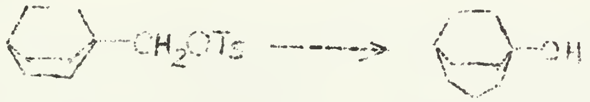
product obtained in 89% yield was a C_{12} acid, but its infrared spectrum did not contain the 966 and 1101cm^{-1} bands characteristic

of adamantanes. (12). The product is probably tricyclo $[4.3.1.1^{1,6}]$ hendecane -1-carboxylic acid formed by ring enlargement. Authentic adamantyl-1-acetic acid was synthesized by the Wolff rearrangement of



diazo acetyl adamantane. The driving force in the carbonium ion rearrangement may be the stabilization gained on rearranging from a primary to a tertiary carbonium ion.

Analogous ring expansions have been observed in the bicyclo [2.2.2] octane series. Solvolysis of the tosylate of 1-hydroxymethyl bicyclo [2.2.2] octane at 145°C in 50% aqueous dioxane gives an almost quantitative yield of 1-bicyclo [3.2.2] nonanol identified



by reduction to the known parent hydrocarbon. (24).

Solvolysis at the Bridgehead

Rate data for the solvolysis of three bridgehead bromides is compared with t-butyl bromide in Table I. (20).

Table I

Solvolysis of Bridgehead Bromides at 25°C

Compound	Medium	K_1 in Sec^{-1}
t-butyl	80% ethanol	4×10^{-4}
1-adamantyl	80% ethanol	1×10^{-7}
1-bicyclcoctyl	70% dioxane*	3×10^{-10}
1-bicycloheptyl	80% ethanol	no reaction

* The ionizing power of 70% dioxane and 80% ethanol are the same.

The steric and electronic environments at the bridgehead substituents in 1- bromo adamantane, 1-bromo bicyclooctane and 1-bromo bicycloheptane are very similar. All of these systems possess rigid carbon skeletons. In addition, the bicyclohexyl system contains a valence bond angle at C-7 compressed considerably below the tetrahedral value. A reaction proceeding via a transition state requiring a planar or near-planar configuration at C-1 in 1-bromoadamantane , 1-bromobicyclo [2.2.1] heptane or 1-bromobicyclo [2.2.2] octane will necessitate a distortion of some or all of the skeletal bond angles and lengths. A reaction involving a carbonium ion transition state is such a reaction; It has been suggested that a tetrahedral carbonium ion is about 24 kcal more energetic than a planar carbonium ion. (25). Such a high energy barrier corresponds to a rate retardation of the order of 10^{17} at room temperature. The strain energy of the carbonium ion can be relieved by allowing the carbonium ion to assume a more planar hybridization. However, this relief of carbonium ion strain energy can

be achieved only by distortion of the remaining carbon bond angles in the skeleton. The relief of carbonium ion strain energy is opposed by increasing skeletal strain energy.

Skeletal strain energy due to distortion of valence angles may be represented to a first approximation by Hookes Law. (25). The force tending to restore a displaced atom is proportional to the angle of displacement, eqn. 2 where the constant of proportionality is the bending force constant evaluated from infrared and raman data.

$$(1)\quad F = K\Delta\theta$$

$$(2)\quad V = \tfrac{1}{2}\Sigma K \cdot (\Delta\theta_i)^2$$

The bending force constant for the C-C bond is about 35 cal/$\frac{\text{mole}}{\text{deg}^2}$. (26). If the distortion of adamantyl carbonium ion were absorbed solely at the three CCC angles adjacent to the carbonium ion, they would be distorted from $109\tfrac{1}{2}$ to 90°. Thus $\Delta\theta = 19\tfrac{1}{2}^\circ$, and the strain energy is given by eqn. 3 , $V(\theta) = \tfrac{1}{2} \cdot 35\ {}^{\text{cal}}/\text{mole/degree}^2\ (19.5^\circ)^2 = 6.6$ Kcal Strain energy of 3 angles is 20 Kcal/mole. An energy minimum for the transition state probably lies somewhere between a tetrahedral and a planar carbonium ion.

An examination of the rate data allows an estimation of the magnitude of strain energy in the quasi-trigonal transition state for solvolysis of the four alkyl bromides. The difference in free energy of activation of 3 bridgehead bromides relative to t-butyl bromide is given in Table II. A more quantitative comparison of strain energies is not possible because of a lack of entropy of activation data for all of the systems. The entropy of activation differences are probably small between the bicyclic systems which have a similar geometry. The trend toward increasing strain energy of bicyclo-(or tricyclo-) alkyl carbonium ions as the number of carbon atoms in the skeleton decreases is to be expected from the fact that to a first approximation strain energy is proportional to the sum of the squares of the angles of deformation , eqn. 2 The more atoms in the skeleton, the less bending of each CCC bond angle is necessary to accommodate a given deformation introduced by a semi-trigonal carbonium ion. Thus at room temperature adamantyl bromide with ten skeletal carbons solvolyses about 400 times as fast as bicyclo [2.2.2]-octyl bromide with eight skeletal carbon atoms.

Table II

Solvolysis of Bridgehead Bromides

Alkyl bromide	$\Delta\Delta F^{\ddagger}$ (Kcal/mole)
t-butyl	0
adamantyl	5
bicyclooctyl	8
bicycloheptyl	→14

Solvolysis at the Methylene Bridge

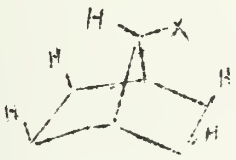
The acetolysis of 2-adamantyl tosylate has been studied and is compared to acetolysis of cyclo hexyltosylate and 7-norbornyl tosylate in Table III. (11). The difference between the acetolysis rates of

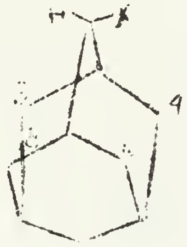
Table III

Rates of Acetolysis at 25°C

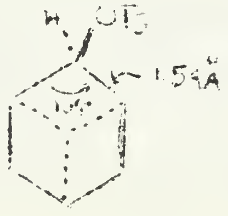
	$K_1 X 10^{-11} sec^{-1}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	ref
cyclohexyl tosylate	4880	27.0 Kcal	-1.1 c.u.	15
2-adamantyl tosylate	325	30.0	+3.2	14
7-norbornyl tosylate	0.0006	37.5	+2.3	16

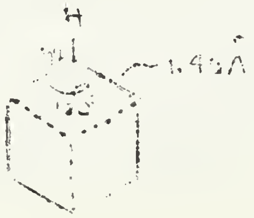
2-adamantyl tosylate and 7-norbornyl tosylate is very pronounced. It has been previously noted that 7-substituted norbornanes solvolyze remarkably slowly, (27,28) and that hydrocarbon substitution reactions on norbornane give little or no 7-substituted product. (17,29). Several possible explanations have been advanced. It is informative to compare the applicability of these arguments to the solvolysis of 2-adamantyl tosylate, whose rate is much closer to cyclohexyl tosylate but whose configuration bears some ressemblance to 7-norbornyl tosylate. It has been suggested that the four exo-hydrogens may hinder solvation of the 7-norbornyl carbonium ion. In adamantyl tosylate four of the hydrogens at C-4, C-8, C-9 and C-10 are actually closer to the functional group than the exo-hydrogens in bicycloheptyl tosylate and should offer about the same degree of hindrance to solvation. Stabilization of the transition state by hydrogen hyperconjugation at the bridgehead is inhibited in solvolysis of both adamantyl and cycloheptyl tosylate by Bredt's rule. The major difference between the two systems is the bond angle imposed at the reacting site. In adamantane $\angle C_1C_2C_3 = 109.5^{\circ}$ and in norbornane $\angle C_1C_7C_4 = 98.^{\circ}$. (30). Thus it appears that the increase in strain energy in going from the ground state to the quasi trigonal transition state is the prime factor determining a 10^7 rate difference between the two systems.





Strain energy may also be responsible for the much smaller rate difference between cyclohexyl tosylate and 2-adamantyl tosylate. The former compound can readily accommodate any angle up to and including the trigonal 120° angle, although some eclipsing of hydrogens is introduced. The more rigid adamantyl system resists the transition from tetrahedral to trigonal bond angles. However, some shortening of the C_2-C_1 and C_2-C_3 bond lengths in the transition state due to increased s-character at C-2 may occur. A 0.08Å reduction in each of these two





bond lengths would allow introduction of the trigonal angle at C-2 with an attendant increase of less than 0.5 Kcal strain energy due to very slight bond bending at C_1 and C_3. The difference between sp^2 and sp^3 carbon covalent bond radii, 0.10A° is of this magnitude.

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SOME ASPECTS OF CARBENE CHEMISTRY

B. H. Klanderman March 13, 1961

Carbene chemistry is a fast-growing field; there have been many surveys of this subject (1-4). This seminar will deal with the ground state of methylene (carbene), the nature of the reacting carbene species, and recent methods for formation of carbenes.

GROUND STATE OF METHYLENE - FORMATION OF CARBENES BY PHOTOLYSIS

Many theoretical calculations for the ground state of methylene have been made (5-11). The energies for a singlet ground state (with all electron spins paired) or a triplet ground state (with one pair of electron spins parallel) lie very close together. An added complication is that the equilibrium positions for the singlet and triplet ground states are predicted at rather similar HCH angles. Depending on the assumptions involved, calculations predict an HCH angle of 90° to 120° for a singlet ground state and an angle of 120° to 180° for a triplet ground state. These facts indicate that determination of the ground state by chemical means may be difficult. Besides, prediction of chemical reactivity of this species is difficult (11). Calculations do agree, however, that for a fairly bent species the lowest allowable excitation should be of lower energy for the singlet ground state (in the visible or IR region) than for the triplet ground state (in the UV region) (10, 11).

Flash photolysis of CH_2N_2 and CD_2N_2 in a 3 m. vacuum spectrograph gives absorptions at 1414.5Å. and 1415.8Å. respectively. Interpretation of these absorptions and their fine structure indicates that these bands definitely arise from CH_2 (or CD_2), that the HCH angle lies between 140° and 180° for the lower state for transition (most likely the ground state), and that the lower electronic state is not totally symmetrical (12). Recently, Herzberg has obtained spectra of methylene from gas phase photolysis showing both singlet and triplet states plus the demonstration that the singlet state is the shorter lived (13). He has also reported the formation of triplet methylene in the presence of a large excess of inert gas (14). Therefore these results support a triplet ground (lower) state.

Another method used to study CH_2 spectroscopically is the trapping of CH_2 in a solid matrix at a very low temperature. In this way CH_2 from the photolysis of CH_2N_2 can be studied before it reacts. Two different techniques have been used. Studies using N_2 and Ar at 20°K. involve the photolysis of CH_2N_2 and partially deuterated CH_2N_2 at different wave-length radiation (15, 16). An unstable substance is stored which produces ethylene after diffusion takes place by warming the sample. Spectra taken from the near UV (2300Å.) through the IR (23.8 μ) regions before and after warming are correlated with known product absorptions. From this analysis, bands attributed to an unstable stored species are observed at 4182, 3968, and 3050-3300Å. The other technique utilizes Kr at 4.2°K. for the trapping of CH_2 from the photolysis of CH_2N_2 and partially and totally deuterated CH_2N_2 (11). In this procedure, called photodeposition, the matrix is produced constantly by depositing a gaseous mixture (low pressure) of the Kr and CH_2N_2 on a quartz window where it is photolyzed (at 4.2°K.). Analysis of the spectra in the 2500-4500Å. region gives indication of bands caused by CH_2 around 3000Å. Thus both techniques using different temperatures and matrices give strong support for the presence of CH_2 with absorption bands around 3000Å. Therefore, a triplet ground state is again favored(11).

Chemical evidence for the ground state of CH_2 has been obtained by the photolysis of CH_2N_2 in the presence of <u>cis</u>- and <u>trans</u>-2-butene with and without an added inert gas, usually N_2 (17, 18). Without

added N_2 stereospecific cis addition occurs, but with added N_2 both cis- and trans-1, 2-dimethylcyclopropane are obtained from either cis- or trans-2-butene. Before drawing any conclusions, a careful comparison of some of these results is necessary. The following table shows the ratio of cis- to trans-1,2-dimethylcyclopropane obtained for different total pressures and the various ratios of inert gas to cis-2-butene. The results using N_2 represent reactions carried out only to a few per cent completion.

Cis-2-butene (mm)	CH_2N_2 (mm)	Inert Gas (mm)	N_2 or Ar /olefin	Tot. Press.	Cis: trans	Ref.
370	400	0	0	770	8:1	17
1.1	1.6	101 (N_2)	92	103.7	1.3:1	17
0.6	5.9	560 (N_2)	933	566.5	0.15:1	17
28	<7	2565 (Ar)	92	2600	1.7:1	18
3	<0.75	2595 (Ar)	850	2600	1.2:1	18

Note: In the experiments using Ar the partial pressures were calculated from the average total pressure of 2600 mm.

These results show that increasing the ratio of inert gas to cis-2-butene results in a loss of stereospecificity, but for the same ratio of inert gas to cis-2-butene the larger total pressure gives rise to more stereospecificity. One explanation for the loss of stereospecificity with added inert gas is that the newly-formed carbene is produced in a singlet state and undergoes a transition to a lower energy triplet state because of collisions with the inert gas (17, 18). It should be pointed out that if a singlet reacts with a double bond such that both new bonds are formed simultaneously, stereospecific addition results; but non-stereospecificity does not rule out a singlet forming one new bond at a time. Stereospecificity does not disprove the existence of a triplet because a triplet may react stereospecifically even though the new bonds are not formed simultaneously. However, if triplet and singlet states are both present, these experiments strongly favor a triplet ground state. A singlet-triplet argument alone cannot explain why the stereospecificity increases for higher total pressure at constant inert gas to olefin ratios. Numerous experiments show that newly-formed cyclopropanes (resulting from the addition of photolytically produced CH_2 to olefins) will have excess vibrational energy which must be lost mainly by third-body collisions and structural isomerization and to a smaller extent by cis-trans isomerization (19-22). The following experimental facts should be noted: the yield of cyclopropane from ethylene and photolytically produced CH_2 increases with pressure (19); the open-chain products from the reaction of trans-2-butene with CH_2 are cis- and trans-2-pentene, 2-methyl-2-butene, and 2-methyl-1-butene (22), but 2-methyl-1-butene can only be formed by structural isomerization of 1,2-dimethylcyclopropane and not by CH bond insertion. These facts support the following theory which assumes that only a singlet (or a triplet) state is present and the lack of stereospecificity results from the cis-trans isomerization of the newly-formed ("hot") cyclopropane. Qualitatively, cis-2-butene should stabilize a "hot" cyclopropane more than Ar or N_2 because of its many rotational and vibrational modes. The efficiency of Ar and N_2 for energy transfer has been found to be approximately 20% compared to methylcyclopropane in kinetic studies of the thermal isomerization of methylcyclopropane at low pressures (25). Unpublished results of Frey indicate that N_2 is 25% as efficient as butene in stabilizing "hot" cyclopropanes (18). Therefore, for the same total gas pressure, increasing the ratio of inert gas to olefin should decrease stereospecificity (as is observed) and, furthermore, for a given ratio of inert gas to olefin, an increase in total pressure should increase the stereospecificity because of the

increased stabilization caused by more collisions of all molecules with each other. An additional observation which can be explained only by the collisional stabilization theory is that at very low pressures without an added inert gas non-stereospecificity occurs (19,22,26). For *cis*- and *trans*-2-butene a 1:3 *cis*:*trans* mixture of 1,2-dimethylcyclopropanes is obtained as the pressure approaches zero (22). Photolytically produced CH_2 reacts at -27° and -70° stereospecifically with olefin in the liquid phase (27, 28). This approximates gas phase reactions at the high pressure limit with no added inert gas. Various results are obtained if O_2 is added to the gas phase reaction of CH_2 with *cis*-2-butene. For reaction at 300° and lower pressures (0-1000 mm.) added O_2 produces no effect on the products (26), but for reaction at 25° and higher pressures (2100-3200 mm.) added O_2 (4 mm.) in the presence of a high ratio (356) of Ar to *cis*-2-butene causes stereospecific products (14:1 *cis*:*trans*) in the same yield as the non-stereospecific products (1.4:1 *cis*:*trans*) obtained without added O_2 (18). These O_2 experiments do not give an obvious conclusion.

Therefore, the nature of the ground state of CH_2 cannot be decided at the present time: spectral evidence supports a triplet ground state but chemical results are inconclusive.

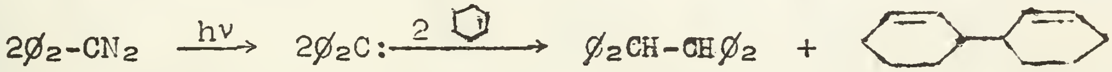
In connection with CH_2 produced by photolysis two more aspects should be discussed. In the first place, the reactivity of CH_2 towards CH bonds has been studied. CH_2 from the photolysis of CH_2N_2 in the gas phase shows less selectivity or discrimination towards primary (1.0), secondary (1.2), and tertiary (1.5) bonds than does CH_2 from the photolysis of ketene (1.0:1.7:?) (28-30). This has been attributed to the excess kinetic energy of carbene from CH_2N_2 (20, 29). Addition of an inert gas will increase selectivity even more, thereby showing that a species deactivated by collision is more selective (30). Photolysis of CH_2N_2 in the liquid phase in the presence of olefins at -70°, -27°, and 15° gives completely random or indiscriminate attack at CH bonds (prim., sec., tert., allyic, or vinyl) (27, 28, 30). It is a question then whether the selective attack in the gas phase is attributable to a triplet attack leading to radicals or simply to loss of kinetic energy of the carbene. Attempts to correlate the A factors and activation energy with the selectivity failed (31, 32).

In the second place, some recent reactions of carbenes produced by photolysis should be mentioned. Photolysis of CH_2N_2 in dry pyridine yields 83% 2-methyl-pyridine (33). Initial attack of carbene at nitrogen followed by intramolecular rearrangement has been suggested. Photolysis of CH_2N_2 in the presence of acetylene yields only allene and propyne but no cyclopropene (34). Evidence for a cyclopropane intermediate is shown by the formation of 1,3-dideuteropropyne and 1,1-dideuteroallene when dideuteroacetylene is used. Irradiation of CH_2N_2 and ethyl diazoacetate in the presence of dimethylacetylene does produce the 1,2-dimethylcyclopropenes (35). Irradiation of 1,1,1-trideuteroethane or a mixture of ethane and hexadeuteroethane yields H_2 and D_2 but very little HD (36). Therefore, evidence for the intermediacy of methyl carbene is presented.

NATURE OF THE REACTING CARBENE

Whether the attacking carbene species is a singlet or a triplet has been the subject of many experiments. The comments about stereospecificity which have been mentioned earlier in this seminar apply to this matter. Therefore, stereospecific *cis* addition does not prove that the attacking carbene is in the singlet state although this is highly probable. Similarly the correlation of activities of carbenes with electrophiles or radicals does not prove the singlet or triplet nature of the reacting carbene. Therefore, the fact that non-aryl

carbenes in gas or liquid phase give cis addition with reactivities toward mono-, di-, tri-, and tetra-substituted olefins that parallel bromination and epoxidation but not radical reactivity cannot be considered as evidence for a singlet state for the attacking species (37, 38). Aryl carbenes yield non-stereospecific products in their reaction with olefins, and their reactivity with olefins parallels that for free radical type intermediates (39). The following reaction for diphenyl carbene further exemplifies radical activity by the allylic attack on cyclohexene (40):

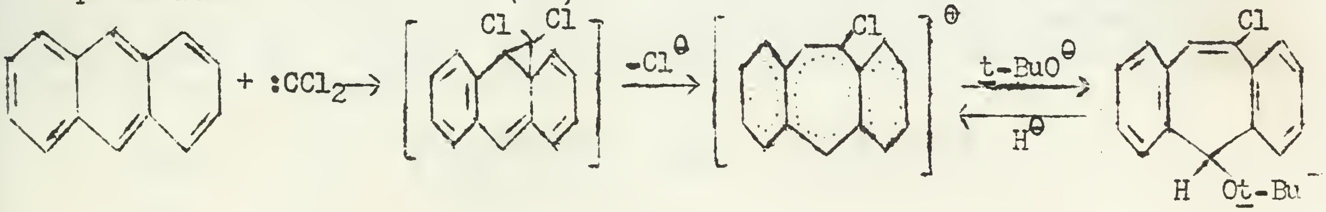


The ESR spectrum of an irradiated solution of di-α-naphthyldiazomethane in methylcyclohexane at -125° shows a signal attributable to the di-α-naphthyl radical formed by hydrogen abstraction by the carbene from the solvent. This same carbene reacts readily with oxygen to form di-α-naphthyl ketone (40). Only with maleic anhydride and such cyclic olefins does diphenyl carbene give stereospecific products (41). On the basis of the preceding observations and in contrast to the non-aryl carbenes, the triplet state cannot definitely be assigned to the attacking aryl carbene, because none of these observations shows directly that a reacting carbene is a triplet or a singlet, even though the evidence is consistent with singlet non-aryl carbenes and triplet aryl carbenes.

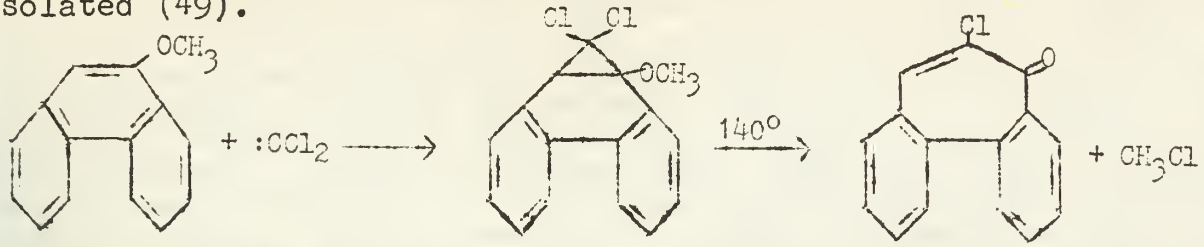
FORMATION OF CARBENES WITH STRONG BASES-ALKOXIDES

Mono- and di-halocarbenes are often produced by the action of strong bases (alkoxides) on di- and tri-halomethanes. Hine and coworkers have continued their studies in this field. The reaction of potassium isopropoxide in isopropyl alcohol with $CHCl_3$ and $CHBr_3$ yields triisopropyl orthoformate, propylene, diisopropyl ether, acetone, carbon monoxide, and a methylene halide as the isolable products (42). With $CHCl_2F$ only triisopropyl formate is formed (42, 43), and with $CHClF_2$ the orthoformate plus difluoromethyl ether and a little fluoroform are produced (44). Evidence for the intermediacy of dihalocarbenes and alkoxyhalocarbenes based on the nature of the products and rates of reaction is similar to that discussed in previous reviews. Similarly, there is evidence for the intermediacy of methoxychloromethylene in the reaction of dichloromethyl ether with isopropoxide (45), and of thiomethoxyfluoromethylene in the reaction of chlorodifluoromethane and sodium thiomethoxide with sodium methoxide (46). The action of sodium methoxide on difluoromethylphenyl sulfone in the presence of sodium thiophenolate yields difluoromethylphenyl sulfide, difluoromethyl ether, and sodium benzenesulfinate; which fact added to the rate of reaction and deuterium exchange studies indicates the intermediacy of difluorocarbene (47).

Halocarbenes will react with aromatic compounds. Reaction of anthracene and chloroform with potassium t-butoxide yields 10-chloro-5-t-butoxydibenzo-(a, e)- cycloheptatriene (10%). The mechanism has been postulated as follows (48):

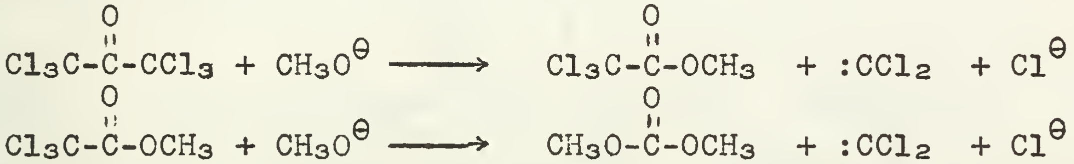


Dichlorocarbene produced from ethyl trichloroacetate and sodium methoxide reacts with 1-methoxynaphthalene, 2-methoxynaphthalene, and 9-methoxyphenanthrene to yield chlorotropones. Only in the case of 9-methoxyphenanthrene can the intermediate cyclopropyl adduct be isolated (49).



Benzene reacts with CH_2Cl_2, CH_2Br_2, or CH_2I_2 in the presence of potassium-t-butoxide to yield the corresponding tropylium halide via the halocarbene in low yields (.1%-2%)(50, 51). Subsequent reaction with HBr produces tropylium bromide. Dihalocarbenes from haloforms do not react with benzene.

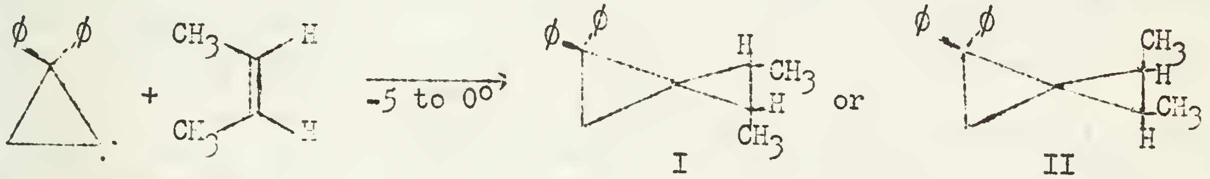
Action of methoxide on hexachloroacetone produces dichlorocarbene as is evidenced by trapping with cyclohexene, 2-methyl-2-butene, or benzalaniline (52, 53). Formation of the carbene can proceed in the following manner:



$$Cl_3C-\overset{O}{\overset{\|}{C}}-CCl_3 + CH_3O^{\ominus} \longrightarrow Cl_3C-\overset{O}{\overset{\|}{C}}-OCH_3 + :CCl_2 + Cl^{\ominus}$$

$$Cl_3C-\overset{O}{\overset{\|}{C}}-OCH_3 + CH_3O^{\ominus} \longrightarrow CH_3O-\overset{O}{\overset{\|}{C}}-OCH_3 + :CCl_2 + Cl^{\ominus}$$

A novel carbene, the cyclopropyl carbene, is produced by treatment of N-(2,2-diphenylcyclopropyl)-N-nitrosourea with lithium ethoxide (54). In the presence of cis- and trans-2-butene stereospecific addition occurs; cis-2-butene may yield I or II, but sterically I is preferred. Thus this reaction affords a new entrance to spiropentane chemistry.



I

II

The intermediacy of a dichlorocarbene intermediate in the Reimer-Tiemann reaction has been demonstrated (55) and discussed in a previous seminar (2). In this reaction only C-alkylation of phenol by CCl_2 produced from $CHCl_3$ and hydroxide ion is observed. In contrast, reaction of phenols with chlorodifluoromethane in the presence of sodium hydroxide yields aryl difluoromethyl ethers (44-66%) and no C-alkylation products (56). The fact that CF_2 gives only O-alkylation indicates that CF_2 is less reactive than CCl_2; the O-alkylation products of CCl_2 reaction are probably hydrolyzed in the work-up procedure. This may account for the poor yields and recovery of phenol in the Reimer-Tiemann reaction.

$$HCClF_2 + OH^{\ominus} \underset{69-70^{\circ}}{\overset{\text{Aq. dioxane}}{\rightleftarrows}} H_2O + :CF_2 + Cl^{\ominus}$$

$$ArO^{\ominus} + :CF_2 \longrightarrow ArOCF_2^{\ominus}$$

$$ArOCF_2^{\ominus} + H_2O \longrightarrow ArOCHF_2 + OH^{\ominus}$$

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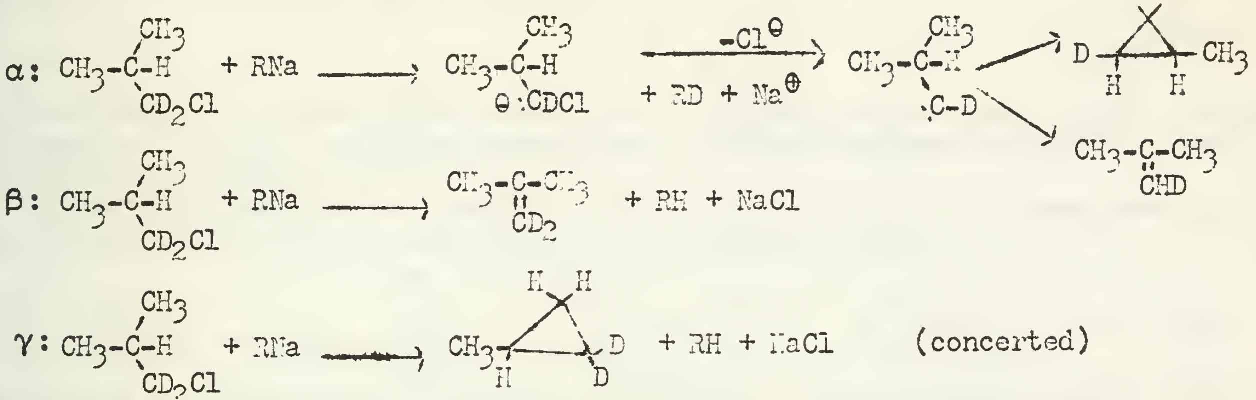
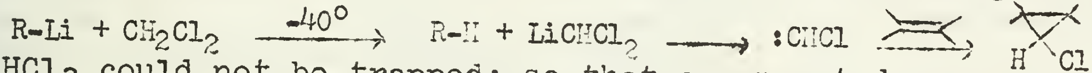
FORMATION OF CARBENES WITH STRONG BASES - METALS AND METAL ALKYLS

Metal alkyls will react with primary alkyl halides to give carbene intermediates. In this way phenyl carbene has been produced from benzyl chloride (57). Benzyl chloride and phenyllithium in the presence of cyclohexene yield the expected 7-phenylnorcarane derivative (14%) plus 3-benzylcyclohexene (11%) and 1,2-diphenylethane (14%). Methyl chloride and phenylsodium yield methylene which can be trapped with cyclohexene (3.2%) or cis-2-butene (1%) (58). In addition benzene (19%), toluene (41%), ethylbenzene (1.9%), n-propylbenzene (0.1%), isopropylbenzene (.08%), and benzoic acid (3%) are formed. Primary alkyl halides with three or more carbon atoms react with metal alkyls or alkali metals (Na or K, not Li) to yield cyclopropanes and olefins in addition to the usual saturated hydrocarbons (59-63). Three possible mechanisms may be proposed for formation of cyclopropanes and/or olefins: α-, β-, γ-elimination.

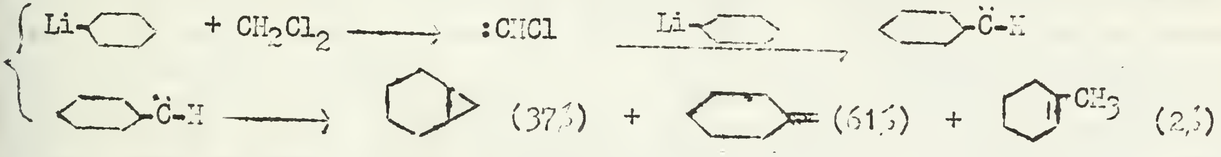


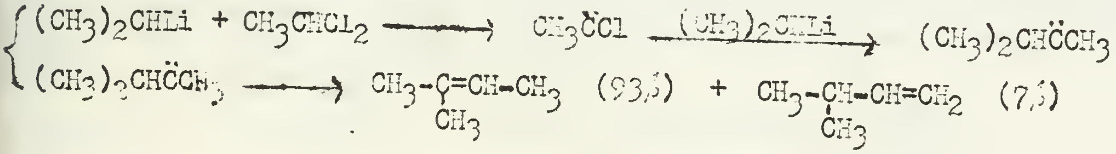
Deuterium labelling studies with 1-chloro-1,1-dideutero-2-methylpropane and Na or K (59, 60), or with 1,1-dideuteroneopentyl chloride and phenyllithium (61, 62) show that the cyclopropyl compound is formed exclusively by α-elimination (one deuterium per molecule) and olefin by 66% α-elimination and 34% β-elimination. Using Li gives no cyclopropyl compound; $NaNH_2$ and $NaOCH_3$ produce lower yields of cyclopropane. Further support of carbene intermediates is that product yields are very similar to those obtained from alkaline carbenoid decomposition of aldehyde tosyl hydrazones (64). Phenylsodium reacts similarly with secondary alkyl halides to yield cyclopropanes by α-elimination (62); however, Na and K produce mainly β-elimination (60).

Metal alkyls react with gem-dihaloalkanes to give haloalkyl carbenes. Thus CH_2Cl_2 reacts with n-butyllithium in the presence of olefins to yield cyclopropanes (65, 66) according to the following mechanism:



$LiCHCl_2$ could not be trapped; so that a concerted process may be taking place. Reaction of the halocarbene with more alkyl lithium leads to alkylcarbenes which may react by intramolecular insertion to produce cyclopropanes or by hydrogen migration to form olefins (60, 67).

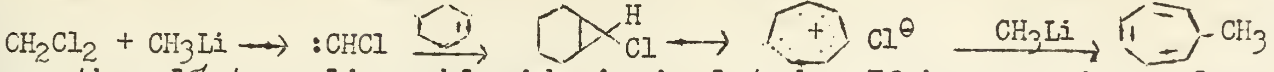




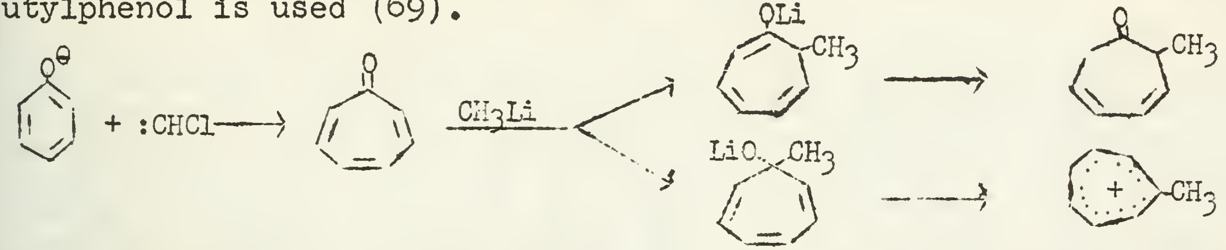
$$(CH_3)_2CHLi + CH_3CHCl_2 \longrightarrow CH_3\ddot{C}Cl \xrightarrow{(CH_3)_2CHLi} (CH_3)_2CH\ddot{C}CH_3$$

$$(CH_3)_2CH\ddot{C}CH_3 \longrightarrow CH_3-\underset{CH_3}{C}=CH-CH_3\ (93\%) + CH_3-\underset{CH_3}{CH}-CH=CH_2\ (7\%)$$

Benzene, CH_2Cl_2, and methyllithium react to give methylcycloheptatriene (20%) (68). Presumably chlorocarbene is an intermediate:

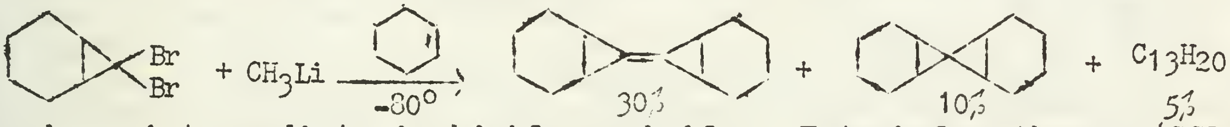


Less than 1% tropylium chloride is isolated. If benzene is replaced by lithium phenolate the expected tropone can be detected in only 0.1% by UV. The isolable products are 2-methyl-3,5-cycloheptadienone (30%) and methyltropylium ion (4%) which probably result from a fast nucleophilic addition of methyllithium at position 2 or 1 respectively of the initally formed tropone. The tropone can be isolated if 2,6-di-*t*-butylphenol is used (69).



Halocarbene (produced from CH_2Cl_2 and *n*-BuLi) also reacts with triphenylphosphine to give triphenylphosphine chloromethylene which is useful in the Wittig reaction (70).

7,7-dibromonorcarane reacts with methyllithium in the presence of cyclohexene to produce the following products (71):



A carbene intermediate is highly probable. Tetrahalomethanes (CCl_4, $CBrCl_3$, $CICl_3$) react with alkyllithium compounds in the presence of cyclohexene to yield the expected dihalonorcaranes (72).

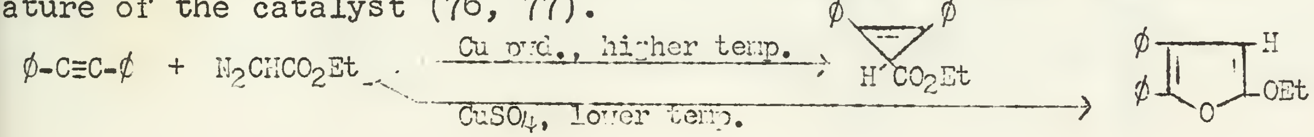
Strong bases can produce carbene intermediates by reaction with non-halogen compounds. Action of *n*-butyllithium on phenyl benzyl ether in the presence of isobutene produces 1,1-dimethyl-2-phenylcyclopropane (low yield) and in the presence of triphenylphosphine produces triphenylphosphine benzylene (<1%) (73). Tetramethylammonium bromide and a 1:10 mixture of phenyllithium: phenylsodium in the presence of cyclohexene yield 5-18% norcarane (74). Thus the formed trimethylammonium-ylid is a methlene donor:

$$(CH_3)_4N^{\oplus}Br^{\ominus} + \phi Li:\phi Na\ (1:10) \longrightarrow (CH_3)_3\overset{\oplus}{N}-\overset{\ominus}{C}H_2 + \phi H + NaBr$$

When the reaction proceeds in the presence of triphenylphosphine, triphenylphosphine methylene is produced.

FORMATION OF CARBENES BY THERMAL DECOMPOSITION

Thermal decomposition of various types of compounds produce carbene intermediates as is evidenced by trapping techniques and product studies. Thermal decomposition of diazo compounds to produce carbenes has been known for many years. Heating diazobenzyl cyanide in the presence of diphenylacetylene yields 1, 2, 3- triphenyl-3-cyanocyclopropene which can be treated with BF_3 etherate to give the triphenylcyclopropenyl carbonium ion (75). Heating ethyl diazoacetate in the presence of diphenylacetylene and a copper catalyst yields a substituted cyclopropane or a substituted furan depending upon the temperature and nature of the catalyst (76, 77).



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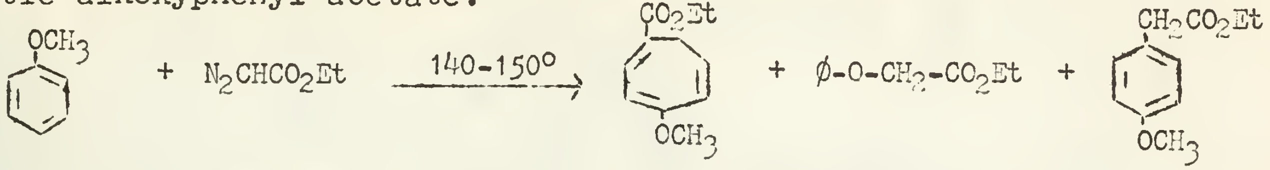
Investigations have been carried out utilizing the thermal decomposition of ethyl diazoacetate in the presence of arylalkyl and dialkyl ethers and acetic anhydride (78-80). For arylalkyl ethers the main product is the 4-alkoxy-cycloheptatriene-1-carboxylic acid besides 6-18% o the alkyl ester of phenoxyacetic acid (from O-attack) and sometimes a little alkoxyphenyl acetate.

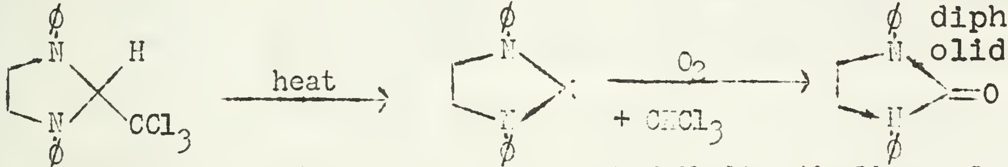


With dialkyl ethers products resulting from O-attack and CH bond insertion are found. For di-n-butyl ether 14.0%, 0%, 4.5%, and 4.7% yields are obtained for the α, β, γ, and δ CH bond insertions respectively. The O-attack yields ethyl n-butoxyacetate (9.3%) and 1-butene (6%) (79). Using CH_2N_2 yields products with CH bond insertion at all positions, but with no O-attack. This does not agree with the photolysis of CH_2N_2 experiment using di-n-butyl ether (81). In this case only ethyl n-butoxyacetate is isolated and the presence of 1-butene is confirmed by its conversion to 1,2-dibromobutane. With acetic anhydride only O-attack occurs (80).

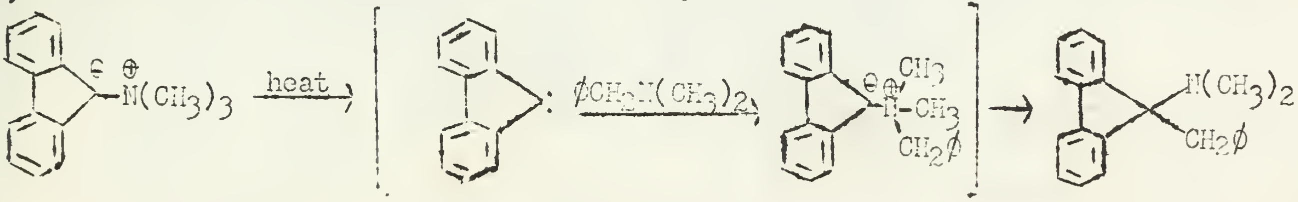
The existence of difluorocarbene has been successfully shown by the formation of 11% 7,7-difluoronorcarane when sodium chlorodifluoroacetate is heated for thirty hours in the presence of cyclohexene (82). The thermal decomposition of silver trichloroacetate in the presence of cyclohexene yields 10% 7,7-dichloronorcarane, but the main product is trichloroacetic anhydride (83). Heating chloroform, bromoform, or trichloroacetic acid with aqueous $AgNO_3$ in the presence of cyclohexene produces 10% of the norcarane derivative, but the major product is trichloronitromethane (84). The presence of a carbene intermediate is thereby shown but reaction with a species other than cyclohexene seems to be more favorable in the above reactions.

An unusual formation for dichlorocarbene has been claimed in the reaction of carbon with tetrachloride at 1300° for ten hours under high vacuum (85). Not only are the typical carbene reactions reported (reaction with cyclohexene to yield the norcarane derivative, reaction with oxygen to yield phosgene), but values are given for molecular weight (84.62, 84.70), melting point (-114°), and boiling point (-20°). This reaction deserves more investigation; it is interesting that mass spectrometric studies show that chlorine or carbon tetrachloride do not react rapidly, if at all, with carbon dissolved in tungsten to give CCl_2 (86).

Thermal decomposition of 1,3-diphenyl-1-trichloromethylimidazolidine produced from the reaction of chloral and N,N'-diphenyldiaminoethane yields a crystalline compound which reacts with oxygen to give 1,3-diphenyl-1-imidazolidone (87).



Trimethylammonium-9-fluorenylid and N,N-dimethylbenzylamine yield 9-dimethylamino-9-benzyl-fluorene when they are heated together in ether (88). A carbene intermediate is likely.



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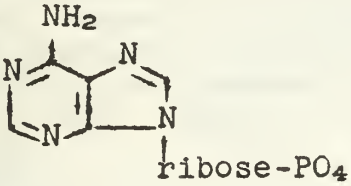
PHOSPHATE LOCATION IN NUCLEOTIDES

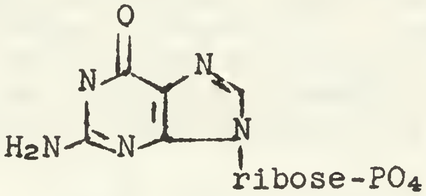
Reported by J. L. Foght March 16, 1961

Introduction

The hydrolysis of naturally occuring nucleic acids yields compounds designated as nucleotides, which contain three components -- a nitrogenous base, a five carbon sugar, and a phosphate group. The nucleotides with which this seminar will be concerned are the four products of ribonucleic acid (RNA) hydrolysis (adenylic acid (I), guanylic acid (II), citidylic acid (III), and uridylic acid (IV)) and the four principal products of deoxyribonucleic acid (DNA) hydrolysis (deoxyadenylic acid, deoxyguanylic acid, deoxycytidylic acid, and thymidylic acid (V)).



(I)



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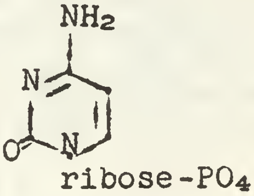

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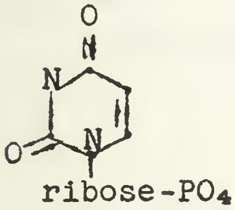
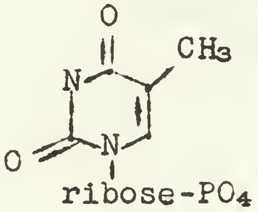


(IV)

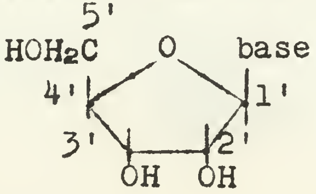


(V)

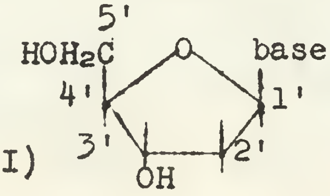
Nucleotide types of structure are also found in such important coenzymes as triphosphopyridine nucleotide (TPN), adenosine-5'-triphosphate (ATP) and coenzyme A(CoA). This group of compounds is certainly one of the most varied and versatile in nature, being concerned with such diverse functions as intermediary metabolism, energy transformations, and heredity (1,2).

In those nucleotides derived from ribonucleic acid (RNA) the sugar group is D-ribofuranose (VI) which is attached by a β-glycosydic bond involving its carbon 1' to the appropriate nitrogenous base. Thus, the phosphate group may be attached at positions 2', 3', or 5'. The sugar group of the nucleotides derived from DNA is 2'-deoxyribofuranose (VII), similarly involved in a glycosydic bond at its carbon 1'. Here, the phosphate group may be attached at positions 3' or 5'. Because of the great significance of these compounds, determination of the exact location of the phosphate groups was extensively investigated (3). Unambiguous chemical synthesis of the nucleotides for the purpose of positively identifying the position of the phosphate, as well as for studies on polynucleotide formation, has thus been of great interest to a number of research teams.

(VI)



(VII)

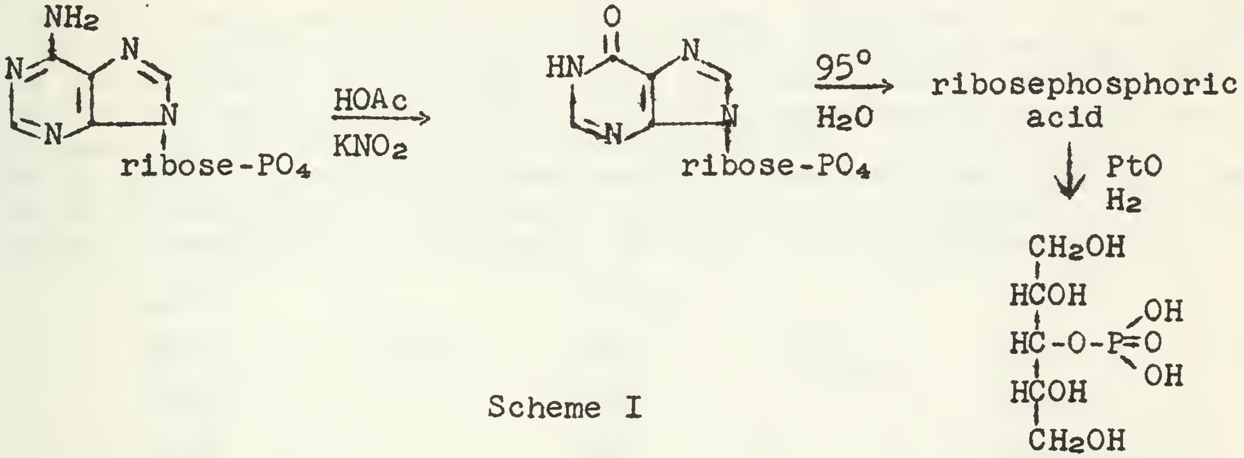


There are two basic problems involved in the synthesis of a specific nucleotide. First, one must select a specific reagent to phosphorylate a particular nucleoside. Second, the position of the introduced phosphate group must be determined.

Determination of Phosphate Position

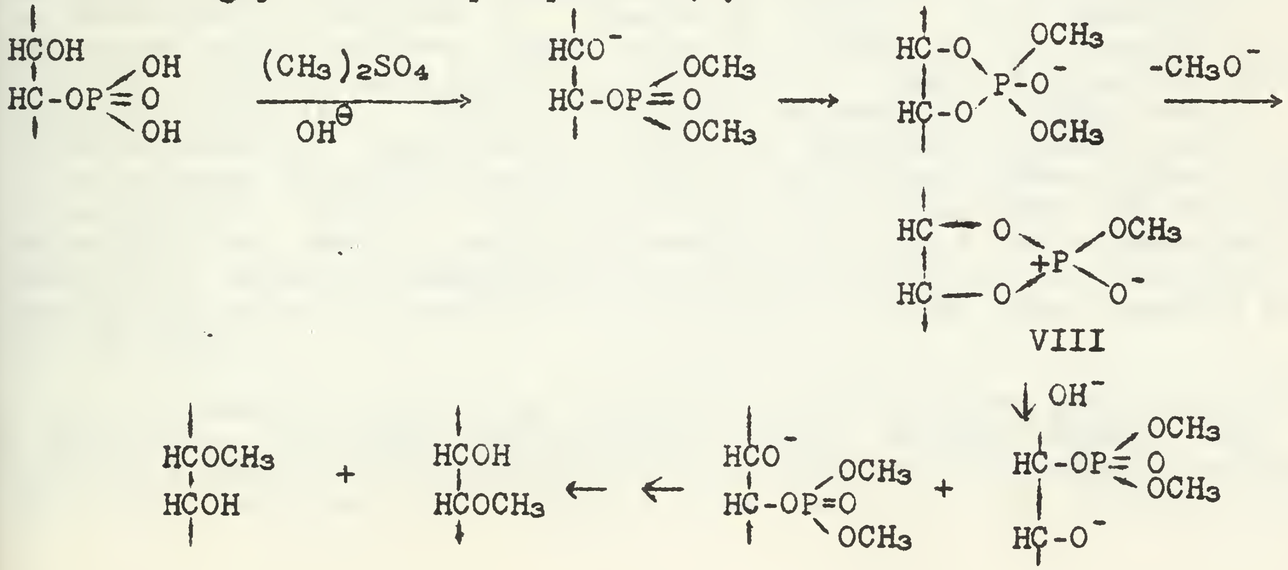
A number of methods have been utilized for the determination of the location of the phosphate ester in the synthesized nucleotide. Ideally, one would devise a reaction scheme which would introduce the phosphate group at only one known position. However, this has been realized in very few of the attempted syntheses.

In the earlier attempts the products were usually characterized by the standard methods of sugar chemistry. Thus, synthesized adenylic acid was completely methylated, then hydrolyzed, and the methylated ribose was compared to known methyl riboses (4). Again, adenylic acid was oxidized to inosinic acid, then hydrolyzed, and the resulting phosphoribose was reduced to the optically inactive ribitolphosphate (scheme I) (5). However, both of these methods are open to criticism.

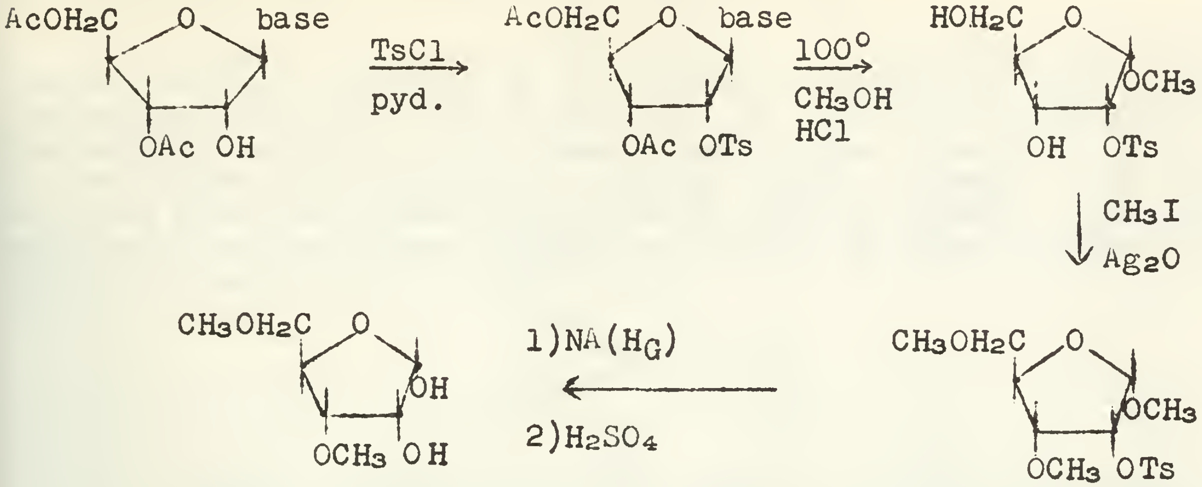


Scheme I

In the methylation procedure, the phosphate may be initially methylated, a cyclic intermediate (VIII) could form, and the methylated ribose would have methyl groups at either of two positions (6). Thus, the original position of the phosphate group would be ambiguous. In the acid hydrolysis procedure the phosphate may also cyclize and thus isomerize (7), probably in a manner analogous to the acidic reaction of glycerol monophosphates (8).

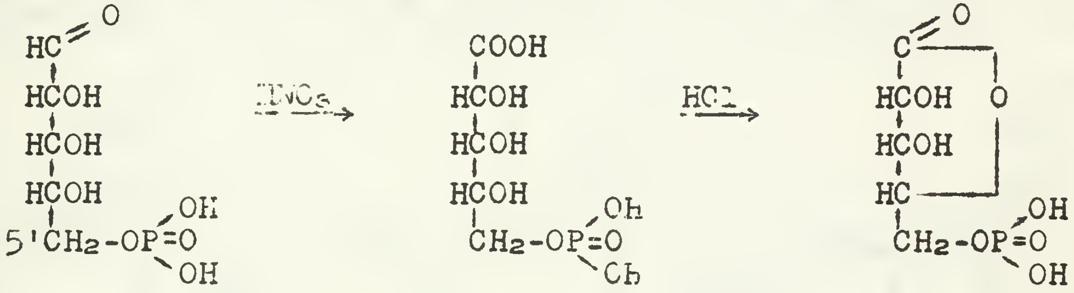


Methylation can be utilized to identify di-o-acetylated material to be used for phosphorylation (scheme II) and thus the phosphate is located indirectly (9).



Scheme II

Another early method of identification, which would be reliable only for 5' phosphates because of phosphoryl migration, was hydrolysis of the nucleotide to the phosphoribose and oxidation of this to the phosphoribonic acid (scheme III). Then the phosphoribonic acid was lactonized and the rate observed by mutarotation. The γ-lactone is formed at a much slower rate than the δ-lactone and thus a 5'-phosphate can be distinguished readily (10). The 5'-phosphate also can be indirectly identified by treatment of the 2',3'-blocked precursors



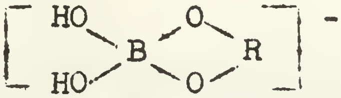
Scheme III

with p-toluenesulfonyl chloride. A primary tosyl group may be easily substituted by sodium iodide to give a nearly quantitative yield of the 5'-monoiodo derivative (11,12b). Uptake of one mole of periodate has been used to indicate a 5'-phosphate (2,13). 2',3'-Blocked precursors also have been tentatively identified by the ease of tritylation of the primary hydroxyl group (14). Once the location of the phosphate group in a nucleotide has been determined, comparison of the same compound, supposedly prepared by some new approach, can of course be made by melting point, optical rotation, ultra-violet, and infra-red(15). However, the dibrucine salts, often used for characterization, may lead to ambiguous results (13,14). The ion-exchange behavior of known phosphates have often been used for the tentative identification of nucleotides (7,12,13,16). Again, these results are open to doubt.

In a number of cases the synthetic route has been used as proof of position, not always very reliably. Thus, various chemists synthesized a number of mono-phosphates of adenosine, guanosine, cytidine and uridine and identified them from the supposed [illegible],5' position of a

at the 3',5'-position only by analogy to the benzylidene derivative of free sugars. However, it was later shown that the blocking group was actually located at the 2',3'-position and the products were 5'-phosphates rather than 2'-phosphates (13).

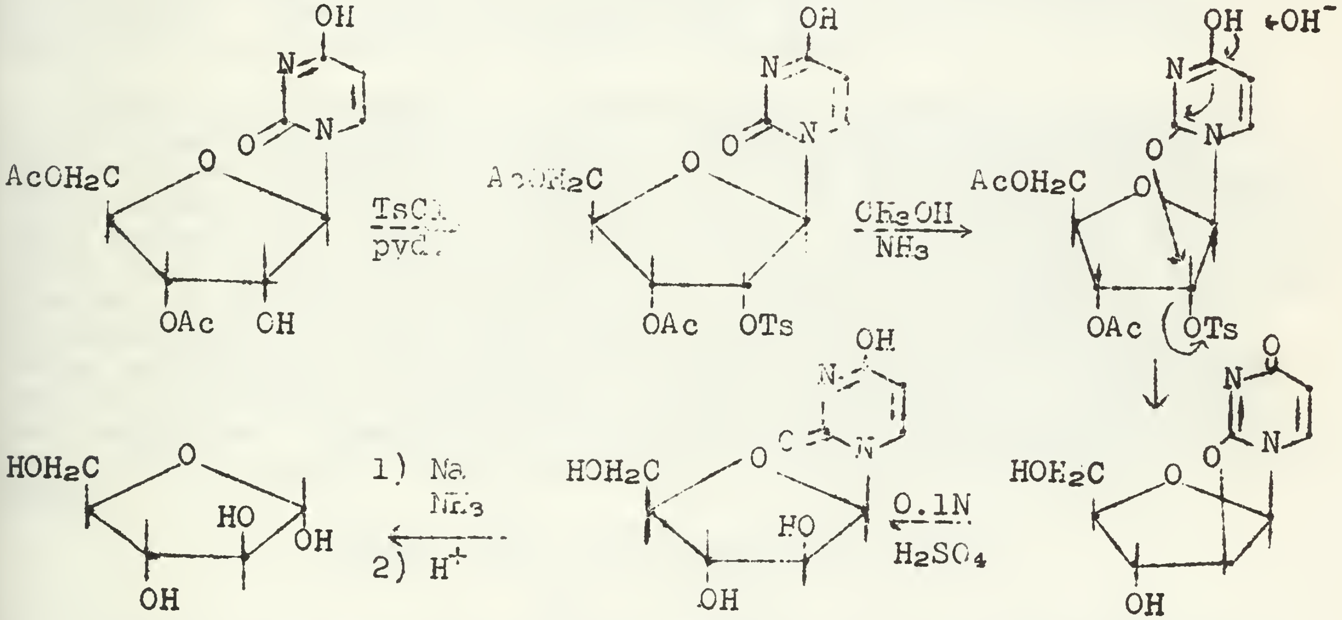
One method, which is quite reliable if the methylated ribose is obtained without possibility of phosphoryl migration (i.e., from a blocked precursor), is the application of zone electrophoresis (18). The methylated ribose will migrate toward the anode in borate solution, if the proper borate-hydroxyl complex (IX) is formed. 1',2'-Complexes are most stable and thus migrate most rapidly, whereas riboses methylated in the proper positions will not be able to form a complex and will remain at the origin (9,19).



IX

An enzymatic method which has found widespread application employs a specific nucleotidase (3'- or 5'-) isolated from snake venom (20.21).

A very interesting example of the location of blocking groups on an intermediate was the work on 3',5'-di-O-acetyl uridine by Todd and co-workers (22). The compound was tosylated and treated with saturated methanolic ammonia (scheme IV). The resultant compound was hydrolyzed to yield arabinose. This reaction was explained by expulsion of a 2'-tosyl by nucleophilic attack of the 2-carbonyl. If the tosyl had been at the 3'-position, xylose should have been obtained.



Scheme IV

The rates of alkaline and acid hydrolysis have been studied to observe any difference for 2'- and 3'-phosphates (23). The 3'-phosphate is more rapidly degraded in alkali, perhaps due to β-elimination. In acid, on the other hand, the 2'-phosphate gives ribose more rapidly. An analogous situation occurs in the glucose phosphates (24).

[illegible] from a 3'- or [illegible] and may [illegible]

[illegible]

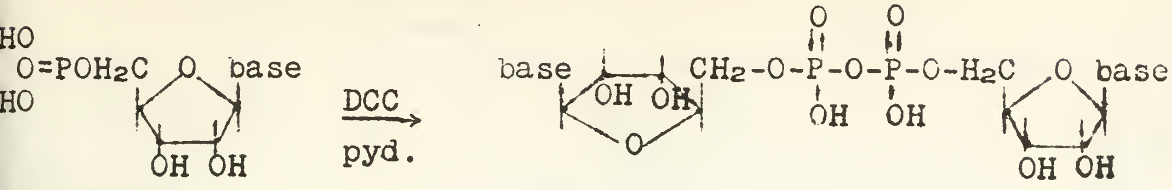
[illegible]

[illegible]

[illegible]

[illegible]

yield P^1, P^2-dinucleoside-5'-pyrophosphate (X) (16), while the 2'- or 3'- phosphates yield cyclic phosphates (25).

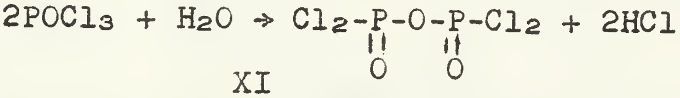


X

Synthesis

The actual synthesis of mono-nucleotides from nucleosides has involved a number of problems. The acid lability of glycosydic bonds generally rules out the more acidic reaction conditions. The base lability of the 6-amino group of cytosine likewise presents difficulties in the base catalyzed phosphorylations (26). Catalytic reduction of pyrimidine rings, with resultant sensitising of the glycosydic bond, may also be a harmful factor in synthesis (27). Two broad classes of reagents have been utilized for phosphorylation of nucleoside hydroxyls. Usually the reactions have been base catalyzed and of a rather mild nature. The second class, involving drastic conditions with a large excess of reagent, have found application in the esterification of the less reactive secondary positions, especially with guanosine. The general phosphorylating agents for all types of hydroxyl containing compounds have been reviewed recently (28). Also, a number of earlier attempts at phosphorylation were reviewed by Todd (2,29). Thus, this discussion will be limited to the more significant and unambiguous synthetic routes.

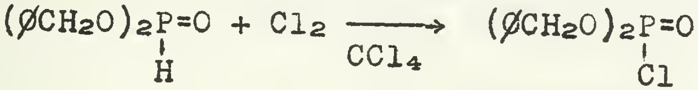
The first successful nucleoside phosphorylations were carried out by Levene and Tipson, using phosphorous oxychloride ($POCl_3$). They prepared uridine -5'-phosphate (11) and adenosine-5'-phosphate (30) in low yield from the respective 2',3'-isopropylidene derivatives. Other workers have since used this reagent, but with yields of no higher than 20 percent (14,17,21,31). Khorana has suggested that the phosphorous oxychloride may react with traces of moisture to give pyrophosphoryl chloride (XI), which could act as a polyphosphorylating agent (21b). He isolated 5'-diphosphate and 5'-triphosphate from the reaction of phosphorous oxychloride with 2',3'-isopropylidene guanosine. Phosphorous oxychloride may be considered as a rather unsuccessful reagent, which gives poor yields and is difficult to handle.



$$2POCl_3 + H_2O \rightarrow Cl_2-\underset{\underset{O}{\|}}{P}-O-\underset{\underset{O}{\|}}{P}-Cl_2 + 2HCl$$

XI

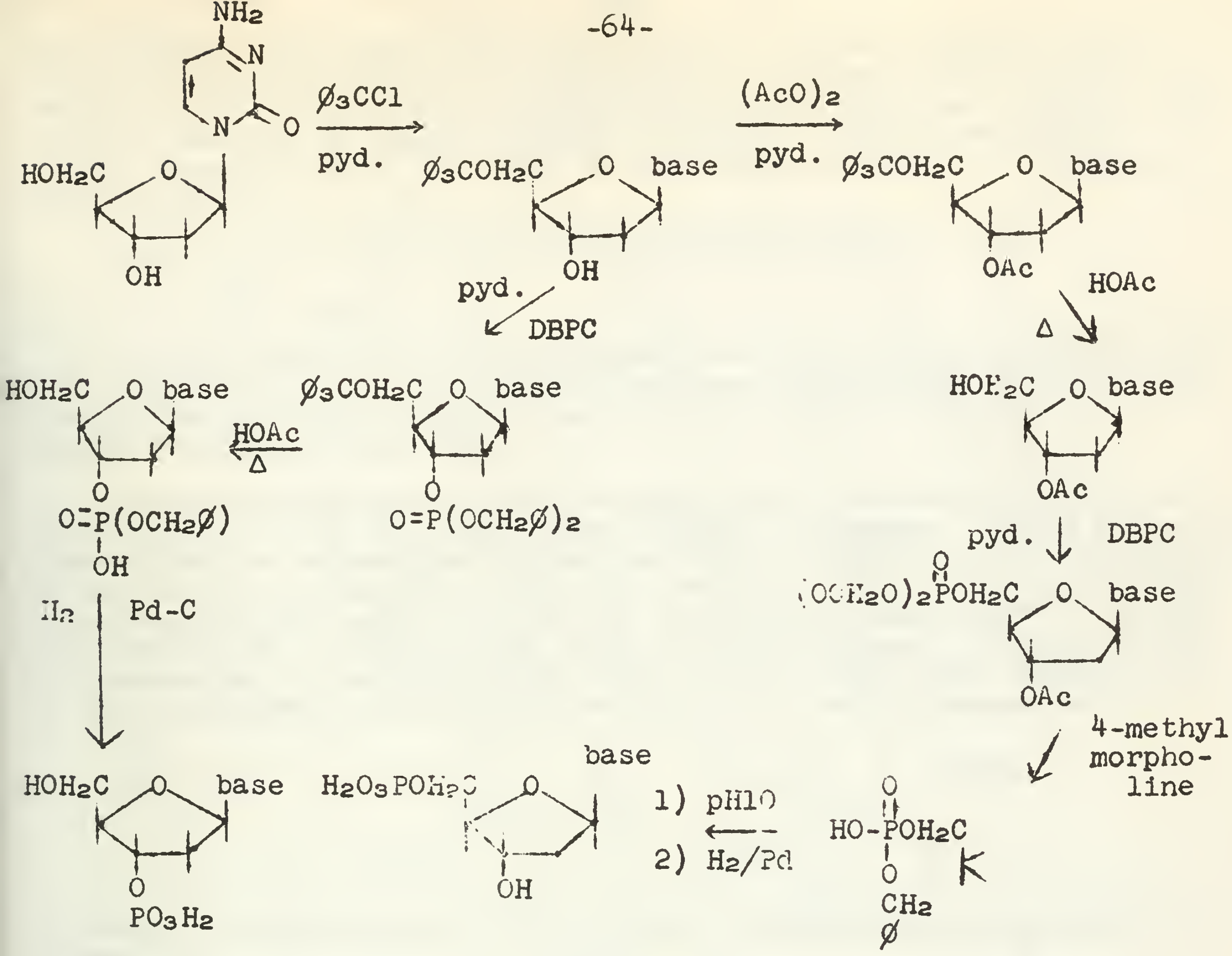
Probably the most widely used reagent is dibenzylphosphochloridate (XII), prepared from chlorine and dibenzyl hydrogen phosphite (32). A typical application was the synthesis of deoxycytidine-3'-



$$(\varnothing CH_2O)_2\underset{\underset{H}{|}}{P}=O + Cl_2 \xrightarrow[CCl_4]{} (\varnothing CH_2O)_2\underset{\underset{Cl}{|}}{P}=O$$

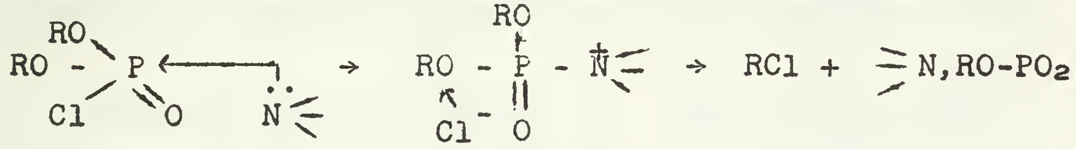
XII (DBPC)

and -5'-phosphates by Michelson and Todd (33), as shown in scheme V.

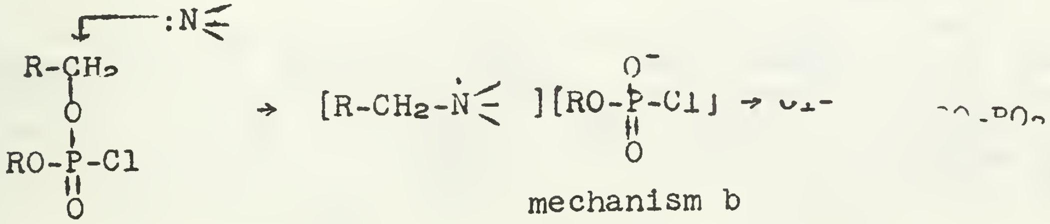


Scheme V

to the relative unreactivity of the secondary hydroxyl. In connection with this reaction sequence it should be noted that monodebenzylation is first carried out on the tri-ester, since hydrogenolysis occurs more readily with the di-ester. This monodebenzylation is due to nucleophilic attack of a base, either at the central P atom (mechanism a) or at an α-c atom (mechanism b) (34). Consequently, if the phosphorylation is carried out in pyridine, the reagent itself may be debenzylated. A better solvent than pyridine would be 2,6-lutidine, which may be sterically hindered from debenzylating the reagent. Definitive syntheses with DBPC have been carried out on a number of

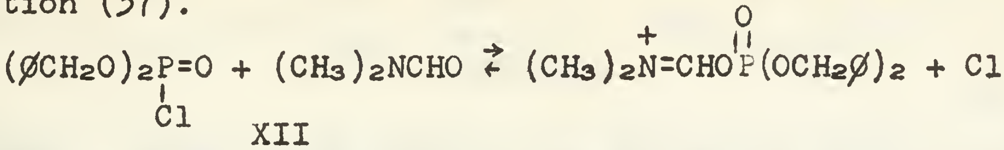


mechanism a



mechanism b

DNA amd RNA nucleosides (12,14,22,35,36). However, yields of secondary phosphates were low and guanosine was insensitive to the reagent. This inability to phosphorylate guanosine was probably due to the necessity of using dimethyl formamide (DMF) as a solvent (21b). Compound (XII) may well be decomposed by DMF in a solvolysis reaction (37).

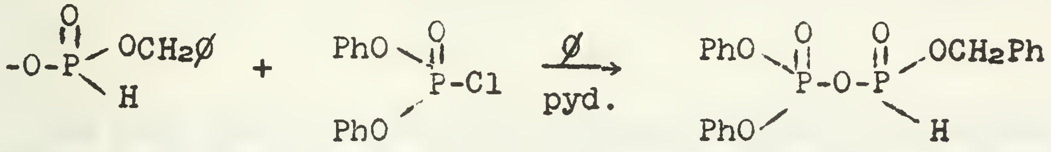


$$(\varnothing CH_2O)_2\underset{\displaystyle Cl}{P}{=}O + (CH_3)_2NCHO \rightleftarrows (CH_3)_2\overset{+}{N}{=}CHO\overset{O}{\overset{\|}{P}}(OCH_2\varnothing)_2 + Cl^-$$

XII

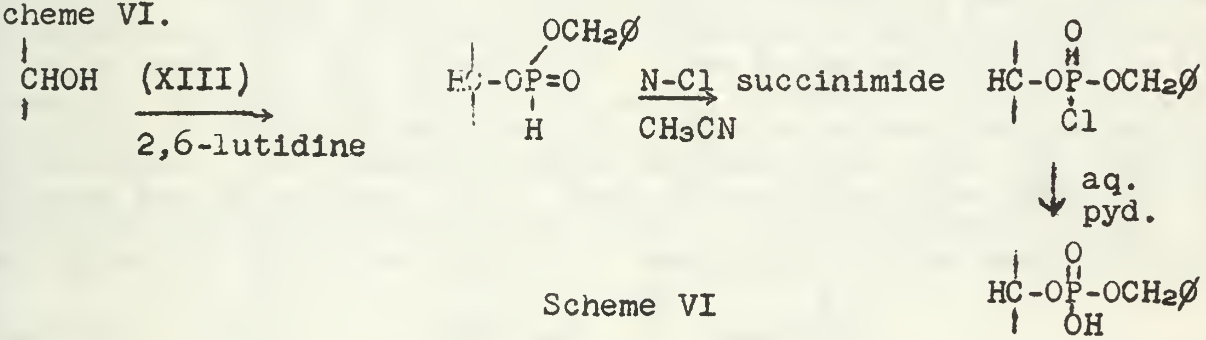
A close analog of (XII), di-*p*-nitrobenzylphosphochloridate has been prepared (38). This compound is more stable than (XII) and its derivatives are less soluble, which would make the compound more useful for phosphorylation.

O-Benzylphosphorous-OO-diphenylphosphoric anhydride (XIII) is more reactive than the usual base catalyzed reagents, but it is not so destructive to nucleosides as are most mixed anhydrides. The reagent is prepared as shown below (39) and used directly for phosphorylation. This compound has been used for the successful preparation of deoxyguanosine-3-and-5'-phosphates (36), deoxyadenosine-3'-phosphate (36), and adenosine-2'-phosphate (9), none of which were very susceptible to dibenzylphosphochloridate. The resulting benzyl phosphite is



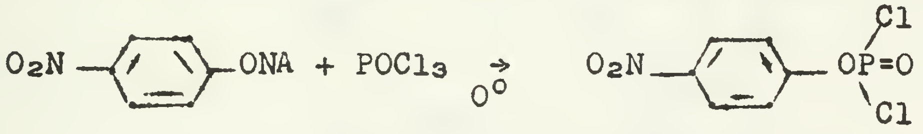
XIII

converted to a phosphate to facilitate hydrogenolysis, as shown in scheme VI.



Scheme VI

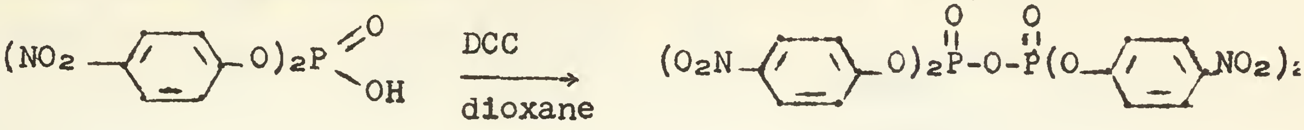
Another reagent more reactive than dibenzylphosphochloridate is *p*-nitrophenyl phosphorodichloridate (XIV), which has given 75% yields of thymidine-3'-phosphate from 5'-o-tritylthymidine (40).



XIV

A very interesting reagent, and also quite powerful is polyphosphoric acid (P_2O_5 and H_3PO_4). This reagent is of undetermined structure, but probably contains pyrophosphate, as well as polymeric materials (41,42). By means of this reagent, uridine-2',5'-and 3',5'-diphosphates, cytidine-2',5'- and 3',5'-diphosphates and uridine 5'-phosphate have been synthesized in high yield (16). Unfortunately, the purine nucleosides are decomposed, thus eliminating a possible

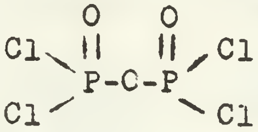
Tetra-*p*-nitrophenyl pyrophosphate (XV) is a quite reactive compound (43,44) but unfortunately the *p*-nitrophenyl groups must be removed from the intermediate by drastic hydrolysis or enzymatic methods. However, the reagent does give an excellent yield of guanosine-5'-



XV

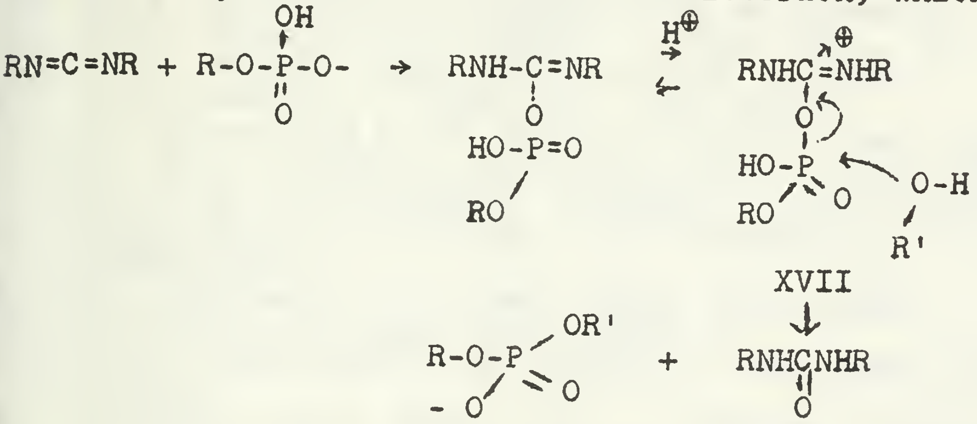
phosphate, using phosphodiesterase from snake venom to remove the last *p*-nitrophenyl group (21). This reagent also has been utilized for the phosphorylation of 6-Cl purine analogs, since a hydrogenolysis of the extra ester group (*i.e.*, benzyl) would also dehalogenate the nucleotide (45).

Pyrophosphoryl chloride (XVI) (46) has also been found reactive enough to give good yields of guanosine-5'-phosphate (47). This reagent offers the advantage of not requiring any strong agent to decompose the intermediate, since the chlorines are removed by room temperature hydrolysis.



XVI

The most useful method of phosphorylation yet devised employs 2-cyanoethyl phosphate and DCC (48). The reagent is prepared from equimolar amounts of hydrocrylonitrile and phosphorous oxychloride in pyridine. A large number of nucleotides including deoxycytidine-3'-phosphate and deoxycytidine-3',5'-diphosphate have been synthesized in high yield by this method (49). The 2-cyanoethyl group is removed from the intermediate diester by means of dilute lithium hydroxide solution, a condition mild enough not to harm even very sensitive nucleotides. The phosphorylation mechanism has been investigated by Khorana and co-workers (50). When excess nucleoside is used, the mechanism probably proceeds by route 1. The protonated adduct (XVII) may actually be in the form of a zwitterion, which should be very

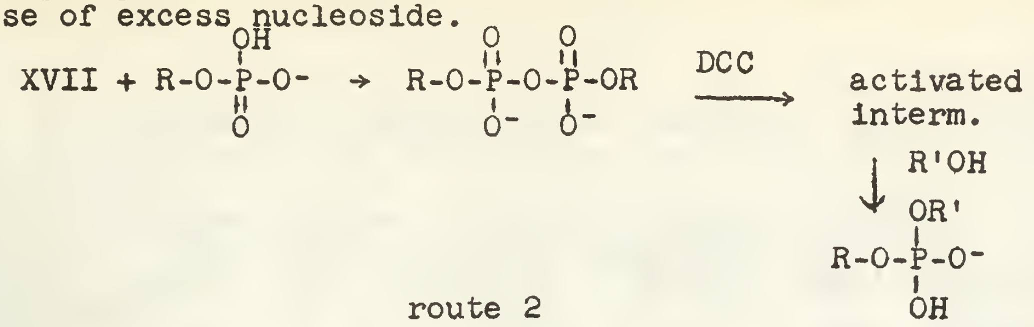


route 1

reactive. Monoalkyl phosphate esters (*i.e.*, 2-cyanoethyl phosphate) react much more readily with the carbodiimide than dialkyl esters (*i.e.*, the desired product); thus pyrophosphate dinucleotides are not formed. This may be due to the higher nucleophilicity of monoalkyl

[illegible]

amounts of the reactants are used, the mechanism probably proceeds by route 2. The character of the activated intermediate is not clear, but pyrophosphate is utilized in this reaction while it is not in the case of excess nucleoside.



$$XVII + R\text{-}O\text{-}\overset{OH}{\underset{O}{P}}\text{-}O^- \rightarrow R\text{-}O\text{-}\overset{O}{\underset{O^-}{P}}\text{-}O\text{-}\overset{O}{\underset{O^-}{P}}\text{-}OR \xrightarrow{DCC} \text{activated interm.} \xrightarrow{R'OH} R\text{-}O\text{-}\overset{OR'}{\underset{OH}{P}}\text{-}O^-$$

route 2

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THE EFFECT OF MOLECULAR CONFORMATION ON N.M.R. CHEMICAL SHIFTS

Reported by Y. E. Rhodes April 3, 1961

Introduction

As a result of the development of the nuclear magnetic resonance phenomenon and its application to the structural elucidation of organic compounds, new techniques have been made available for the study of processes which were previously difficult or impossible. Recently this technique has made possible the study of time-dependent processes (1) which involve exceedingly rapid changes in the electronic environment of atoms which have a nuclear spin of one-half. Thus measurements of the rates of proton exchange in acid-base equilibria (2), the rates of hindered rotation about chemical bonds (3), and the rates of inversion of pyramidal nitrogen compounds (4) have recently been studied. The derivation of the appropriate formulae and the discussion of the physical basis of these determinations have been treated rigorously by Pople, Schneider, and Bernstein (5). For a treatment of the principles of nuclear magnetic resonance spectroscopy several reviews are currently available (5,6,7,8,9).

This seminar will cover the application of the nuclear magnetic resonance method to the problems of rotation about carbon-carbon single bonds in terms of the effect of changes in the spatial orientation of other bonds in the molecule on the chemical shift of substituent atoms.

Theoretical Discussion

It is known that the relationship, $\nu = \gamma H/2\pi$, is generally applicable for a resonance signal in the nuclear magnetic resonance spectrum, where ν is the precession frequency of the nuclear magnet and the radio frequency, γ is the gyromagnetic ratio which is a constant for a given nucleus, and H is the magnetic field strength. Normally the field in the nuclear environment is not the same as the external field and the extent to which it is different is a function of the electronic environment about the nucleus. Thus a measure of this field permits deductions about the number of nuclei in this environment and their spatial distribution. Neglecting constants due to the method of measurement, it is found that the external field (H_o), inducing resonance in the nuclei, is reduced by the shielding constant (σ) as a result of the intramolecular circulation of electrons within the molecule in the presence of the external field.

$$H = (1-\sigma)\, H_o$$

The shielding of the nucleus from the external field is caused by two factors, namely, the electron density in the bonds directly involved with the nucleus and the presence of magnetically anisotropic groups within the molecule (10). Narasimhan and Rogers (11) have calculated the relative magnitudes of these two effects assuming that they are separable into two terms, σ_1, the primary shielding due to the surrounding electron cloud and σ_d, the secondary shielding due to magnetically anisotropic charge distributions farther away from the nucleus. The primary shielding can be evaluated from the wave function(s) of the bond(s) pertaining to the nucleus in question. The secondary shielding can be evaluated from the relationship derived by McConnell (12) which assumes that the electrons in the bonds which interact with the nucleus can be approximated by point dipoles induced by the magnetic field at the position of maximum electron density of the bond. If it is assumed that the interaction is due to an axially symmetric bond, the contribution to the shielding of the ith nucleus from each bond in the molecule is:

$$\sigma d_i = (1-3\cos^2\theta)\Delta X/3r^3$$

and the total contribution to the shielding is a summation over all th bonds in the molecule, where ΔX is the difference between the longitudinal susceptibility along the axis of the bond (X_L) and the transvers susceptibility perpendicular to the axis of the bond (X_T) and θ is the angle between the axis of the bond and the radius vector, r, joining the center of the bond and the nucleus. It is apparent that bonds for which the longitudinal diamagnetic polarizability is greater than the transverse polarizability will "shield" the nucleus when θ is greater than 55° and will "deshield" the nucleus when θ is less than 55° (10).

It can be seen from Figure 1 that secondary shielding contributions to proton "a" from the C_2-C_3 bonds are dependent on molecular conformation since both r and θ change with changes in conformation.

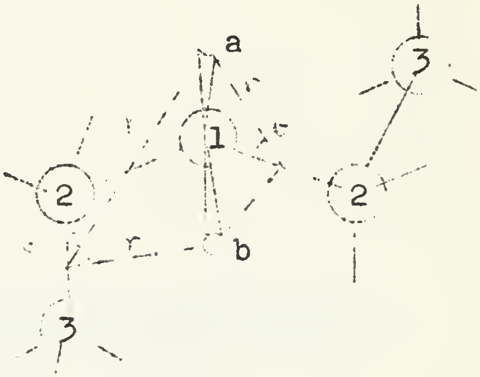


Figure 1

As a result of this secondary shielding due to the circulation of electrons in distant bonds it is found that nuclear magnets in substituted ethanes, cyclic and polycyclic systems resonate at different external field strengths depending on the molecular conformation of the molecule, trans or gauche orientations in the ethanes and axial or equatorial in the cyclic systems (10). Unfortunatel there are very few cases in the substituted ethane series for which bond anisotropies have been calculated since it is difficult to state precisely the position of the induced dipole of the bonds. Rogers and Narasimhan (11), however, have treated the spectrum of propane as a methyl substituted ethane and have calculated the chemical shift difference between the methyl and methylene protons from the model assumec above in good agreement with that observed. Assuming that the only difference in the screening constant for cyclohexane, cyclopentane and open-chain methylene protons arises from differences in molecular conformation, Bothner-By and Naar-Colin (10) estimated the molar susceptibility of carbon-carbon bonds to be 5.5×10^{-30}cm^3, in agreement with other work (11), by comparing the observed chemical shift with that calculated using the equation of McConnell (12). Using this value for the susceptibility of the carbon-carbon single bond Jackman (7) has calculated a difference of 0.4 ppm in the chemical shifts of axial and equatorial protons in cyclohexane with the axial proton appearing at higher field. These estimates do not include contributions from susceptibilities of carbon-hydrogen bonds which have been shown to be appreciable in some cases (11).

Up to this point these calculations have considered only rigid molecules whereas it is known that the rotational isomers of substituted ethanes and cyclohexanes rapidly interconvert (13,14). As a result of rapid rotation about the carbon-carbon bonds in these molecules the chemical shift that is observed is a weighted average unless the rotation is extremely slow. Gutowsky and Saika (2) have treated systems in which protons are rapidly exchanged with the environment and have developed relationships between the average lifetime of a magnetic nucleus at a given position and the shape of the resonance signal in the nuclear magnetic resonance spectrum. These relationships are applicable to internal rotation of molecules if it is considered that, for instance, axial and equatorial protons in cyclohexane are converted, one into the other, for each chair-chair interconversion. There are three types of spectra possible in general depending on the relative magnitudes of the rate of internal rotation and the difference

in the chemical shifts (in cycles per second) of the nuclei involved. If the rate of internal rotation is less than the chemical shift differences of the nuclei in different conformations, the spectrum is a superposition of the spectra expected for non-rotating or rigid molecules (Figure 2a). If the rate of rotation and the chemical shift difference are of the same order of magnitude, the observed spectrum is a broad resonance signal (Figure 2b) with a chemical shift corresponding to a weighted average of the isomers present. If the rate of rotation is much larger than the chemical shift difference the observed spectrum consists of a single sharp resonance signal again with average chemical shift as before (Figure 2c).

Figure 2. NMR Spectra for conformational isomers with a) slow, b) intermediate and c) rapid internal rotation. Intensities are not to scale.

If it is assumed that the process of interconversion of rotational isomers is a first order process for state A going to state B then:

$$dN_A/dt = -k_AN_A \quad \text{and} \quad dN_B/dt = -k_BN_B$$

where N_A and N_B are the number of molecules in states A and B, respectively and k_A and k_B are rate constants related by:

$$k_AX_A = k_BX_B$$

and X_A and X_B are the mole fractions of molecules in states A and B (15). It has been shown that a transition from two resonance signals to one resonance signal occurs when the lifetimes of two states A and B are of the same order as the chemical shift difference (3). Applying the simplifying conditions that the lifetimes and populations of the two states are equal and that the transverse relaxation times are large so that their reciprocals are negligible, it is found that the shape of the curve depends only on the product $\tau|\delta_A - \delta_B|$, where $\delta_A - \delta_B$ is the difference in the chemical shifts of the two states and

$$\tau = \tau_A\tau_B/(\tau_A + \tau_B)$$

If τ is large it may be found from the width of the separated resonance signals. In the case of partial collapse, τ may be estimated by comparison of the observed shape of the curve with the series of curves given by Pople, Schneider and Bernstein (5) or by comparing the separation of the lines with the separation obtained when the interconversion is slow.

$$\frac{\text{separation of peaks}}{\text{separation of peaks for large }\tau} = \left[1 - \frac{1}{2\pi^2\tau^2(\delta_A - \delta_B)^2}\right]^{1/2}$$

For smaller values of τ when only one resonance signal is observed, τ is determined from the width of the signal at half-height.

Once τ is determined (and therefore τ_A) the rate of interconversion of the two states can be calculated since τ_A, the lifetime of the molecule in state A, is the reciprocal of the first order rate constant k_A. Thus if the two states A and B are different in energy it is

possible to change their relative populations and lifetimes by varying the temperature. If the NMR spectra are obtained at sufficiently low temperatures the three possible types of resonance signals indicated in Figure 2 can be obtained. From these spectra the dependence of τ_A and thus k_A on the temperature can be determined. If the condition that the transverse relaxation times are large is not met, it is not possible to determine τ from the peak width. However, in this case it is possible to estimate the rate of interconversion at the temperature at which the two signals coalesce into one, (the coalescence point) since:

$$1/\tau_A = k_A = \pi(\delta_A - \delta_B)/\sqrt{2}$$

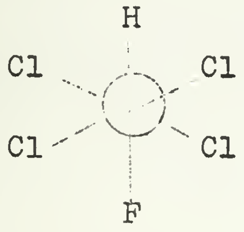
If the rates of interconversion at several temperatures are known it is possible to evaluate the energy barrier to interconversion by application of the Eyring equation (16).

It is to be noted that spin multiplets arising from spin-spin coupling may be treated in an analogous manner (17). Since spin-spin coupling constants also depend on the molecular conformation, the fine structure is simplified when rotational isomerization proceeds rapidly. The net result is a less complex fine structure having a coupling constant which is a weighted average of the coupling constants for each conformation (5). The coupling constants are largest when the magnetic nuclei are oriented in a trans configuration as shown by the calculations by Karplus (18).

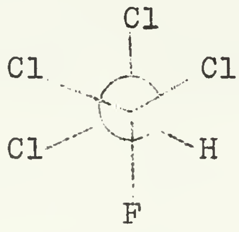
Applications to Organic Compounds

The internal rotation of many substituted ethanes have been studied by the NMR technique (5,19,20) but mainly through the temperature dependence of the coupling constants and not by chemical shift differences.

Abraham and Bernstein (21) have studied the rotational isomerism of 1,1,2,2-tetrachlorofluoroethane over a series of temperatures from -55°C to 99.7°C and have evaluated the coupling constants and the energy barrier to rotation from the spectrum. This compound has three possible conformations, one in which hydrogen and fluorine are oriented trans to each other (I), and two equivalent structures (mirror images) in which hydrogen and fluorine are in the gauche orientation (II and III).



I



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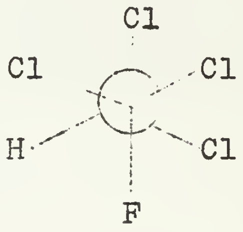


III

If the fraction of molecules in the trans conformation is p then the fraction of molecules in each gauche conformation is (1 - p)/2 and the total number of gauche molecules is (1 - p). Therefore:

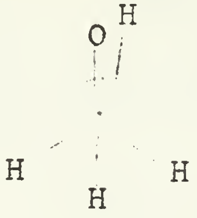
$$p/(1 - p) = 1/2\ (\exp) - \Delta F/RT$$

The observed spacing depends on the number average of the coupling constants for the trans configuration (J_t) and the gauche configuration (J_g).

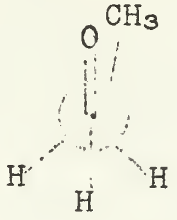
$$J_{average} = pJ_t + (1 - p)J_g = J_t - \frac{J_t - J_g}{1 + 1/2(\exp) - \Delta F/RT}$$

By graphical evaluation it was found that $J_g = 1.03$ cps, $J_t = 18.08$ cps, and $\Delta F = 0.4$ kcal/mole.

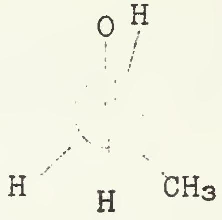
Using a similar type of treatment Abraham and Pople (22) studied the temperature dependence of the spectra of acetaldehyde and propionaldehyde. As expected only the spectrum of propionaldehyde changes with a change in temperature. Assuming that the gauche and trans coupling constants are the same for the two compounds it is found that J_g = 0.1 cps and J_t = 8.3 cps and that V is favored over VI by 1.0 kcal/ mole.



IV



V



VI

Jensen and coworkers (23) have recently analyzed the temperature dependent spectrum of cyclohexane and demonstrated the broadening of the single peak until at low temperatures two signals were observed. These workers calculated a first order rate constant at the coalescence temperature (-66°C) using the chemical shift difference between axial and equatorial protons obtained at lower temperatures (27.3 cps). It was found that k_1 = 60.5/sec. Using the Eyring equation a value for the free energy of activation was calculated to be 9.7 kcal/mole. This has been previously calculated to be in the range 1.3 to 10.6 kcal/mole (13). It was also assumed in this work that the entropy of activation would be approximately zero and that the free energy of activation would provide a good estimate for the enthalpy of activation. In the light of later work to be presented it will be seen that the entropy change is fairly large. Moniz and Dixon (27) have recently investigated the spectrum of cyclohexane at still lower temperatures and showed that more splitting occurs and makes Jensen's estimate of the chemical shift difference only approximate.

The NMR spectrum of perfluorocyclohexane consists of a single sharp line at 118° which shows considerable broadening when the temperature is lowered, and eventually is separated into two signals at -50°C. (Table I). Using the signal width at half-height, Tiers (25), calculated a rate constant, k_1, equal to 3.48×10^4/sec at 25.5°C and 69/sec at -66°C, which is essentially the same as that for cyclohexane itself. The energy barrier to chair-chair interconversion at 25.5°C is $\Delta F^{\neq}$ = 10.9 kcal/mole, $\Delta H^{\neq}$ = 7.5 kcal/mole and $\Delta S^{\neq}$ = -10.7 e.u. The observed chemical shift difference for axial and equatorial fluorine atoms is 18.2 ppm.

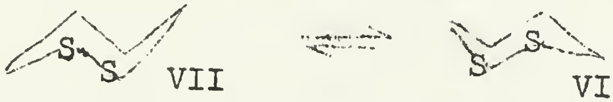
Table I

Temp (°C)	δ (ppm)	Peak Width at Half-height	k_1 (sec^{-1})	$\Delta F^{\neq}$ (kcal/mole)
118	---	1.5 ± 0.2	0.6×10^6	12.3
83	---	2.97 ± 0.11	2.80×10^5	11.6
54	133.21±0.01	8.7 ± 0.16	0.96×10^5	11.3
25.5	133.23±0.01	23.93 ± 0.08	3.48×10^4	10.9
-50	124.23±.07 (ax) 142.45±.07 (eq)	48 ± 2	---	---
-66	124.24±.05 (ax) 142.44±.05 (eq)	38.1 ± 0.6	69[a]	9.9[a]

([a] by extrapolation of log k_1 vs. 1/T)

It is surprising to note that the barriers to chair-chair interconversion in cyclohexane and perfluorocyclohexane are essentially the same. These results are best interpreted in terms of ring distortion as a result of 1,3 diaxial fluorine-fluorine repulsions in the ground state of perfluorocyclohexane so that the activation energy is reduced from the value that would be expected on an a priori basis.

Similarly the spectrum of 1,2-dithiane ($\overline{VII}$) shows the same type of phenomenon over a temperature range of -63°C to 150°C (26). At the coalescence point (-43°C) the first order rate constant was calculated to be 41.1/sec. Thus the activation energy, $\Delta F^{\neq}$, is 11.6 kcal/mole and the lifetime of each conformation is 0.02 seconds at -43°C. The predicted energy barrier is 9.2 to 12.3 kcal/mole.



VII VIII

Since the chemical shift for a rapidly rotating molecule is a weighted average of the possible conformations, it is possible to determine the equilibrium constant for comformational equilibria and thus the standard free energy difference between conformational isomers provided that the chemical shift for the axial and equatorial protons in the absence of rotation is known (27).

$$K = \frac{\delta\ \text{axial} - \delta\ \text{average}}{\delta\ \text{average} - \delta\ \text{axial}}$$

If the spectrum of the compound is studied at a sufficiently low temperature, the signals of the axial and equatorial protons will be separated into two sharp signals. The position of the averaged chemical shift at higher temperatures is then extrapolated to the lower temperature spectrum in which the peaks for the isomers are well separated. Thus Eliel (28) and Berlin and Jensen (29) have determined the conformational equilibria for several cyclohexyl halides through a study of the resonance lines of the -CHX- proton which are shifted downfield from the signals of the other methylene protons in the molecule. However, it was found that the position of the equilibrium is solvent dependent (28), undoubtedly due to hydrogen bonding. Nevertheless, it has been demonstrated (29) that the free energy difference between conformational isomers of the cyclohexyl halide in carbon disulfide increases in the following order: F, I, Br, Cl, where the conformation which has the halogen in the equatorial orientation is more stable. A possible explanation of this order lies in the fact that while the size of the atoms increases in the order F, Cl, Br, I, the polarizability of the atoms decreases in this order. Thus atoms of larger radii having more easily deformed electron clouds have smaller conformational preferences, possibly as a result of a decrease in the magnitude of 1,3-diaxial interactions.

Table II

Conformational Equilibria of $C_6H_{11}X$ (3M in CS_2)

X	ΔF (cal/mole)	δ average	δ ($-CH_{ax}X-$)	δ ($-CH_{eq}X-$)	Difference δ ax - δ eq
F	241	-4.03	-3.84	-4.32	0.48
H	-	-4.82	-4.68	-5.13	0.45
Cl	478	-3.88	-3.73	-4.44	0.71
Br	439	-4.10	-3.89	-4.96	1.07
I	407	-4.41	-4.08	-4.83	0.75

(δ in ppm relative to tetramethylsilane; T = -81°C)

This fact is borne out by the work of Reeves and Stromme (30) which shows that cyclohexyl bromide and chloride exist in the form with the halogen equatorial to the extent of 73.2% and 77.4% respectively. The absolute values of these equilibria are probably in error

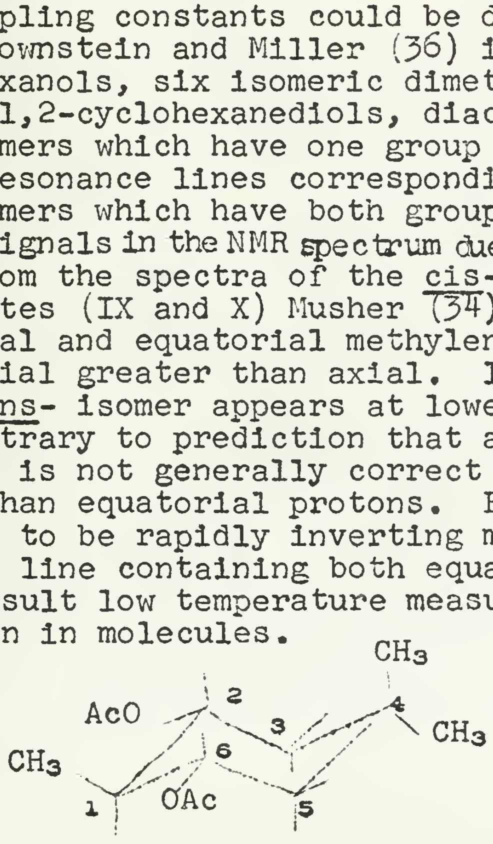
by no more than 10%, but the data are significant in that the change is in the same direction as that determined previously (28). With the formula for the lifetime of the isomers at the coalescence temperature (-55°C) given previously these authors estimated the barrier to interconversion for cyclohexyl bromide to be 10.85 kcal/mole if it is assumed that the entropy of activation is zero. This is a crude estimate at best since it has been shown previously (25) that the entropy of activation is large for the chair-chair interconversion of perfluorocyclohexane and is probably of appreciable magnitude for cyclohexyl bromide also.

Feeney and Sutcliffe (31) have recently studied the spectra of the five available isomers of the cis- and trans- 1,2-,1,3-, and 1,4-dihydrodecafluorocyclohexanes. It is expected that for disubstituted cyclohexanes which have conformations differing greatly in energy, interconversion will be slow, as in the case of equatorial-equatorial to axial-axial transitions. Whereas if the conformations are similar in energy the rate of interconversion may be faster. The NMR spectra of these compounds are best explained by one fixed conformation for the trans-1,2- isomer with both protons axial, one fixed conformation for the cis-1,3- isomer with both protons equatorial, slow interconversion for the trans-1,3- isomer and rapid interconversion for the cis-1,2- and the cis-1,4- isomers.

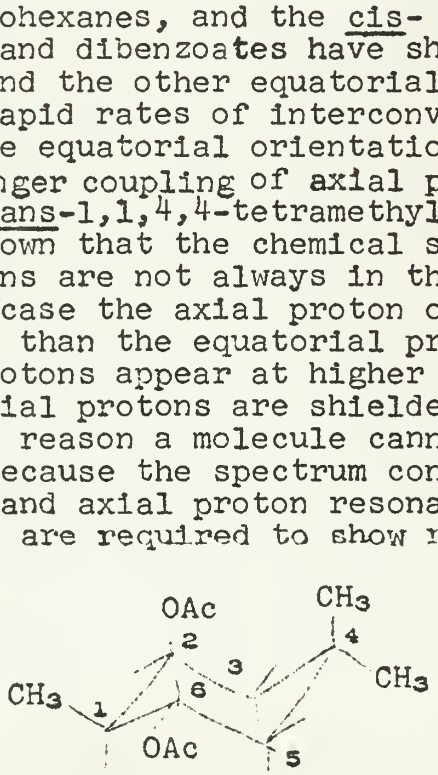
Lemieux and coworkers (32) applied this method to the cis- and trans- isomers of the 4-t-butylcyclohexyl alcohols and acetates and showed that a measure of the widths of the broad signals observed in the spectrum for the axial (trans-) and equatorial (cis-) protons at the one position of the ring gave a measure of the relative magnitude of the spin-spin coupling constants for axial-axial and axial-equatorial protons. Thus the axial-axial coupling constant is at least twice as large as the axial-equatorial coupling constant. This conclusion was verified in other work in which the fine structure was resolved and the coupling constants could be determined quantitatively (33,34,35,36)

Brownstein and Miller (36) in a study of the six isomeric methylcyclohexanols, six isomeric dimethylcyclohexanes, and the cis- and trans- 1,2-cyclohexanediols, diacetates and dibenzoates have shown that the isomers which have one group axial and the other equatorial give sharp resonance lines corresponding to rapid rates of interconversion. The isomers which have both groups in the equatorial orientation give broad signals in the NMR spectrum due to stronger coupling of axial protons.

From the spectra of the cis- and trans-1,1,4,4-tetramethyl-2,6-diacetates (IX and X) Musher (34) has shown that the chemical shifts of the axial and equatorial methylene protons are not always in the order equatorial greater than axial. In this case the axial proton of C_3 in the trans- isomer appears at lower field than the equatorial proton of C_3, contrary to prediction that axial protons appear at higher field. Thus it is not generally correct that axial protons are shielded differently than equatorial protons. For this reason a molecule cannot be assumed to be rapidly inverting merely because the spectrum consists of a sharp line containing both equatorial and axial proton resonances. As a result low temperature measurements are required to show rapid rotation in molecules.

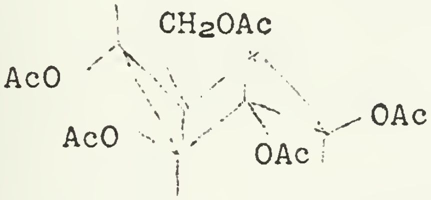


IX

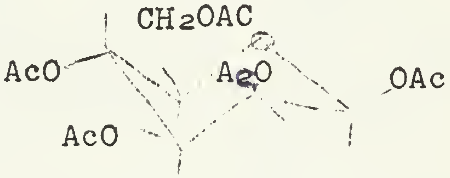


X

As a test of the theory of shielding differences due to differences in conformation, the work of Lenz and Heeschen (38) is of interest. This work compares the differences in shielding of ring protons in β-D-glucose (XI) and β-D-mannose (XII) as calculated on the basis of diamagnetic bond anisotropies and as observed experimentally. The agreement is excellent in view of the fact that only carbon-carbon and carbon-oxygen bonds with different orientations relative to the proton in question (C_2-C_3 in the terminology of Figure 1) were considered in the calculation. Thus the shielding of the anomeric proton of β-glucose (XI) includes anisotropy contributions from the following bonds C_2-O, C_2-C_3 and C_5-O. The anisotropic susceptibility for a carbon-oxygen bond was estimated to be 10.8×10^{-30} cm^3.



XI



XII

Table III

Shielding Differences in the Ring Protons of β-D-Glucose and β-D-Mannose

Ring Proton	[σ(glucose) - σ(mannose)]	
	Calculated	Observed
C1	0.28	0.29
C2	0.46	0.48
C3	0.42	0.37
C4	0.02	0.12
C5	0.05	-

Lenz and Heeschen (38) have also shown that it is possible to determine whether a sugar exists in a pyranoside or a furanoside ring in aqueous solutions. The carbohydrates with a hydroxymethylene group substituted on either a pyranoside or furanoside ring always exhibit a peak in the NMR spectrum at approximately -3.80 ppm (relative to 2,2-dimethyl-2-silapentane-5-sulfonate). Thus the spectra of ribose and glucose in aqueous media show this peak but it is not observed in the spectrum of xylose which must therefore mean that the preferred form of xylose in aqueous solution is the pyranoside ring system.

Lemieux and coworkers (32) observed that the anomeric configuration of sixteen acetylated sugars can be assigned on the basis that an axial proton nearly always appears at higher field strength in the NMR spectrum than an equatorial proton and that the coupling constant between axial protons is greater than the coupling constant between axial and equatorial protons or between two equatorial protons. In addition it has been observed that the protons of substituent methoxy and acetoxy groups appear at higher magnetic field strengths when the group is in the equatorial conformation than when it is axially oriented. These observations are generally valid and have been successfully applied to the studies of configurations of steroids (39,40), bicyclic compounds (41,42) and some nucleosides and nucleotides (43, 44,45,46).

Recently the temperature dependence of the spectra of the *cis*- and *trans*- hydrindans and decalins have been studied by Moniz and Dixon (24). The spectra of *cis*-hydrindan show progressive broadening as the temperature is decreased indicating a slowing of the rate of chair-

chair interconversion of the six-membered ring. Both *trans*-hydrindan and *trans*-decalin, however, do not show any appreciable temperature dependence in the NMR spectra but have broad unresolved spectra even at room temperature. The broad spectra observed are presumably due to differences in the chemical shifts of the axial and equatorial protons of this rigid system. *Cis*- decalin on the other hand gives rise to a sharp resonance signal in the spectrum at all the temperatures studied. This indicates that the energy barrier to chair-chair interconversion in *cis*-decalin is lower than the barrier in *cis*-hydrindan since the former has a greater apparent rate of interconversion. A rigorous calculation of the energy barrier is not possible in this case since no structure is clearly resolved even at very low temperatures (-140° C). However, it is possible to calculate a probable maximum value for the energy barrier of 6.4 kcal/mole at -133°C by comparison of the shape of the signals observed with those described previously (2,5). Comparing the magnitudes of the energy barriers for cyclohexane (10 kcal/mole) and *cis*-hydrindan it is apparent that the ground state energy of the latter is higher than the ground state energy of cyclohexane as a result of the strain introduced into *cis*-hydrindan by the fused ring system.

In conclusion it is imperative to emphasize that the observation of a single sharp resonance line in the nuclear magnetic resonance spectrum of a molecule cannot be interpreted in terms of rapid interconversion of two conformers of the same or nearly the same energy unless broadening of the signal in the low temperature spectrum or narrowing of the signal in the high temperature spectrum is observed. Thus all ring protons must be magnetically equivalent for the resonance signal to be a single sharp line. This phenomenon has been observed in many cases with the resulting conclusion that the protons are all magnetically equivalent due to rapid interconversion. Thus, even though the spectrum of *cis*-decalin consists of a single sharp resonance line, the bridgehead protons and the methylene ring protons are only accidentally magnetically equivalent since they are chemically different (47).

It is apparent that a thorough analysis of the NMR spectrum of a compound can yield much information about the absolute configuration and conformation of the molecule and the orientation of substituent groups with respect to each other. It is possible to determine the position of conformational equilibria and thus the relative stability of conformational isomers. By a careful study of the temperature dependence of the spectra the rate of interconversion of conformational isomers may be readily determined.

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BIMOLECULAR AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

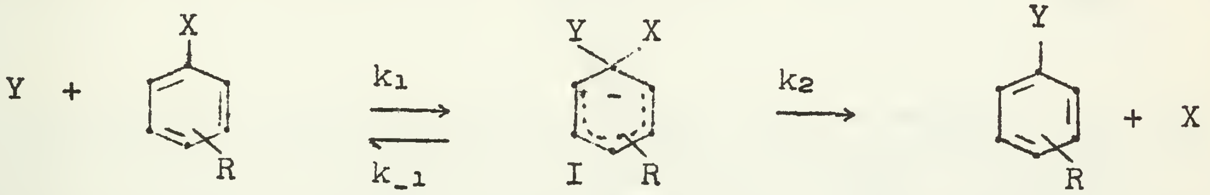
Reported by C. G. McCarty April 10, 1961

Introduction

Much work has been done in recent years in attempts to elucidate the mechanism of nucleophilic displacement at an aromatic carbon atom on an activated substrate. This subject has been reviewed by Bunnett (1) and by Sauer and Huisgen (2). Seminars have been given on this topic at this University (3) and at M.I.T. (4). The purpose of this seminar is to review some of the recent work on this subject which has not been dealt with in these reviews.

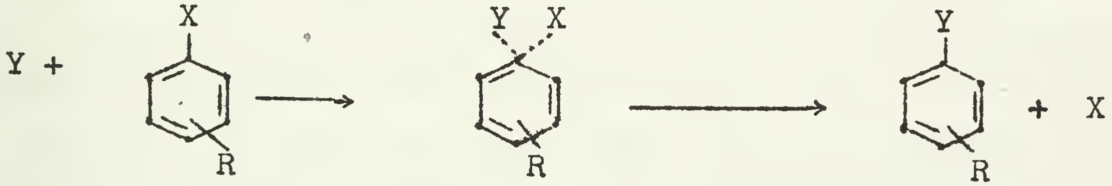
Mechanism

The most widely accepted mechanism of aromatic nucleophilic substitution can be represented as follows (5)



(A)

where R represents one or more activating groups such as $-NO_2$. This two-step mechanism involving a metastable intermediate complex, I, has been criticized. The observed mobility orders for the displacement of halogen from activated aromatic substrates have, in some cases (6,7,8), led chemists to advocate a one-step, S_N2-like mechanism which has often been represented as



(B)

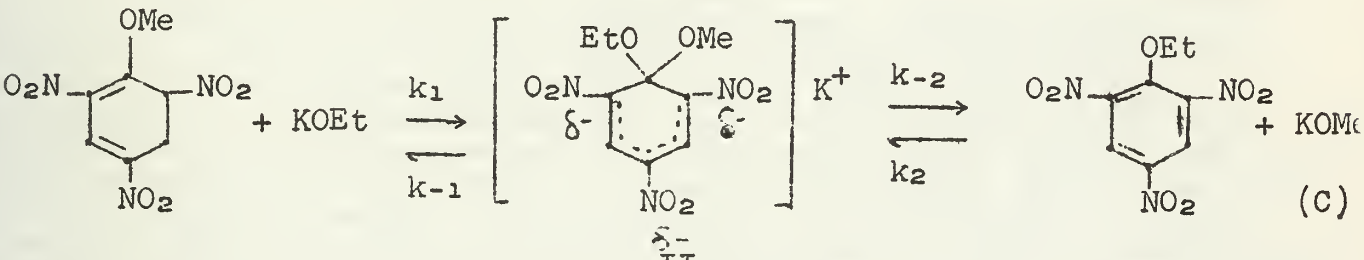
Proponents of mechanism A favor an intermediate with a fully covalent structure and sp^3 hybridization at the attacked carbon atom (1). On the other hand, mechanism B has been claimed to proceed by the rate-controlling formation of one transition state which involves hybridization towards sp^3 at the seat of substitution; the degree of hybridization depending upon the reactants (8-11).

Bunnett (5) has presented the following principal arguments in support of the intermediate complex mechanism: 1) The transition states and intermediate for mechanism A are much more easily rationalized quantum mechanically than is the transition state for mechanism B (1a). 2) Intermediate complexes similar to I have been isolated in some reactions involving highly activated aromatic substrates. 3) The carbon-fluorine bond is broken much slower than other carbon-halogen bonds in reactions known to involve the breaking of a carbon-halogen bond in the rate-determining step. In most nucleophilic aromatic substitutions the observed order of mobility is $F \gg Cl \sim Br \sim I$. This is taken as evidence that the C-X bond is not broken in rate-determining steps. 4). The lack of an "element effect" indicates that little or no breaking of the old bond has occurred at the rate-determining step (12). Furthermore, Bunnett (5) has shown that by assuming suitable relative

magnitudes for k_1, k_{-1}, and k_2, the data which led people to favor mechanism B can be explained in terms of mechanism A.

The Intermediate Complex

The intermediate complex mechanism depends for much of its plausibility on the isolation of intermediates from the reactions of alkoxides with picryl ethers and similar highly activated substrates. Several of these adducts were isolated in the late 19th century (13, 14). Their constitution was elucidated by Meisenheimer (15) who showed that the same adduct, II, could be prepared by either of the routes shown in reaction C.



II

(C)

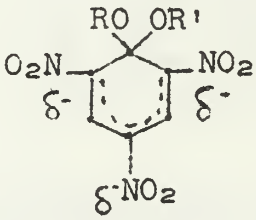
The equivalence of visible spectra (16), infrared spectra (17), and the composition of the mixtures of picryl ethers produced upon acid decomposition of II (15,18) have proven the identity of samples of II prepared by the two different reaction paths. These data have often been accepted as unequivocal proof that II has a covalent structure at the carbon atom being attacked. However, they do not rule out the possibility that II may be a charge-transfer type complex; i.e., the reaction might be

$$\mathrm{PicOR} + {}^{-}\mathrm{OR'} \rightleftarrows \underset{\mathrm{III}}{(\mathrm{PicOR},\ {}^{-}\mathrm{OR'})} \rightleftarrows \underset{\mathrm{IV}}{(\mathrm{PicOR'},\ {}^{-}\mathrm{OR})} \rightleftarrows {}^{-}\mathrm{OR} + \mathrm{PicOR'}$$

If the charge-transfer complexes, III and IV, were of sufficiently different stabilities, then only one complex might be isolated.

The role of charge-transfer complexes in nucleophilic aromatic substitution is still uncertain. The reaction of aniline with 2,4-dinitrochlorobenzene is reported to be decelerated to some extent by charge-transfer complex formation (19). Evidence has also been presented to show that such complexes are formed in the reactions of sodium ethoxide with trinitroanisole, trinitrobenzene, and with trinitrotoluene (20). Other examples have been described in detail in a recent University of Illinois seminar (21). In most cases, however, the results reported do not allow one to decide whether the steps of charge-transfer complex formation and substitution are competing or successive.

Dyall (22) has isolated the seven Meisemheimer complexes shown in the table to the right. He has obtained their infrared spectra in an attempt to distinguish between a charge-transfer and a covalent structure for these intermediates. The main absorption bands, common to all of the complexes, are shown in the table below. Included in the table are the four characteristic C-O-C-O-C absorption bands found by Bergman and Pinchas (23) in a study of 18 ketals and acetals.



R	R'
OMe	OMe
OEt	OEt
OEt	OCH$_2$
OEt	O i-P
OEt	OMe
OMe	O i-Pr
OMe	OCH$_2$

Complex absorption(cm^{-1})	COCOC absorption(cm^{-1})
1222-1206 vs	. .. . .
*1163-1152 ms	1190-1158
*1125-1122 ms	1143-1124
1097-1076 m	1098-1063
*1063-1053 vs	
*1053-1045 vs	1058-1038

*These strong bands do not appear in the spectra of the parent ethers.

If these complexes were of the charge-transfer variety the infrared spectra should, by analogy with those of known charge-transfer complexes (24), closely resemble those of the parent ethers with the addition of the internal frequencies of the added alkoxy group. The appearance of new, strong bands and their correspondence with ketal absorption bands indicates that the complexes studied do have the fully covalent structure which is usually assigned to them. The transfer of a negative charge to the ring leads to a decreased N-O bond order of the nitro groups and, thus, to a lowering of the symmetric and asymmetric stretching frequencies. The asymmetric N-O stretching band at 1552 cm^{-1} in the parent compounds is missing in the complexes and new bands appear at 1513 and 1489 cm^{-1} (one of these is a ring vibration). The 1347 cm^{-1} symmetric N-O stretching band in the picryl ethers appears as a strong band near 1300 cm^{-1} in the complexes. Potassium picrate has a strong symmetric N-O absorption at about 1330 cm^{-1}, so it appears that the transfer of negative charge to the nitro groups is more complete in the complexes than in the picrate ion.

Meisenheimer complexes are rapidly decomposed in aqueous acidic media into both of the two possible picryl ethers (15,18,25). Some data on the acid decomposition of the complexes studied by Dyall (22) are given below. In this study, 60-100 mg. of the pure, solid complex was added to a mixture of 20 ml. benzene and 20 ml. aqueous H_2SO_4 (0.1N). The composition of the resultant mixture of picryl ethers was then determined by quantitative infrared analyses. By analogy with the alkyl picryl ethers, the addition of potassium methoxide to trinitrodiphenyl ether might be expected to give the methoxy-phenoxy intermediate. However, the red crystals which are obtained in this reaction (> 90% yield) are the dimethoxy compound (26) and acidification gives

Ether	KOR	Solvent	% Yield*	Avg. Composition Upon Decomposition; Mole %	
OMe	KOEt	EtOH	51-57	65.8 OEt	34.3 OMe
OEt	KOMe	MeOH	14-39	65.0 OEt	35.0 OMe
OMe	$KOCH_2\phi$	ϕCH_2OH	36-51	43.7 OMe	56.4 $OCH_2\phi$
$OCH_2\phi$	KOMe	MeOH	28-29	43.4 OMe	56.6 $OCH_2\phi$
$OCH_2\phi$	KOEt	EtOH	47-50	35.0 OEt	65.1 $OCH_2\phi$
Oi-Pr	KOMe	MeOH	52-71	28.9 OMe	71.1 Oi-Pr
Oi-Pr	KOEt	EtOH	55-60	36.8 OEt	63.2 Oi-Pr

* range covered by two or more runs

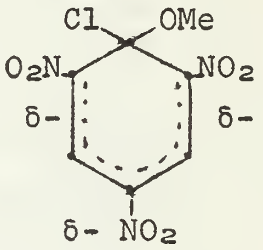
96% of methyl picrate. It is possible that the mixed methoxy-phenoxy compound is formed momentarily but rapidly interchanges methoxy for phenoxy. In contrast to this, the complexes formed by the action of alkoxide ion on picramide, N-methyl picramide, or N-phenyl picramide lose the alkoxy group upon acidification and the amino or anilino group remains intact (27). Dyall has interpreted the results of these studies on the basis of the ease of anion separation from the picryl ether

complexes. On this basis the ease of anion separation decreases in the order $ØO^- > MeO^- >$ other alkoxides $>$ amide ions $> H^-$. This interpretation is based on the assumptions that the function of the acid is to irreversibly remove the anions produced by decomposition of the complex according to reaction C and that the relative magnitudes of k_{-1} and k_{-2} determine the proportions of ethers in the resulting mixture. The available data do not, however, seem to rule out a mechanism involving direct protonation of the complex. If this were the case, one would have to consider the leaving group abilities of ROH and R'OH. Without additional information any attempt to assign an unequivocal interpretation to the data appears unjustified.

Picric acid itself does not give isolable complexes with methanolic alkali, but on shaking a colorless solution of picric acid in toluene with sodium methoxide at 0° a red solution is obtained (18). The converse reaction of trinitroanisole with sodium hydroxide also is reported to give a red solution, but in each case the red solution soon gives the yellow picrate. The reactions of picryl chloride with potassium methoxide and with potassium phenoxide have also been studied by Farmer (18,26). The methoxide reaction appears to occur in two distinct stages; the first being very rapid and characterized by an intense red color. This stage is followed by a gradual fading of the red color and the formation of yellow methyl picrate. Examination of the intermediate products led Farmer to propose the following mechanism

Stage I (rapid at room temperature)

A: $(NO_2)_3C_6H_2Cl + MeO^- \longrightarrow$

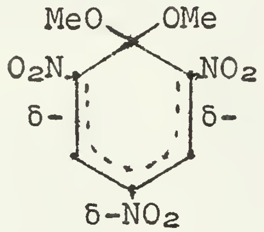


V

B_1: V $\longrightarrow (NO_2)_3C_6H_2OMe + Cl^-$

B_2: $V + MeO^- \longrightarrow$

VI



$+ Cl^-$

Stage II (gradual conversion of VI to methyl picrate)

Crystals of the salt of VI separate out of solution shortly after the reactants are mixed. Conceivably the action of methoxide on the methyl picrate formed in B_1 could also explain the formation of this salt. However, even with an excess of methoxide, unchanged picryl chloride remains in solution at the end of stage I and a separate competition experiment showed picryl chloride to be more reactive than methyl picrate toward methoxide. Thus, Farmer feels that reaction B_2 is necessary to explain the formation of the dimethoxy compound. The reaction of potassium phenoxide with picryl chloride is analogous to that just described for methoxide; but whereas the methoxide reaction occurs in two distinct stages, the action of phenoxide is rapid throughout.

Bolton (28) and Miller (29) have investigated complex formation in less reactive aromatic systems. The reaction of sodium azide in

dimethyl formamide (DMF) with 4-fluoronitrobenzene is first-order in azide ion and in aromatic substrate. The reaction proceeds until a mole of azide per mole of 4-fluoronitrobenzene is consumed. A deep red color is produced but no NaF is precipitated. Separate experiments showed NaF to be extremely insoluble in DMF. Reactions carried out in the presence of a weighed amount of NaF produced no change in weight. The disappearance of azide ion is paralleled by the formation of a substance which absorbs strongly at 397 mμ. Neither 4-fluoronitrobenzene nor 4-nitrophenylazide absorb at this wave length in DMF. The spectrum resembles those of diphenyl quinomethanes and p-aminoaryl diazonium compounds. The addition of 5 ml. of water per 100 ml. of DMF precipitates NaF and addition of excess water precipitates 4-nitrophenylazide in quantitative yield. The authors conclude that this evidence demonstrates formation of the intermediate complex, VII, which is stabilized in the absence of a protic solvent to remove the fluoride ion.

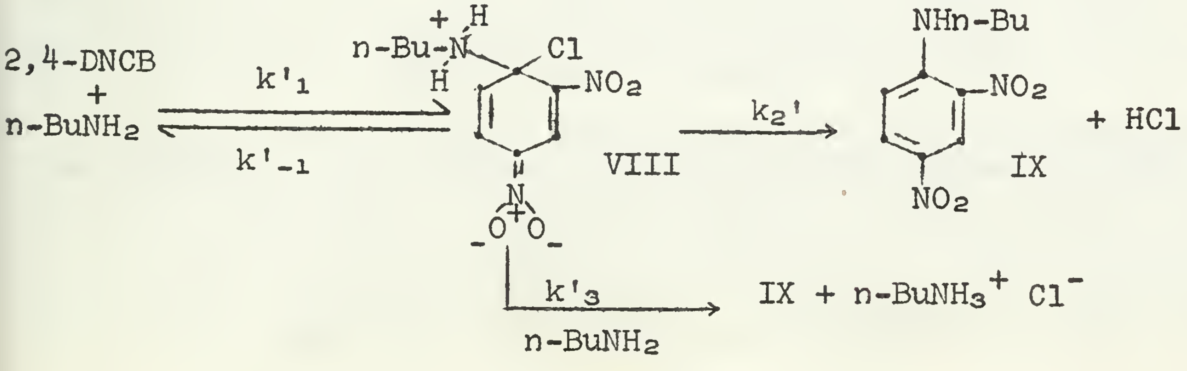
VII

Base Catalysis

The essentials of a mechanism involving base catalysis in certain aromatic nucleophilic substitution reactions were first suggested by Brady and Cropper (30). They observed that triethyl amine catalyzes the reaction of methylamine with 2,4-dinitrochlorobenzene (2,4-DNCB) even though it itself does not react with 2,4-DNCB to an appreciable extent under the experimental conditions. The rate of the reaction of 2,4-DNCB with n-butylamine has been measured at several concentrations of amine in both ethanol and chloroform (31). In both solvents the reaction is clean and the only isolablereaction product is N-n-butyl-2,4-dinitroaniline (>90% yield). Some of the data for this reaction at 24.8° C are given below. n-Butylamine is not unique. Piperidine, 2-phenylethylamine, and di-n-butylamine give results very similar to those obtained with n-butylamine. At constant 2,4-DNCB concentration the calculated second order rate constants increase with increasing amine concentration and plots of k_2's vs. the initial amine concentrations are linear in every case. The linear equation: $k_2 = k_1 + k_3\ (RNH_2)$- encompasses all of the results obtained by Ross and Finkelstein.

$CHCl_3$			$EtOH$		
2,4-DNCB (m/l)	n-$BuNH_2$ (m/l)	$k_2 \times 10^4$ (l/mole-sec)	2,4-DNCB (m/l)	n-$BuNH_2$ (m/l)	$k_2 \times 10^4$ (l/mole-sec)
0.05165	0.1038	2.47	0.05005	0.1724	1.04
0.05111	0.1985	3.07	0.05040	0.3326	1.10
0.05168	0.8018	6.22	0.04950	0.6607	1.35
0.05196	1.009	7.20	0.04960	0.8838	1.51

These results can be interpreted in terms of the intermediate complex mechanism as follows



If $k'_{-1} \gg k'_2 + k'_3(RNH_2)$, the over-all rate for this reaction can be given by

$$dIX/dt = k'_2K(2,4\text{-DNCB})(RNH_2) + k'_3K(2,4\text{-DNCB})(RNH_2)^2 \qquad (D)$$

where K is the equilibrium constant for formation of VIII, and k'_2K and k'_3K correspond to k_1 and k_3, respectively, in the linear equation given above for the specific rate. The lack of a specific effect due to added t-butylammonium salts and consideration of the low value of the autoprotolysis constant for n-butylamine in these solvents makes the probability of a reaction involving n-butylamide ion or n-butylammonium ion almost negligible. The mechanism shown above suggests that the function of the second amine molecule in the third-order term is to facilitate product formation by removal of a proton from the intermediate, VIII. If a triethylamine molecule can perform the same function as the second n-butylamine molecule then the over-all rate of the preceding reaction in the presence of triethylamine should be given by

$$dIX/dt = k_1(n\text{-BuNH}_2)(2,4\text{-DNCB}) + k_3(2,4\text{-DNCB})(n\text{-BuNH}_2)^2 + k_4(2,4\text{-DNCB})(n\text{-BuNH}_2)(Et_3N) \qquad (E)$$

The results of Ross and Petersen (32) are consistent with this rate equation. The values which they obtained for k_1 and k_3 in equation E agree quite well with the values previously obtained (31) for the corresponding k's in equation D (k'_2K and k'_3K). The need for the third-order term to fully describe the reactions of 2,4-DNCB with primary and secondary amines is equally true for the reactions of both 2,4-DNBB and 2,4-DNIB with n-butyl amine in chloroform (33). In both of these systems the measured second-order rate constants increase with increasing initial amine concentration and plots of the rate constants vs. the initial amine concentrations are linear. Thus, the rate expression for these systems can be written in a general form such as

$$d(\text{product})/dt = k_1(A)(B) + k_3(A)(B)^2$$

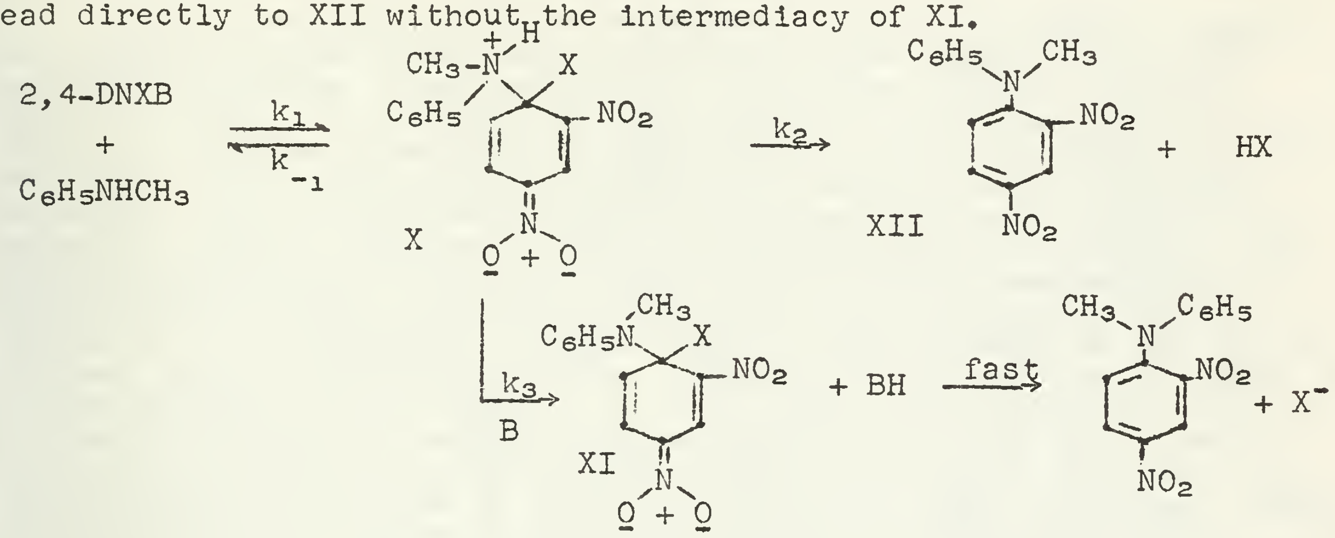
where A is the 2,4-dinitrohalobenzene and B is the amine. The measured rate constant, k_2, can be equated to: $k_2 = k_1 + k_3(B_o)$-where B_o is the initial amine concentration. The values of k_1 and k_3 found by Ross et al. for the reactions of the three halobenzenes with n-butylamine in chloroform at 24.8°C are summarized below (30,32).

Halogen	$k_1 \times 10^4$ (l/mole-sec)	$k_3 \times 10^4$ (l^2/mole^2-sec)	k_3/k_1 (l/mole)
Cl	2.2	5.4	2.45
Br	3.0	7.0	2.33
I	0.94	1.7	1.81

The order of mobility, as indicated by the magnitudes of k_1 and k_3, is $Br \sim Cl > I$. This order is the one usually found for nucleophilic substitution reactions involving 2,4-dinitrohalobenzenes (5,34). This is to be contrasted with the order $I > Br > Cl > F$ usually found in displacement reactions at saturated carbon atoms for both S_N2 and S_N1 mechanisms (35) in solvents such as those considered here.

Bunnett (5) has found that in the reaction of N-methylaniline with 2,4-DNXB in absolute ethanol added potassium acetate (0.104M) accelerates the displacement of fluorine by about 1400%, or about one-hundred times what the normal salt effect would be. The rates of displacement of Cl and Br are not abnormally affected by the added potassium acetate. The reaction was studied at several concentrations of added KOAc and in several runs acetic acid was added in concentrations equal to that of

the KOAc. A plot of the observed rate coefficients vs. KOAc concentration reveals that the catalyzed rate is linearly dependent upon the KOAc concentration. Furthermore, added acetic acid does not depress the base catalyzed rate. Thus, this reaction is general base catalyzed The mechanism proposed by Bunnett is very similar to those proposed earlier by Ross, et al. (31-33). In Bunnett's mechanism a second intermediate is shown, but a concerted elimination effected by the base may lead directly to XII without the intermediacy of XI.



Use of the steady state assumption leads to

$$k_{XII} = (k_1k_2 + k_1k_3[B])/(k_{-1} + k_2 + k_3[B])$$

where k_{XII} is the rate coefficient for the reaction of 2,4-DNXB with N-methylaniline to form XII. If $k_{-1} \gg k_2 + k_3[B]$ then this expression reduces to

$$k_{XII} = (k_2 + k_3[B])k_1/k_{-1}$$

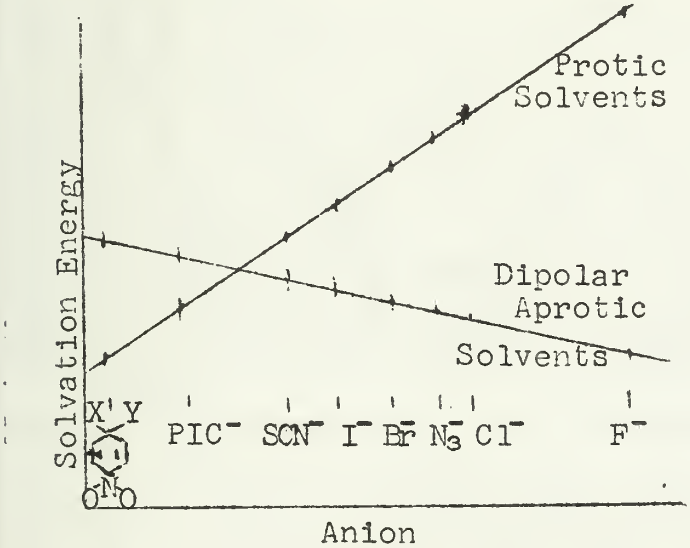
The rate is then directly proportional to [B] as is the case with the KOAc catalysis of the 2,4-DNFB reaction in ethanol. The insensitivity of 2,4-DNCB and 2,4-DNBB to base catalysis could best be explained by this mechanism if $k_2 + k_3[B] \gg k_{-1}$; for then the rate expression reduces to $k_{XII} = k_1$. The order of mobility of halogens in S_N1 reactions is usually Br>Cl≫F. Thus, it is not unreasonable that k_2 might be much greater for reactions with 2,4-DNCB and 2,4-DNBB than with 2,4-DNFB (assuming the intermediate complex mechanism to be correct). The possibility that acetate ion displaces halogen to form 2,4-dinitrophenylacetate which is then attacked by N-methylaniline to form XII is ruled out by the observation that 2,4-dinitrophenylacetate does not react with N-methylaniline in ethanol to form XII.

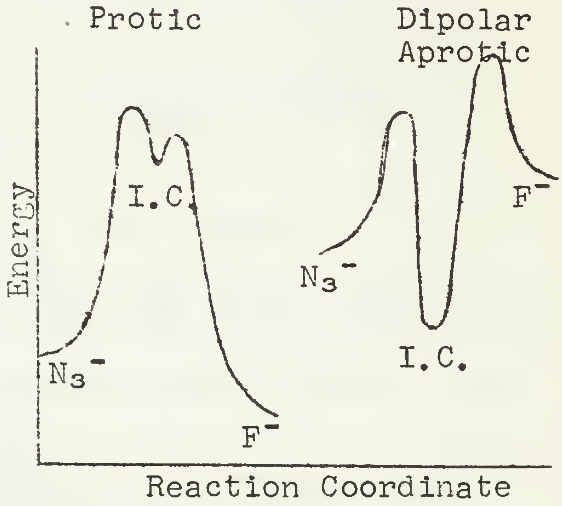
Solvent Effects

It has been suggested that a general medium effect, linear with amine concentration, might be a better interpretation than base catalysis for some of the rate accelerations observed in the reactions of dinitrohalobenzenes with primary and secondary amines (5). Except for the studies of these systems in chloroform, this proposed medium effect is the opposite of what would be predicted on the basis of dielectric constants (36). However, possible medium effects cannot be ruled out on this basis since the dielectric constant of a medium is neither a

unique nor a reliable criterion for solvent effects. In a study of th reaction of 2,4-DNCB with p-toluidine in solvent mixtures ranging from 100% dioxane to 50-50% dioxane-water it has been found that log $k_{obs.}$ vs. 1/D is not linear, as is often predicted (37-39). A nice linear plot is obtained, though, when Winstein's Y values (40) are used in place of the reciprocal of the dielectric constant.

Rates of reactions of five different anionic nucleophilic agents with four activated halobenzenes (29) have been measured in protic solvents (alcohols, some amides) and in dipolar aprotic solvents (acetone, DMF). The results of this study can be summarized as follows: 1) Rate constants for reactions in dipolar aprotic solvents are up to 10^5 times greater than for the same reactions in protic solvents. 2) In many cases a decreased energy of activation is responsible for the increase in rate in dipolar aprotic solvents. 3) Reactions of large, polarizable ions (SCN^-, I^-) are less sensitive to solvent change than reactions of smaller, less polarizable ions (N_3^-, Br^-). 4) Thiocyanate reacts readily with 2,4-DNIB in DMF and in acetone but neither SCN^- nor I^- can displace fluorine from 2,4-DNFB in either of these two solvents. 5) The reaction of iodide ion with an equimolar amount of 2,4-DNBB reaches equilibrium after 67% forward reaction in methanol and after 53% forward reaction in acetone. 6) Displacements of halogen by fluoride ion are at least 10^3 times faster in dipolar aprotic solvents than in alcohols. Miller and Parker believe that the observed solvent effect can be explained if solvation of anions in dipolar aprotic solvents is the reverse of that generally accepted for protic solvents; i.e., transition state$^-$ > picrate$^-$ > SCN^- > I^- > Br^- > N_3^- > Cl^- >> F^-. They have used a diagram similar to the one below to schematically represent their data. Support for the relative solvation energies shown in this diagram can be found in the solubilities (40) and conductivities (41) of the salts in the two classes of solvent. This diagram can also be used to explain the azide ion-4-fluoronitrobenzene reaction described earlier in this abstract. The free energy diagrams for this reaction in the two classes of solvent may be drawn from a consideration of the solvation energy diagram.





Conclusions

Some of the criticisms of the intermediate complex mechanism for nucleophilic aromatic substitutions concern the proximity of the transition state structure to that of the intermediate, and do not necessarily question the structure of the intermediate. Probably the best support for the intermediate complex mechanism is the fact that in the many varieties of aromatic nucleophilic substitution reactions which have been studied, there seems to be no evidence definitely requiring the one-step, S_N2-like mechanism. On the other hand, several independent types of evidence incompatible with the S_N2-like mechanism and consistent with the intermediate complex mechanism have been reported. The role of solvent effects in these reactions is just beginning to be fully realized. Because of the lack of a good understanding of the effects on reaction rates caused by added neutral salts (5,31,34,37), more studies of salt effects in nucleophilic aromatic substitution reactions will probably be forthcoming.

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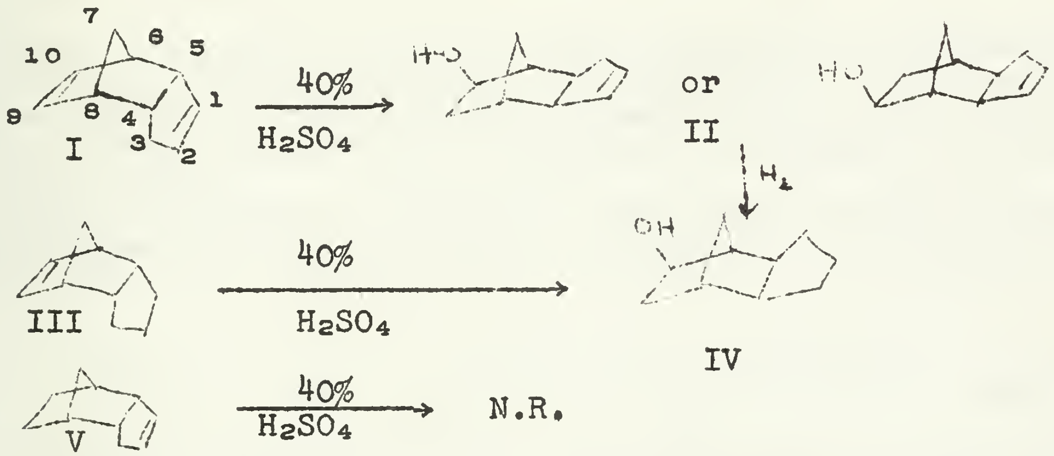
IONIC ADDITION REACTIONS IN THE DICYCLOPENTADIENE SERIES

Reported by H. W. Moore April 17, 1961

Ionic addition reactions in the dicyclopentadiene series are usually accompanied by novel rearrangements. This report will discuss the addition-rearrangement reactions of those compounds in the dicyclo pentadiene series that contain a double bond in the 6-membered ring. Dicyclopentadiene and its saturated analogs are quite similar in structure to the well known bicyclo-(2.2.1)-2-heptene (norbornene), the addition reactions of which have been studied extensively (1). Therefore, where possible, analogies and correlations between the two systems will be noted.

In 1945, Bruson and Riener (2) studied the hydration of endo-dicyclopentadiene (I) with 40% H_2SO_4. The monoalcohol (II) which was obtained as the major product appeared to have a ring system quite different from that of endo-dicyclopentadiene. The reaction was shown to take place at the double bond of the 6-membered ring by the fact that the Diels-Alder adduct of cyclopentadiene and cyclopentene, viz. 1,2-dihydro-endo-dicyclopentadiene (III), upon hydration under the same conditions gave an alcohol (IV) which was identical to the reduced alcohol obtained by Bruson and Riener. Furthermore, no reaction was observed with 9,10-dihydro-endo-dicyclopentadiene (V) under the same hydration conditions.



Bruson and Riener made the saturated ketone, hydrocarbon, and alcohol from their original alcohol (II) and showed that they were not identical to the previously known endo compounds (VI), (VII) and (VIII) which were prepared by Alder and Stein (3) and Wieland and Bergel (4).

VI X=H
VII X=OH
VIII X= =O

Bartlett and Schneider (5) have pointed out that the conditions of this reaction were those of a Wagner-Meerwein rearrangement. In using this ionic mechanism the reaction would involve an endo to exo rearrangement of the trimethylene group in the dicyclopentadiene ring system.

This mechanism is the same as that proposed by Alder and Stein (6) to account for the conversion of exo-cis-3,6-endomethylene-Δ⁴-tetra-

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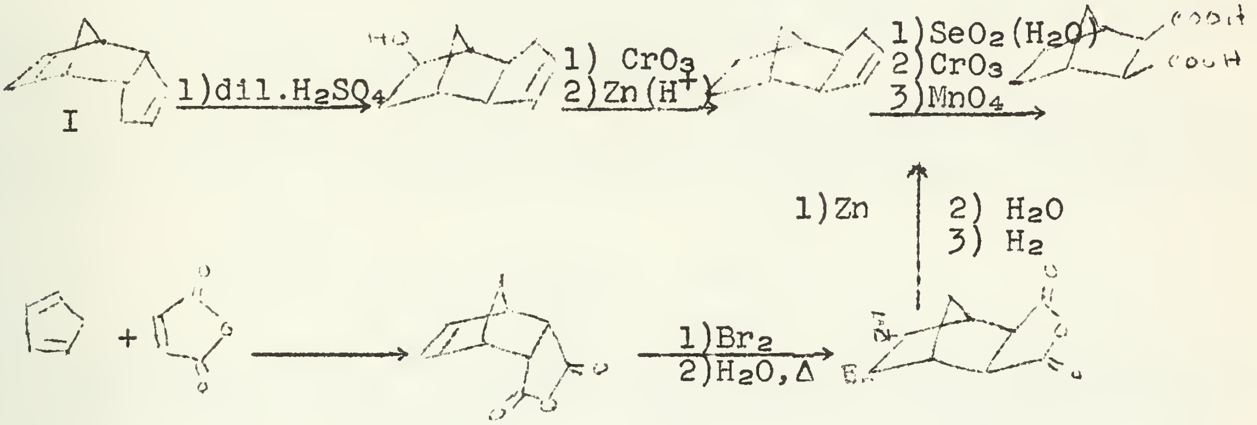
hydrophthalic acid by means of 50% H_2SO_4 into a lactonic acid having the endo configuration. In fact, Bartlett has shown that Bruson and Riener's hydration product was indeed the exo isomer by converting it into Alder's β(exo)-3,6-endomethylene-hexahydrophthalic acid and establishing the identity of the latter compound by mixed melting points of the corresponding anhydride and phenylazide adducts with specimens prepared by the Alder and Stein method from the addition product of maleic anhydride and cyclopentadiene.



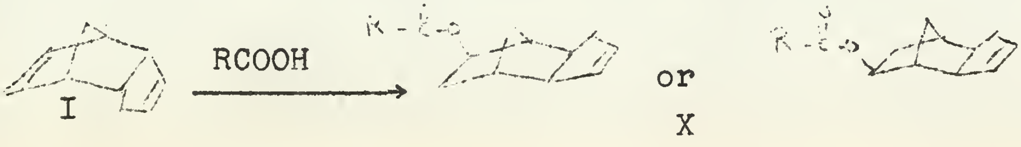
Bruson and Riener have also shown that endo-dicyclopentadiene reacts with a variety of hydrogen donors (2,7). These reactions involve the usual addition-rearrangement and thus lead to convenient methods for the preparation of hundreds of derivatives of exo-dicyclopentadiene.

Aqueous solutions of inorganic acids such as HCl, HBr and HI add to dicyclopentadiene giving rise to compounds of the monohalo exo series (IX).

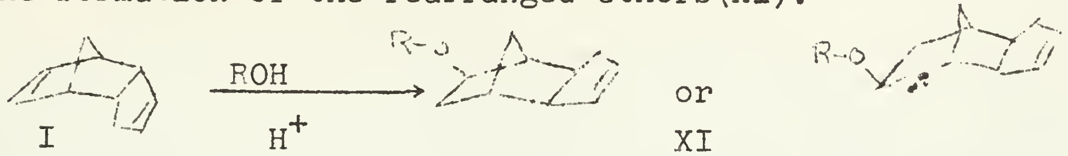
X=Br,Cl,I

The residual double bond in the products is quite resistant to the addition of a second molecule of acid, but it does add a mole of halogen. No reaction was observed with aqueous HF.

This interesting addition-rearrangement is definitely not limited to inorganic acids. Strong organic acids will also add and initiate the endo to exo rearrangement with the formation of esters (X). Bruson has pointed out in a patent (8) that organic acids with dissociation constants of 1.5×10^{-3} or more will initiate the reaction without the aid of a catalyst. However, in such cases the reaction may be accelerated and the yields improved by the presence of stronger acids such as HCl or H_2SO_4 or by Lewis acids such as $ZnCl_2$, $AlCl_3$ or BF_3. In fact, when catalysts are used it is possible to add even fatty acids. Contrary to the acidity limitations which Bruson stated in his patent, Bergmann and Japhe (9) have shown that boiling formic acid ($K_a^{25}=1.77 \times 10^{-4}$, $K_a^{60}=1.55 \times 10^{-4}$) adds directly to endo-dicyclopentadiene to produce the rearranged dicyclopentadienyl formate in nearly quantitative yields.

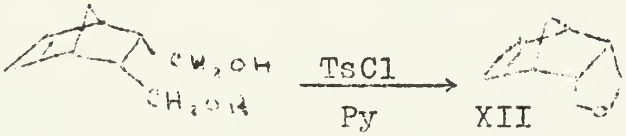


Bruson and Riener (10) have also shown that alcohols and phenols add in the presence of H_2SO_4 or BF_3/ether to endo-dicyclopentadiene with the formation of the rearranged ethers(XI).



Wilder and Culberson (11,12) have recently reported some very interesting results in the investigation of acidic addition reactions in two heterocyclic dicyclopentadiene **series**--2-oxa and 2-aza-1,2-dihydro-exo and endo-dicyclopentadiene.

2-Oxa-1,2-dihydro-endo- and exo-dicyclopentadiene were prepared by the action of one equivalent of p-toluenesulfonyl chloride on the corresponding endo and exo-cis-bicyclo-(2.2.1)-heptane-2,3-dimethylol.



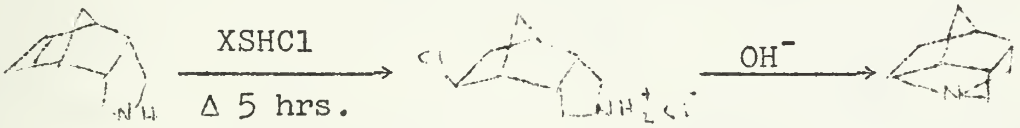
The liquid exo isomer was obtained in good purity by this method, but the solid endo compound (XII) was very difficult to purify and the reactions of this compound were carried out on the crude material.

The authors report that most acid-catalyzed addition reactions of 2-oxa-1,2-dihydro-endo-dicyclopentadiene do not involve rearrangement. They investigated the action of such reagents as HCl, HBr, HOAc and CH_3OH in the presence of sulfuric acid catalyst. In the case of the addition of HBr the authors claim that endo to exo rearrangement takes place to about 17%. However, this observation seems to be rather presumptuous since the endo ether was not pure.

The structures of the addition products were proved by dehydrohalogenation and comparison of these products with the corresponding endo or exo ethers.

Addition reactions involving the exo ether take place in the normal manner and no rearranged products are observed.

Acid addition reactions were also studied on 2-aza-1,2-dihydro-endo and exo-dicyclopentadiene. Neither isomer undergoes rearrangement but the endo isomer allows intramolecular cyclization leading to the formation of a novel tertiary amine (XIII).



XIII

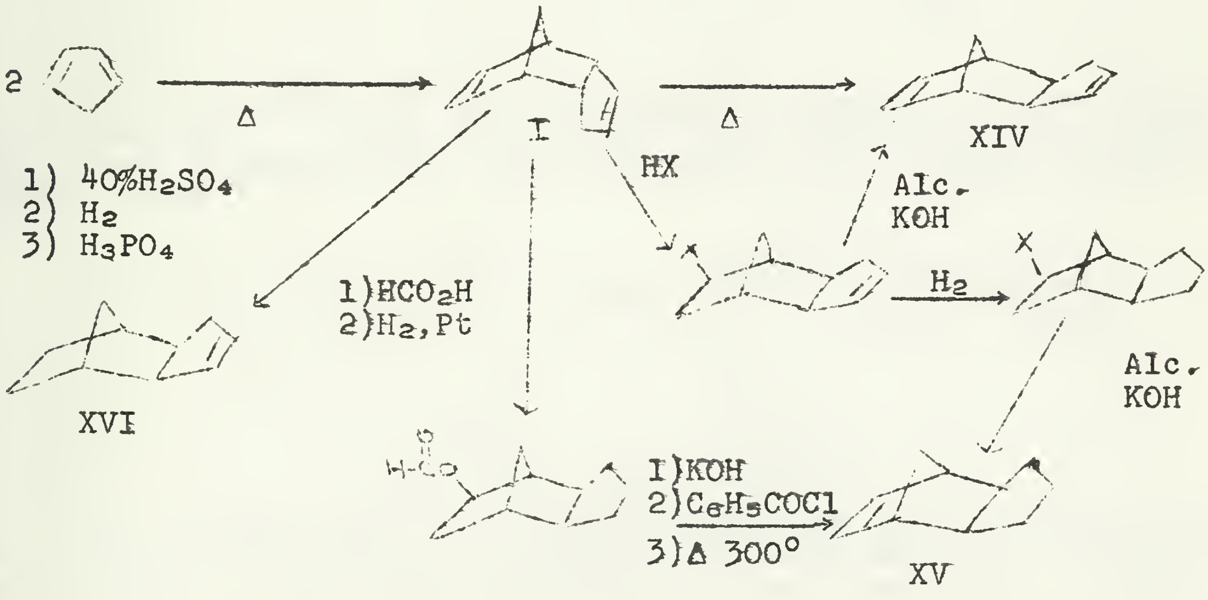
The structure of XIII was proved by Hofmann degradation to the known compound, N-methyl-1,2-dihydro-endo-dicyclopentadiene.

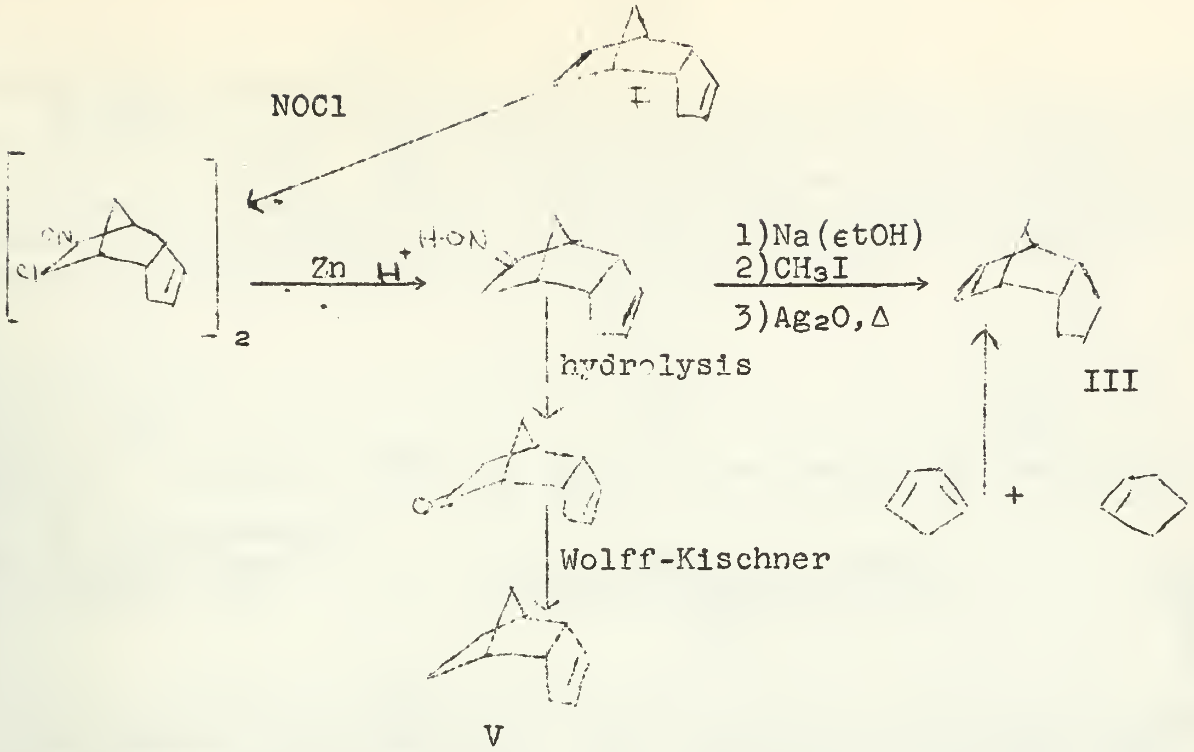
As in the case of the 2-oxa exo isomer addition of acidic reagents to 2-aza-1,2-dihydro-exo-dicyclopentadiene gave additions without rearrangements.

Before taking up addition reactions of nonprotonic reagents a brief discussion of the preparations of dicyclopentadienes and their saturated analogs is in order. Alder and Stein (13) first showed that the Diels-Alder dimer of cyclopentadiene was endo-dicyclopentadiene (I) by reduction of the norbornene double bond and oxidative degradation to the known endo-cis-3,6-endomethylene-hexaphthalic acid. Exo-dicyclopentadiene (XIV) has been prepared by the dehydrohalogenation of exo-9-halo-tetrahydro-exo-dicyclopentadiene (14,15). Wilder and Youngblood (16) have prepared 1,2-dihydro-exo-dicyclopentadiene (XV) in the same manner, i.e. dehydrohalogenation of the corresponding

exo-9-halo-tetrahydro-exo-dicyclopentadiene. The stereochemistry of the 1,2-dihydro-exo-dicyclopentadiene was established by reduction to the known tetrahydro-exo-dicyclopentadiene (17). Bruson and Riener (16) have reported the preparation of 1,2-dihydro-exo-dicyclopentadiene by the dehydration of exo-9-hydroxy-tetrahydro-exo-dicyclopentadiene with phosphoric acid. However, the olefin obtained in this manner and that obtained by the dehydrohalogenation of exo-9-halo-tetrahydro-exo-dicyclopentadiene were not identical. In fact, Wilder and Youngblood (17) and Schleyer and Donaldson (18) have shown that the phosphoric acid dehydration of exo-9-hydroxy-tetrahydro-exo-dicyclopentadiene actually leads to the formation of 9,10-dihydro-exo-dicyclopentadiene (XVI). The structure and stereochemistry of this latter compound has already been discussed on page 2. In Bruson and Riener's studies of acid catalyzed hydration and rearrangement of endo-dicyclopentadiene they reported the preparation of a dihydro-dicyclopentadiene by the reaction of cyclopentene and cyclopentadiene at elevated temperature and pressure. However, at that time no data bearing upon the stereochemistry were obtained. Later, Wilder, Culberson and Youngblood (19) solved this problem by identifying Bruson and Riener's olefin as 1,2-dihydro-endo-dicyclopentadiene (III) by comparison with an authentic sample, which was prepared by Hofmann elimination of the corresponding exo-9-amino-tetrahydro-endo-dicyclopentadiene. Cristol, Siefert and Soloway (20) have recently synthesized endo and exo 1,2-dihydro-dicyclopentadiene by the pyrolysis of the corresponding benzoate esters. The last isomer of this series, 9,10-dihydro-endo-dicyclopentadiene (V) was prepared by Alder, Stein and Finzerhagen (3). They added nitrosyl chloride to endo-dicyclopentadiene with formation of the nitroso chloride dimer, reduced this dimer to the oxime, hydrolyzed the oxime to the ketone and the ketone was reduced under Wolff-Kischner conditions to the hydrocarbon (V). The stereochemistry of the hydrocarbon was determined by oxidative degradation to endo-cis-3,6-endomethylene-hexahydrophthalic acid.

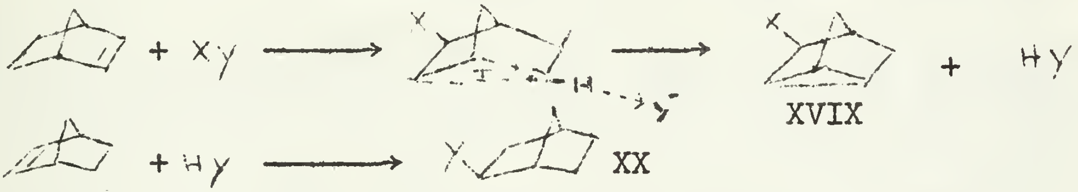
These methods of preparation are summarized in the following manner:



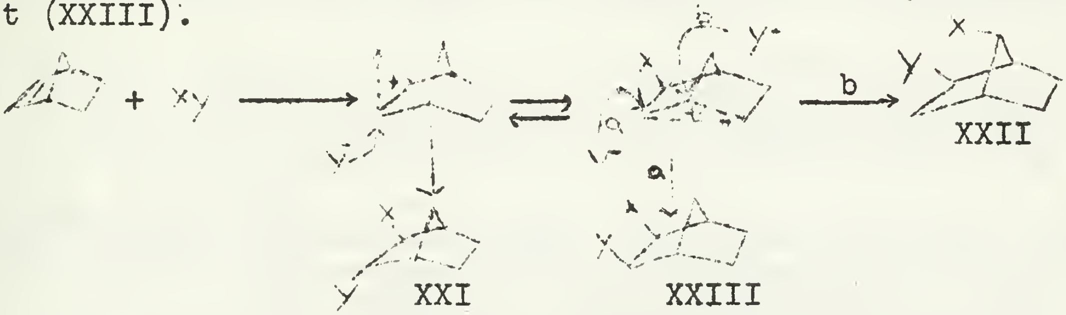


A large number of nonprotonic reagents, XY, have been added heterolytically to the double bond of norbornene under a variety of experimental conditions (1). In such cases in which neither X nor Y is hydrogen it is possible to determine the structural and stereochemical course of the reaction. The results of these addition reactions, as generalized by Schleyer (21,22), are classified into two main groups.

1) Attack of the electrophile is followed by the loss of a proton. This gives rise to a nortricyclenic derivative (XVIX) and a molecule of a protonic acid, HY. This acid, in a competing side reaction, can add to norbornene in the usual manner to form a norbornyl derivative (XX).



2) If the attack of the electrophilic reagent, X^+, is followed by the attack of Y^-, the products which result are the normal trans-2,3 (XXI), the rearranged syn-7-exo-2 compound (XXII) and/or the cis-vic product (XXIII).



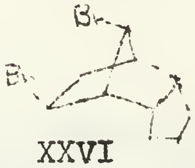
Until recently only carboxylic acid derivatives of norbornene had been studied extensively to determine the influence of structural modifications of the olefin towards addition reactions. In 1960, Schleyer and his co-workers (22) realized this deficiency and investigated some addition reactions of 1,2-dihydro-exo-dicyclopentadiene with the hope of determining the influence of the exo trimethylene group on the reaction.

Bromination in Br_2/CCl_4

Bromination of 1,2-dihydro-exo-dicyclopentadiene was carried out with Br_2/CCl_4 at 0°. The dibromide material which was formed appeared to be one component. Three possible structures were considered--trans-9,10-dibromo-1,2-dihydro-exo-dicyclopentadiene (XXIV), exo-cis-9,10-dibromo-1,2-dihydro-exo-dicyclopentadiene (XXV) and exo-9-syn-7-dibromo-1,2-dihydro-endo-dicyclopentadiene (XXVI).

XXIV

XXV



XXVI

The trans structure (XXIV) was shown to be correct by the following data:

a) Dipole Moments

Obs. Dipole Moment	Calculated Dipole Moment	Compound
2.3D	2.0D	XXIV
	3.8D	XXV
	3.9D	XXVI

We see that structure XXIV is the only one which corresponds closely to the observed dipole moment. Also, the previously found value for the dipole moment of the analogous compound, trans 2,3-dibromo-norbornane, was 2.3D, which is in very good agreement.

a) Chemical Degradation studies confirmed this trans dibromo assignment.

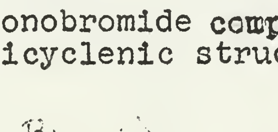
The vinyl bromide (XXVII) was rigorously established by oxidation to the known dicarboxylic acid (XXVIII), hydrolysis to the known ketone (XXIX), and IR and NMR data. In the IR a band at 1575 cm^{-1} was present which is characteristic of a disubstituted norbornene type structure (24). The trisubstituted nature of the olefin bond was revealed by a strong doublet at 816-807 cm^{-1} and by the absence of a band at 714 cm^{-1} which has been attributed to a disubstituted olefin.

The NMR data indicated that the vinyl bromide (XXVII) has half as many vinylic as bridgehead proton resonances and no halomethinyl proton peaks.

Wilder and Youngblood (23) have also obtained the trans dibromide by the action of Br_2/CCl_4 at 0° on 1,2-dihydro-exo-dicyclopentadiene. They have shown that the product is a vic dibromide since it was reconverted to the starting olefin by I^- in acetone and Zn in alcohol.

Bromination in pyridine

When Schleyer and his co-workers (22) carried out the bromination of 1,2-dihydro-exo-dicyclopentadiene in pyridine, two dibromo and one monobromo products were obtained. The main product was again the 9,10-trans product. The monobromide compound was obtained in 1.5% yield and was assigned the nortricyclenic structure (XXX) on the following grounds:



XXX

a) The IR indicated by a band at 853 cm^{-1} a saturated compound of the nortricyclene type with an alkyl substituent on the 3-membered ring (25).

b) Hydrogenolysis with alkaline palladium on charcoal gave a bromine-free compound which was assigned the structure (XXXI).

XXXI

This compound showed the same characteristics of the 3-membered ring (846 cm^{-1}) and gave no olefin bands in the IR. Elemental analysis also pointed to structure XXXI. However, several attampts to synthesize XXXI by oxidation of the hydrazone of the ketone (XXIX), failed. The other dibromide product, in addition to the trans dibromide, obtained from this reaction was isolated in 8.5% yield and was assigned syn-7-exo-9-dibromo-1,2-dihydro-endo-dicyclopentadiene (XXVI).

XXVI

Evidence which confirmed this structure was the following:

a) Dipole Moment

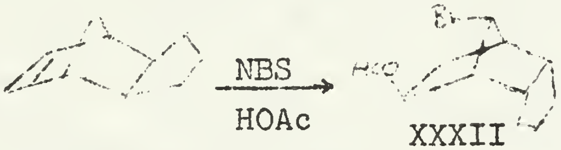
Calculated	Observed
3.8D	3.7D

b) Dehydrohalogenation gave a monobromo compound which was different from the vinyl bromide (XXVII) in all properties and yet gave absorption bands in the IR at 1575 and 730 cm^{-1}, characteristic of the norbornene type structure. The NMR data on the dehydrohalogenated compound confirmed its structure since they showed three peaks corresponding to vinylic, halomethinyl, and bridghead hydrogens in the ratio of 2.1.2.

The rearranged dibromide (XXVI) is very interesting because its formation represents the first known case of exo to endo rearrangements in the dicyclopentadiene series. The rearrangement involves conversion of a thermodynamically more stable exo substituted norbornane to a product in which the same substituent has the less stable endo configuration.

Bromination with NBS in Acetic acid.

Recently Cristol and co-workers (20) have shown that 1,2-dihydro-exo-dicyclopentadiene reacts with NBS in acetic acid to give syn-7-bromo-exo-9-acetoxy-1,2-dihydro-endo-dicyclopentadiene (XXXII).



XXXII

This reaction represents another example of the unusual exo to endo rearrangements. The stereochemical assignment of the bromo and acetoxy groups is rather vague. Cristol has based this assignment of the stereochemistry on the analogy to addition reactions to norbornene together with the knowledge that rearrangement has occurred. Cristol has shown that the bromine and hydroxyl groups of the hydrolysis product of the bromo acetoxy compound are not vic by the following observations: a) Base did not convert the compound to an epoxide or ketone. b) Zn did not convert it to an olefin. Both of these reactions would be expected to occur with a vic bromohydrin.

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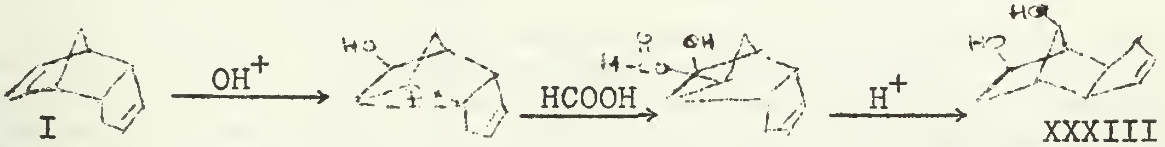
[illegible] will be expected to cover all major developments.

Reaction with Performic acid

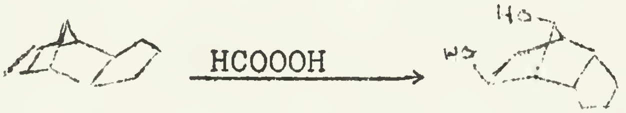
The reaction of performic acid with compounds in the dicyclopentadiene series has been well characterized. In 1954, Gates and Malchick (25) investigated the reaction of the performic acid with endo-dicyclopentadiene. The reaction yielded a glycol monoformate from which a glycol (XXXIII) was obtained upon hydrolysis. The glycol did not react with periodic acid or lead tetraacetate, which indicated that it was not a 1,2-glycol.

The following mechanism accounts for this reaction.



The stereochemical assignment of the two substituents here again is entirely speculative. However, it appears to be valid by analogies to the norbornene series. For example, Vosburgh and Kwart (26) have shown that norbornene, upon oxidation by performic acid, gives a 1,4-gylcol with the syn-7-exo-2 configuration in almost quantitative yields. As can be seen from the above mechanism the stereochemistry arises from the initally preferred exo attack of the OH^+ after which the reaction of the ion with formate ion or formic acid at the side opposite the unsaturated 5-membered ring yields the given configuration.

Another example of the action of performic acid on compounds of the dicyclopentadiene series was studied by Schleyer and co-workers (22), who ran the reaction of performic acid on 1,2-dihydro-exo-dicyclopentadiene and observed the formation of the rearranged 9,7-glycol(XXXIV).



XXXIV

This product was characterized by its phenylurethan derivative. It failed to react with periodic acid and formed a p-nitrobenzylidene derivative which is characteristic of 2,7-glycols in the norbornane series (26). No degradative studies were made on this compound but the endo orientation of the trimethylene substituent appears to be correct on the basis of the above evidence and by analogies to the norbornene series. Note that this is another example of the exo to endo rearrangement of the trimethylene substituent.

Addition of Nitrosyl Chloride

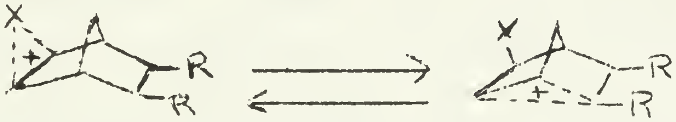
Nitrosyl chloride adds to endo-dicyclopentadiene without rearrangement. This lack of rearrangement has been shown by Wilder, Culberson and Youngblood (18) who reduced the resulting nitroso chloride dimer to the amine and the amine was subjected to Hofmann exhaustive methylation to form 1,2-dihydro-endo-dicyclopentadiene (XVII). These reactions preclude rearrangement. The lack of rearrangement in this case is probably due to the greater stability of the nitronium ion as compared to that of the non-classical carbonium ion.

The alkyl substituents on the norbornene ring in the dicyclopentadiene series appears to have a marked effect upon the ionic addition reactions when the results are compared to those obtained with norbornene itself. Of the cases studied, this is particularly true of bromination. As pointed out earlier, bromination of 1,2-dihydro-exo-

dicyclopentadiene in CCl_4 gives entirely the unrearranged trans dibromide (XXIV). On the other hand, bromination of norbornene under the same conditions gives 35% of the nortricyclene derivative, 15% of the 2,3-trans product and 26% of the 2,7-rearranged coupound (27). The trimethylene substituent appears to reduce both the tendency towards rearrangement and that of nortricyclene formation. Even the bromination of 1,2-dihydro-exo-dicyclopentadiene in the polar pyridine solvent gives only 1.5% yield of the nortricyclenic derivative while norbornene, under the same conditions gives about 27% yield of the nortricyclenic bromide (27).

No detailed mechanistic work has been reported on the ionic addition reactions of dicyclopentadiene and its analogs. However, since the compounds of this series are derivatives of the well known norbornene, the mechanism which has been used to explain the addition reactions of this compound would also appear to be applicable to the dicyclopentadiene system (see page (5).

The addition reactions in this series appear to be greatly influenced by the stability of the onium ion with respect to the bridged carbonium ion and/or the equilibrium between these two species.



The addition reactions of norbornene also point to this factor and Scheyler has pointed this out and summarized the results in the following manner:

a) Sulfenyl halides give trans addition products of norbornene due to the greater stability of the tertiary sulfonium ions.

b) In addition to monobromo compounds, bromination of norbornene gives a mixture of 2,3-trans and 2,7-rearranged dibromides. On the other hand, in the case of chlorination, the only dichloro compound which is isolated is the rearranged compound, viz. syn-7-exo-2-dichloronorbornene. This is consistant with the fact that the bromonium ion is more stable than the chloronium ion.

Therefore, as Schleyer has pointed out, it is apparent that ionic addition reactions in both the norbornene and the dicyclopentadiene system depend upon reaction conditions, structural variations and the nature of the attacking agent.

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POLYFLUOROBUTADIENES: THEIR SYNTHESIS AND CHEMISTRY

Reported by R. R. Haynes April 24, 1961

Because of their interesting physical and chemical properties, fluorinated hydrocarbons have received a great deal of attention in the past two decades. This report will be a critical review of a small segement of the field of polyfluorinated aliphatic compounds, namely, polyfluorobutadienes. A short review of these dienes and other aliphatic fluorine compounds can be found in an ACS monograph published in 1958 (1).

SYNTHESIS

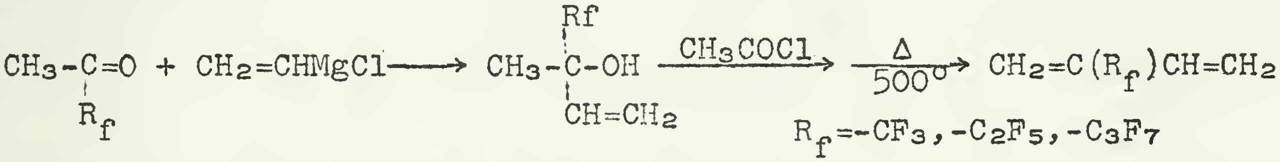
One of the commonest methods used in the preparation of polyfluorobutadienes involves the removal of one or two molecules of halogen, hydrogen halide, water, or acetic acid from the appropriate polyhalobutane or butene. For example, the dehydrohalogenation of 1,1-difluoro-1,3-dichloro-3-methylbutane with tri-n-butylamine yields 1,1-difluoro-3-methyl butadiene (2), and the reaction of zinc on 1,2,3,4-tetrachloro-2,3-difluorobutane gives 2,3-difluorobutadiene (3). As can be seen from the preceding illustrations, the chemical techniques employed here are not new. However, the presence of a $-CF_2-$ or CF_3- group within a molecule has a marked effect upon the elimination step in the synthesis. Since the carbon adjacent to a polyfluorinated carbon is electron-deficient, a proton is readily eliminated from it, but a halogen is stabilized towards elimination from it during a dehydrohalogenation reaction. Therefore, it is not surprising that the dehydrohalogenation of $CF_3CHClCH_2CH_3$ with base failed, but HCl was cleanly eliminated from $CF_3CH_2CHClCH_3$ under similar conditions (4). Alcohols bearing the hydroxyl group on the same carbon as a trifluoromethyl group are difficult to dehydrate. Attempts to dehydrate 1,1,1-trifluoro-2-octanol by heating with $KHSO_4$, concentrated sulfuric acid, 85% phosphoric acid, or with phosphorous pentoxide at 235° all failed (5). Dehydration of such alcohols is best achieved by pyrolysis of their acetates (5,6,7).

SYNTHESIS OF THE PRECURSOR TO THE DIENE

Since, as mentioned earlier, the chemistry employed in the final step of the synthesis of polyfluorobutadienes is generally of common nature, the interest in the synthesis of the dienes has been in the preparation of the precursor.

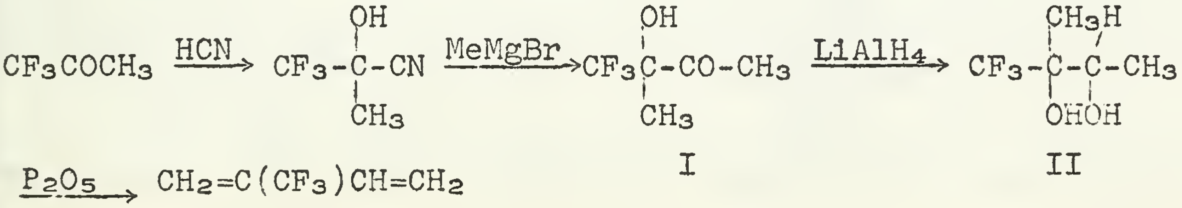
I Use of a Grignard Reagent

A series of perfluoroalkylbutadienes has been prepared by Richardson and Tarrant (7) from the tertiary alcohols prepared by the reaction of vinylmagnesium chloride and perfluoroalkylketones. Acetylation of the alcohols followed by pyrolysis of the acetates gave the dienes in good yields. The diene in which $R_f=-CF_3$ had previously been prepared by Tarrant and Taylor (6). After converting trifluoroacetone to its cyanohydrin, they were able to bring about reaction of it with methylmagnesium bromide to give the methylketone (I). Reduction of this



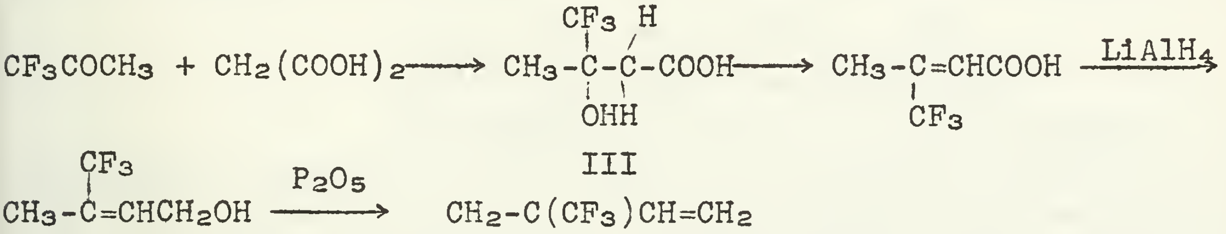
$$CH_3-\underset{R_f}{C}=O + CH_2=CHMgCl \longrightarrow CH_3-\overset{R_f}{\underset{CH=CH_2}{C}}-OH \xrightarrow{CH_3COCl} \xrightarrow[500^{\circ}]{\Delta} CH_2=C(R_f)CH=CH_2$$

$R_f=-CF_3, -C_2F_5, -C_3F_7$



$$CF_3COCH_3 \xrightarrow{HCN} CF_3-\overset{OH}{\underset{CH_3}{C}}-CN \xrightarrow{MeMgBr} \underset{I}{CF_3\overset{OH}{\underset{CH_3}{C}}-CO-CH_3} \xrightarrow{LiAlH_4} \underset{II}{CF_3-\overset{CH_3}{\underset{OH}{C}}-\overset{H}{\underset{OH}{C}}-CH_3} \xrightarrow{P_2O_5} CH_2=C(CF_3)CH=CH_2$$

ketone with $LiAlH_4$ gave the diol (II), and dehydration of this substance gave a crude product of which 37% proved to be the desired diene. The low yield was attributed to the influence of the trifluoromethyl group, but no attempt was made to identify the product(s) formed by the competing side reaction(s). Another path to 2-trifluoromethylbutadiene was devised whereby the activating effect of a carboxyl group was used to overcome the influence of the trifluoromethyl group in the dehydration step. Trifluoroacetone was condensed with malonic acid to give the hydroxybutyric acid (III) which was readily dehydrated to β-trifluoromethylcrotonic acid. Reduction of this acid with $LiAlH_4$ gave the hydroxybutene (IV). Dehydration with phosphorous pentoxide gave the diene in 60% yield.



$$CF_3COCH_3 + CH_2(COOH)_2 \longrightarrow CH_3\text{-}\overset{CF_3}{\underset{OH}{C}}\text{-}\overset{H}{\underset{H}{C}}\text{-}COOH \longrightarrow CH_3\text{-}\underset{CF_3}{C}{=}CHCOOH \xrightarrow{LiAlH_4}$$

III

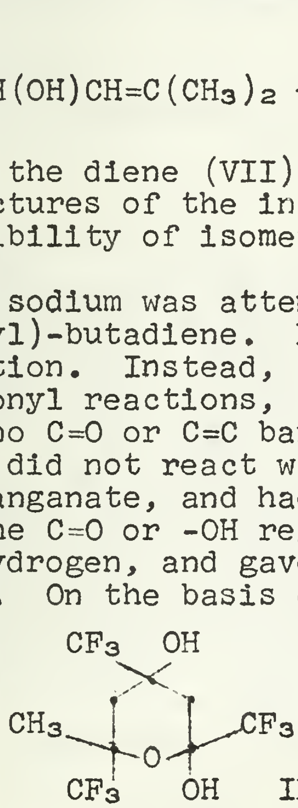
$$CH_3\text{-}\overset{CF_3}{C}{=}CHCH_2OH \xrightarrow{P_2O_5} CH_2\text{-}C(CF_3)CH{=}CH_2$$

Henne and Hinkamp (8) have utilized trifluoroacetylacetone in the synthesis of three trifluoromethylbutadienes. Reduction of the diketone to the diol followed by pyrolysis of the corresponding acetate gave the fluorodiene (V) in 75%. Reaction of the diketone with two moles of methylmagnesium bromide yielded the tertiary alcohol (VI) which was dehydrated to the vinylketone (VIII). The carbonyl compound was reduced to the alcohol and then acetylated. Pyrolysis of the acetate gave the diene (VII). The physical and chemical evidence given for the structures of the intermediate and final products do not rule out the possibility of isomeric products. The coupling of trifluoroacetone with sodium was attempted to prepare a precursor of 2,3-bis-(trifluoromethyl)-butadiene. But no dimeric product could be isolated from the reaction. Instead, a trimeric product was formed which gave no positive carbonyl reactions, and whose infrared showed -OH and -CF absorption, but no C=O or C=C bands. Dehydration of the trimer gave a compound that did not react with sodium, reacted only slowly with bromine or permanganate, and had infrared absorption in the region of C=C but none in the C=O or -OH regions. The dehydration product absorbed two moles of hydrogen, and gave a magenta color when treated with $AlCl_3$ in chloroform. On the basis of the preceding evidence the trimer was assigned the structure (IX) and the dehydration product the structure (X).

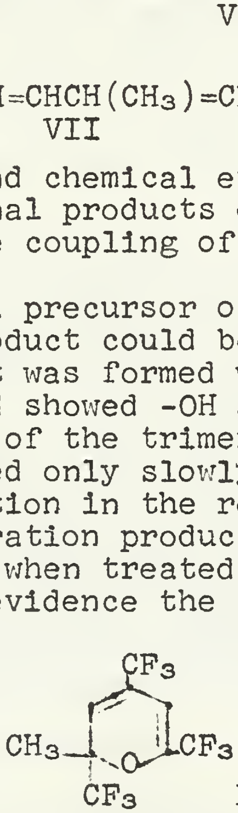
$$CF_3COCH_2COCH_3 \xrightarrow[H_2]{Ni} CF_3C(OH)HCH_2CH(OH)CH_3 \xrightarrow{Ac_2O} \xrightarrow{\Delta} \underset{V}{CF_3CH{=}CHCH{=}CH_2}$$

$$CF_3COCH_2COCH_3 \xrightarrow{2MeMgBr} \underset{VI}{CF_3COCH_2C(OH)(CH_3)_2} \longrightarrow \underset{VIII}{CF_3COCH{=}C(CH_3)_2} \xrightarrow{Al(iprO)_3}$$

$$CF_3CH(OH)CH{=}C(CH_3)_2 \xrightarrow{Ac_2O} \xrightarrow{\Delta} \underset{VII}{CF_3CH{=}CHCH(CH_3){=}CH_2}$$



IX



X

II FREE RADICAL ADDITION OF POLYHALOMETHANES AND POLYHALOETHANES TO OLEFINS

Tarrant and co-workers (9,10,11,12) have studied the free radical addition of bromotrichloromethane, dibromodifluoromethane, and 1-chloro-1,2-dibromo-1,2,2-trifluoroethane to olefins, and of dibromodifluoromethane, 1,2-dibromo-2-chloro-1,1,2-trifluoroethane, and 1,2-dichloro-

-2-iodo-1,1,2-trifluoroethane to fluoroolefins. The general reaction scheme for the addition of dibromodifluoromethane is represented as follows:

$$CF_2Br_2 + R\cdot \longrightarrow CF_2Br\cdot + RBr$$

$$CF_2Br\cdot + CH_2{=}CHR \longrightarrow CF_2BrCH_2\dot{C}HR$$

$$CF_2BrCH_2\dot{C}HR + CF_2Br_2 \longrightarrow CF_2BrCH_2CHBrR + CF_2Br\cdot \text{ et}$$

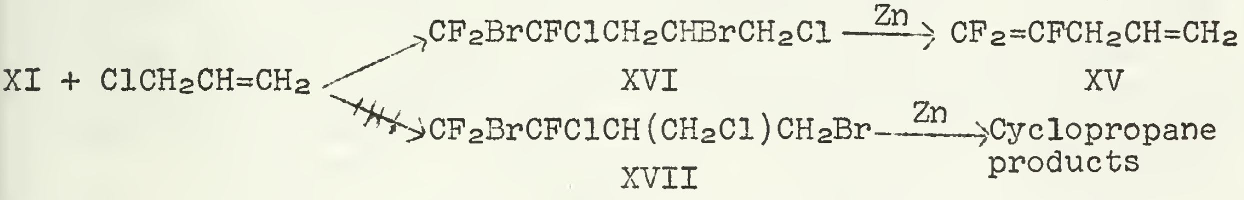
The products obtained by the addition to propylene and isobutylene were dehydrohalogenated to 1,1-difluoro- and 1,1-difluoro-3-methyl-butadiene. With 1-chloro-1,2-dibromo-1,2,2-trifluoroethane where two radicals (XI or XII) were possible, it was shown by reaction with propylene that XI was formed in preference to XII. Dehydrohalogenation, followed by

$CF_2BrCFCl$ XI $\qquad$ $CFClBrCF_2$ XII

dehalogenation of the adduct yielded the olefin (XIII) rather than (XIV). The point of attack of the radical on the olefin was shown by

$CF_2{=}CFCH{=}CHCH_3$ XIII $\qquad$ $CFCl{=}CFCH{=}CHCH_3$ XIV

reaction with 3-chloropropene. Since the product could be converted in one step to the trifluoropentadiene (XV), it was evident that the adduct had the structure (XVI) rather than the alternative structure (XVII) The latter compound would give rise to some cyclopropane products when



$$XI + ClCH_2CH{=}CH_2 \longrightarrow \underset{XVI}{CF_2BrCFClCH_2CHBrCH_2Cl} \xrightarrow{Zn} \underset{XV}{CF_2{=}CFCH_2CH{=}CH_2}$$

$$XI + ClCH_2CH{=}CH_2 \not\longrightarrow \underset{XVII}{CF_2BrCFClCH(CH_2Cl)CH_2Br} \xrightarrow{Zn} \text{Cyclopropane products}$$

treated with zinc. Tarrant et al (11) were also successful in synthesizing polyfluorobutadienes with more than two fluorine atoms on the double bonds by reaction of dibromodifluoromethane with fluoroölefins. With olefinic fluoro compounds, an added factor, besides the expected normal order of stability of radicals (tert.>sec.>prim.), must be considered before assigning the structure to the intermediate adduct radical. In the case of 2-fluoro-2-butene, where there are two secondary adduct radicals possible, the bromodifluoromethyl radical attacks at the olefinic carbon bearing the greatest number of hydrogens. With 1-fluoropropene, a secondary radical intermediate will arise if attack occurs at the carbon with the lesser number of hydrogens, and a primary radical adduct if attack occurs at the carbon bearing the greater number of hydrogens. In this system the radical attacks to give the secondary adduct radical. But with 1,1-difluoropropene, a branched product was

$$CHF{=}CHCH_3 + CF_2Br_2 \xrightarrow{R\cdot} CF_2BrCHFCHBrCH_3$$

$$\text{BUT } CF_2{=}CHCH_3 + CF_2Br_2 \xrightarrow{R\cdot} CF_2BrCH(CF_2Br)CH_3$$

obtained indicating that the primary adduct radical was the intermediate.

The question of the stability of polyhalo radical adduct intermediates has been studied by Haszeldine (27,28,29,30,31). After consideration of the products formed from the radical addition of trifluoromethyl iodie and hydrogen bromide to a variety of fluoroölefins, he concluded that the stability of the intermediate radical adduct was of the order tert'> sec'> prim'. The tertiary radical is defined as any carbonbearing the odd electron and any three atoms or groups except hydrogen (e.g. $CF_3\cdot$). A secondary radical has one hydrogen (e.g.$-CHCl\cdot$), and a primary two hydrogens. This order, tert' >sec'> prim', may be altered to sec' tert' prim' in cases where the secondary radical contains atoms (e.g. Cl, Br) or groups (e.g. aryl,-COOH,-CN) which have a powerful stabilizing effect on the radical whereas the tertiary radical has atoms (e.g.F) or groups (e.g.alkyl, perfluoroalkyl) which can only weakly stabilize the radical. Thus when trifluoromethyl iodide is added to 1,1-difluorochloroethylene, the product, CF_3CF_2CHICl, suggests that the intermediate radical $CF_3CF_2CHCl\cdot$ (secondary) is more stable than the radical $CF_3CHClCF_2\cdot$ (tertiary)[2]. The only shortcoming of this work was that no considerations have been given to steric effects.

The polyfluorobutadienes (XVIII), (XIX), and (XX) were synthesized by reaction of dibromodifluoromethane with the appropriate fluoroölefin. The fluoroölefins (XXI) and (XXII) failed to react with the dibromodifluoro compound under conditions employed for the synthesis of the other

$CF_2{=}CFCHCCH_2$	$CF_2{=}CHCF{=}CH_2$	$CF_2{=}C(CH_3)CF{=}CH_2$	$CH_3C(CF_3){=}CH_2$	$CF_3CH{=}CF_2$
XVIII	XIX	XX	XXI	XXII

dienes. In these works (11,12) it was noted that as the number of fluorine atoms on the reacting olefin increased, the amount of telomeric products also increased. Thus, the intermediate adduct radical produced from the polyfluoroölefin and the bromodifluoromethyl radical was a more stable substance than the corresponding adduct from hydrocarbon or monofluoroöleins. Hence, the termination reaction (step I) was often superceded by a further propagation reaction (step II) when

$$CF_2BrCHXCX_2\cdot + CF_2Br_2 \longrightarrow CF_2BrCHXCX_2Br + CF_2Br\cdot \qquad \text{(Step I)}$$

$$CF_2BrCHXCX_2\cdot + CHX{=}CX_2 \longrightarrow CF_2BrCHXCX_2CHXCX_2\cdot \qquad \text{(Step II)}$$

the more selective polyhalo intermediate radical was formed. Utilizing the polyhaloethyl radicals (XI) and (XXIII) generated from the corresponding bromo compounds, Tarrant and Lilyquist (12) synthesized the

$CF_2BrCFCl\cdot$	$CF_2ClCClF\cdot$	$CF_2{=}CFCF_3$	$CR_2{=}CHCF_3$
XI	XXIII	XXIV	XXV

polyfluorobutadienes shown in the table below. Neither radical gave any adduct products when reacted with the polyfluoroölefins (XXIV) or (XXV).

Olefin	Polyfluorobutadiene
$CH_2{=}CH_2$	$CF_2{=}CFCH{=}CH_2$
$CH_2{=}CHF$	$CF_2{=}CFCH{=}CHF$
$CH_2{=}CF_2$	$CF_2{=}CFCH{=}CF_2$
$CHF{=}CF_2$	$CF_2{=}CFCF{=}CF_2$
$CH_3CH{=}CF_2$	$CF_2{=}C(CH_3)CF{=}CF_2$

In all cases the adducts were dehydrohalogenated with KOH and then dehalogenated with zinc.

III FREE RADICAL ADDITION OF FLUOROVINYLIODIDES TO OLEFINS

The generation of vinyl radicals by the action of ultraviolet light on trifluoroiodoethylene and 1,1-difluoro-2-iodoethylene has

been used by Park and Lacher (13,14) to synthesize polyfluoroidobutenes which are readily dehydrohalogenated to polyfluorobutadienes. The general reaction scheme is given below.

$$CF_2{=}CFI \xrightarrow{hv} CF_2{=}CF\cdot + I\cdot$$

$$CF_2{=}CF\cdot + CH_2{=}CH_2 \longrightarrow CF_2{=}CFCH_2CH_2\cdot$$

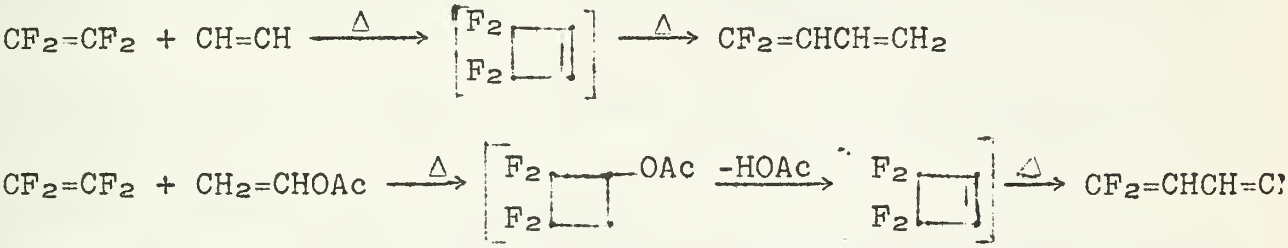
$$CF_2{=}CFCH_2CH_2\cdot + CF_2{=}CFI \longrightarrow CF_2{=}CFCH_2CH_2I + CF_2{=}CF\cdot \quad \text{etc.}$$

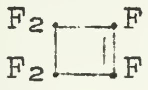
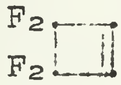
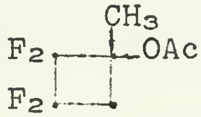
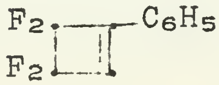
The polyfluorobutadienes prepared by these authors are given below. Examination of the dienes shows that Haszeldine's order was maintained in all cases.

Fluorovinyl Iodide	Olefin	Polyfluorobutadiene
$CF_2{=}CFI$	$CH_2{=}CH_2$	$CF_2{=}CFCH{=}CH_2$
"	$CH_2{=}CHF$	$CF_2{=}CFCH{=}CHF$
"	$CH_2{=}CF_2$	$CF_2{=}CFCH{=}CF_2$
"	$CHF{=}CF_2$	$CF_2{=}CFCF{=}CF_2$
$CF_2{=}CHI$	$CH_2{=}CH_2$	$CF_2{=}CHCH{=}CH_2$
"	$CH_2{=}CF_2$	$CF_2{=}CHCH{=}CF_2$

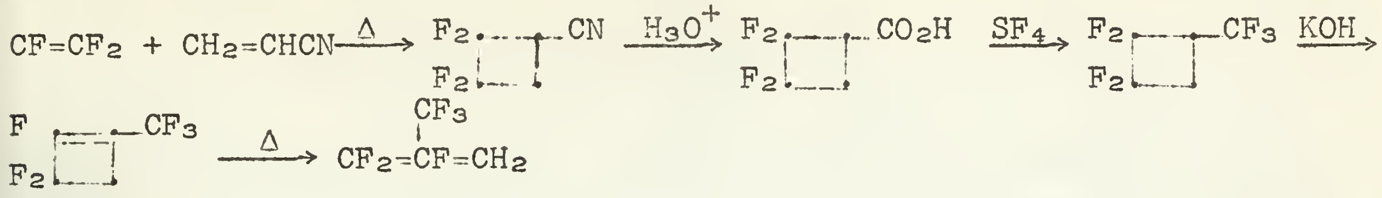
IV MOLECULAR ADDITION REACTIONS

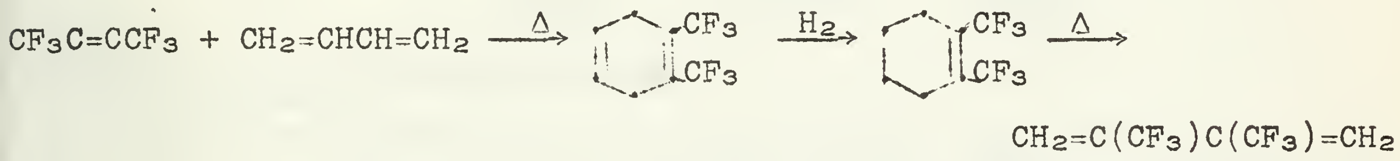
The discoveries by Haszeldine (15) that perfluorocyclobutene and perfluorobutadiene could be equilibrated by heat (500-700°), and by Putnam (16) that 3,3,4,4-tetrafluorocyclobutenes bearing at least one ethylenic hydrogen could be thermally isomerized to polyfluorobutadienes, opened the door to a new and more direct synthesis of these fluorodienes. The molecular addition products of acetylene and fluoroethylene are readily formed and then cleaved with heat into polyfluorobutadienes. The adducts of vinyl acetate and fluoroethylenes also give dienes upon pyrolysis presumably through loss of acetic acid to form the cyclobutene intermediate. The table below gives the various polyfluorobutadienes prepared by this method.

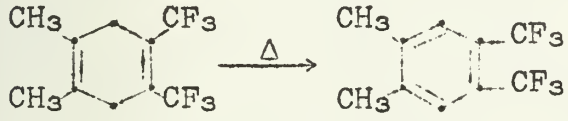


Molecular Addition Product	Polyfluorobutadiene
	$CF_2{=}CFCF{=}CF_2$
 or 	$CF_2{=}CHCH{=}CF_2$
	$CF_2{=}C(CH_3)CH{=}CF_2$
	$CF_2{=}C(C_6H_5)CH{=}CF_2$

Using the same principle, Putnam (17) has prepared 1,1,2-trifluoro-3-trifluoromethylbutadiene (XXVI) by a five-step synthesis culminating with the pyrolysis of the cyclobutene (XXVII). Putnam has also prepare 2,3-bis-(trifluoromethyl) butadiene (XXVIII) by pyrolysis of the partially reduced Diels-Alder adduct of butadiene and hexafluoro-2-butyne(18 Preparation of this diene was also attempted by pyrolysis of the Diels-Alder adduct of 2,3-dimethylbutadiene and hexafluoro-2-Butyne, but only the fluorinated durene (XXIX) was obtained.

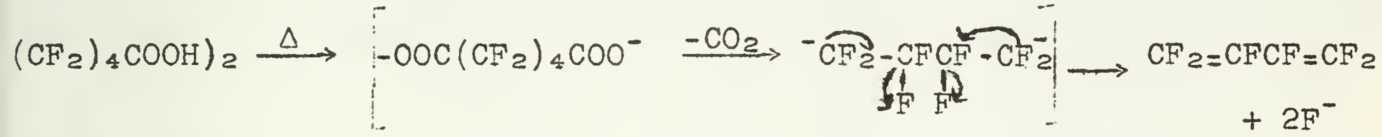

XXVII XXVI


XXVIII


XXIX

V MISCELLANEOUS PREPARATIONS OF POLYFLUOROBUTADIENES

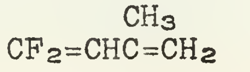
The pyrolysis of disodium octafluoroadipate (19) yields perfluorobutadiene. The reaction was postulated as proceeding stepwise since 2,2,3,4,5,5-heptafluoropent-4-en-1-oic acid was isolated from the hydrolysis of the less volatile products from the pyrolysis. Also, unsaturated fluorocarboxlyic acids can be converted into the dienes by pyrolysis of their salts.



$$CF_2{=}CFCF_2CF_2COONa \xrightarrow{\Delta} CF_2{=}CFCF{=}CF_2$$

Perfluorobutadiene can also be prepared by the dehalogenation of the polyhalobutane obtained by the light-catalyzed reaction of mercury and 1,1,2-trifluoro-1,2-dichloro-2-iodoethane (20). Fluorination of polychlorobutanes followed by dehalogenation and dehydrohalogenation is also another way of synthesizing polyfluorobutadienes. The reaction of HF and HgF_2 and 1,2,2,3,4-hexachlorobutane yields, among other products, 1,2,3,4-tetrachloro-2,3-difluorobutane, which is readily converted into the diene (3). Tarrant, Lilyquist, and Attaway (21) have prepared 1,1-difluorobutadiene by fluorination of 1,1,1,4-tetrachloro-3-bromobutane by $SbF_3 \cdot SbF_3Cl_2$ to give 1,1-difluoro-1,4-dichloro-3-bromobutane which was dehalogenated and dehydrohalogenated to 1,1-difluorobutadiene. These same authors (2) have prepared 1,1-difluoro-3-methylbutadiene (XXX) by the reaction scheme shown below.

$$(CH_3)_2CHCH{=}CCl_2 \xrightarrow[110°]{HF} (CH_3)_2CHCHCF_2Cl \xrightarrow[h\nu]{Cl_2} (CH_3)_2CClCH_2CF_2Cl \xrightarrow{base}$$



$$CF_2{=}CH\overset{CH_3}{C}{=}CH_2$$ XXX

Although not a polyfluorobutadiene, 1,1,4,4-tetrafluoro-1,2,3-butatriene (XXXI), prepared by Martin and Starky (22), is of interest sinc it is the second member of the family of perfluorocumulenes. Treatmen of 1,1,4,4-tetrafluorobutadiene with bromine gave the expected 1,4-addition product (XXXII). Reaction of this compound with molten KOH yielded the triene. Proof of its structure was shown by a parent mass spectrograph peak for C_4F_4; infrared verified the presence of the $F_2C=C$ group, and NMR showed only one type of fluorine atom. The triene reacted with three moles of chlorine to form the hexachlorotetrafluorobutane, and two moles of bromine to give 1,2,3,4-tetrabromo-1,1,4,4-tetrafluoro-2-butene.

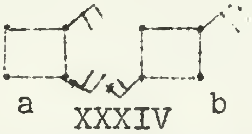
$$CF_2=CHCH=CF_2 \xrightarrow{Br_2} \underset{XXXII}{F_2BrCCH=CHCF_2Br} \xrightarrow[\text{molten}]{KOH} \underset{XXXI}{CF_2=C=C=CF_2}$$

REACTIONS OF POLYFLUOROBUTADIENES

I Polymerization

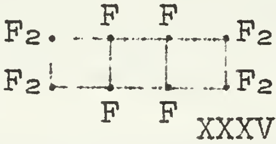
The polymerization of polyfluorobutadienes has been the most widely studied of their reactions (17,18,21,23,24). Thermal polymerization of hexafluorobutadiene between 150-180° yields hexafluorocyclobutene, dimers, trimers, and polymers. (23). The dimeric product was shown to be a mixture of isomers as it did not possess a sharp melting point and its cooling curve possessed no plateau. Reaction with chlorine gave tetrachloro-and hexachlorocyclobutanes in a 2.5:1 ratio. Both chloro co pounds were saturated to permanganate. Possible skelatal structures for the dimer, with the exclusion of those arising from rearrangement, are (XXXIII), (XXXIVa or b), and (XXXV). Hydrocarbon dienes preferentially form cyclohexenes upon dimerization, but fluorodienes are known to favor cyclobutane dimeric products. The possibility that the hexachloride arose from a ring cleavage reaction was eliminated because the ratio of products (2.5:1) was invariant when reaction conditions for the chlorination was varied from 0-100°. Also fluorinated cyclobutenes are known to be cleaved by chlorine only under more drastic conditions. The dimer upon being heated at 200° for 164 hr. was converted into an isomeric product that was stable to chlorination and oxidation by permanganate. The structure (XXXVI) was assigned to this isomer on the basis of the meager preceding chemical evidence, and on the basis of preliminary X-ray data. Such a structure, unprecedented and so poorly validated, should be reexamined with some of the modern physical techniques (e.g. NMR). The trimer upon being heated at 300° for 116 hr. was converted into a C_{24} fraction and higher polymers. Hexafluorobutadiene could be isomerized quantitatively to hexafluorocyclobutene by heating at 500°; butadiene under the same conditions dimerizes to the cyclohexene product. With benzoyl peroxide as an initiator, hexafluorobutadiene forms polymers whose molecular weight is dependent upon initiator concentration, temperature, and pressure. The highest molecular weight products were obtained when the initiator concentration and temperature were low, and the pressure high.


XXXIII



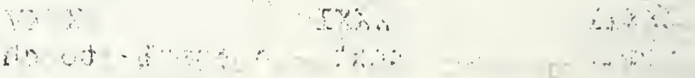
XXXIV


XXXV

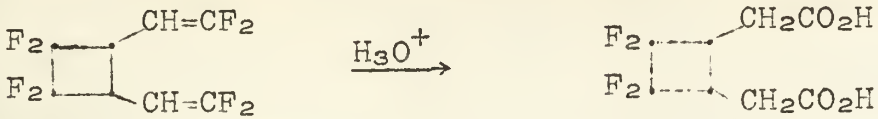


XXXVI

The thermal polymerization of 1,1,4,4-tetrafluorobutadiene at 175° yields a dimer, stereoisomeric trimers, and polymers (25). No cyclobutene product was isolated. The dimer, assigned structure (XXXVII), possessed infrared absorption at 1775 cm.$^{-1}$ characteristic of a difluoro vinyl group, and absorption in the saturated CH and vinyl CH regions. Fluorine NMR exhibited a quadruplet having the characteristic weak/strong/strong/weak pattern of a symmetrically disubstituted 2,2,3,3-

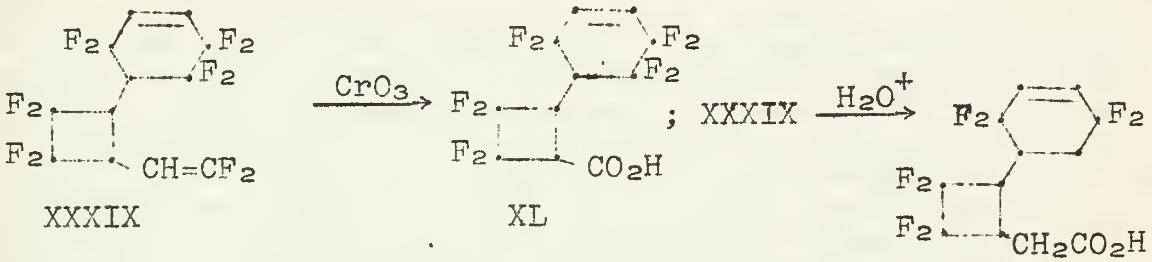


tetrafluorocyclobutane (32), and peaks in the region of a vinyl fluorine. The dimer was oxidized to perfluorosuccinic acid by permanganate



XXXVII XXXVIII

and hydrolyzed to the dibasic acid (XXXVIII) by sulfuric acid. The trimer is the most interesting of the products obtained from thermal polymerization because its physical and chemical properties suggest the structure (XXXIX). The trimer had infrared absorption in the regions of a difluorovinyl group, ethylenic linkage, vinyl hydrogen, and saturated CH (weak) groupings. No fluorine NMR data were reported. Chromic acid oxidation yielded a monobasic acid (XL) that possessed no infrared absorption in the region of a difluorovinyl group. Reaction of XXXIX with sulfuric acid gave a monobasic acid with one more methylene than XL and an infrared spectrum similar to XL. Absorption of one mole of hydrogen by the trimer gave a product whose infrared showed only



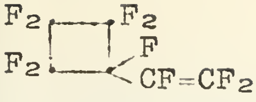
XXXIX XL

difluorovinyl group absorption in the region of unsaturation. The most striking feature of the assigned structure of the trimer is that it represents the Diels-Alder adduct of the dimer and monomer. Such a reaction, where a polyfluorodiene acts as a diene in the Diels-Alder reaction is not known. Dienes possessing one or more trifluoromethyl groups on the double bonds are known to undergo Diels-Alder reaction (8), but polyfluorobutadienes that bear fluorine atoms on the double bond(s) do not react with a variety of dieneophiles (21,24,25). Their failure to undergo this type reaction has been attributed to their inability to assume a cis coplanar configuration because of steric hindrance.

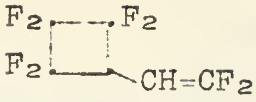
By initiation with azo-bis-isobutyronitrile,2,3-bis-(trifluoromethyl)-butadiene undergoes polymerization to a chemically and thermally stable polymer (18). It was insoluble in common organic solvents and refluxing organic bases. Thermally, it did not depolymerize below 350°. These properties are thought to arise from the bulky trifluoromethyl groups shielding the C-C and C=C bonds. Using the same initiator or ultraviolet light, Castle and Putnam (17) have polymerized 1,1,2-trifluoro-3-trifluoromethylbutadiene. The light-initiated polymer was shown to have formed by 1,4-addition as its infrared showed no $=CF_2$ of $=CH_2$ absorption.

II Cycloalkylation

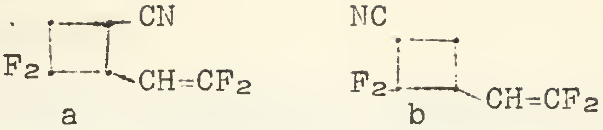
As mentioned earlier, fluorodienes dimerize to form cyclobutyl compounds. The dienes also undergo cycloalkylation when treated with certain ethylenic compounds. The cyclobutane (XLI) is formed from hexafluorobutadiene and tetrafluoroethylene when the two are heated, and 1,1,4,4-tetrafluorobutadiene reacts with tetrafluoroethylene and with acrylonitrile to give the cyclobutyl compounds (XLII) and (XLIII a or b), respectively. Neither of the structures XLIII a or b has been established, although NMR would give a definitive answer. The structure of XLIII was shown by infrared data and by chemical reaction.



XLI

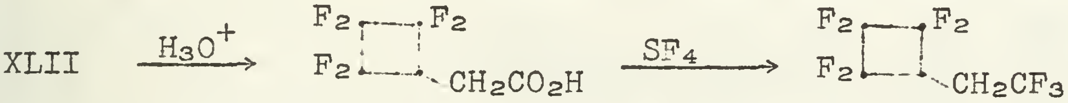


XLII



XLIII

The vinylcyclobutane was hydrolyzed to the monobasic acid (XLIV), which was further allowed to react with SF_4 to give the trifluoromethyl compound (XLV) (25).



XLIV XLV

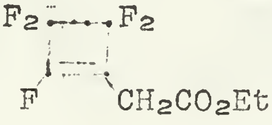
III Reaction with Alkoxides

Alkoxides react with fluoroölefins to give saturated ethers, vinyl ethers, or a mixture of the two ethers (26). The reaction is postulated as proceeding through a carbanion that can either abstract a proton from the solvent to give the saturated ether, or lose a F^- to give the vinyl ether. The product(s) from the reaction is dependent upon the structure of the fluoroölefin, the alcohol, and the strength of the base Perfluoroisobutene reacts with methanol to give only the saturated ether, but reacts with ethanol to give a mixture of saturated and vinyl ethers. A variety of the saturated fluoroethers have been dehydrohalogenated with base to the vinyl ethers. This observation along with the fact that a mixture of ethereal products is sometimes obtained has been used as evidence against the formation of the vinyl ethers by direct displacement of fluoride by the base. However, this argument does not eliminate this remote possibility.

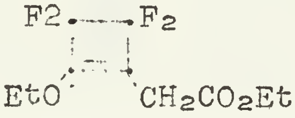
1,1,4,4-Tetrafluorobutadiene reacts with NaOEt to give an ethereal product that is hydrolyzed to diethyl succinate when treated with water. Reaction of the same diene with sodium thiophenoxide gives only the thio ether (XLVII). When the vinylcyclobutane (XLII) is treated with OEt^-, elimination of hydrogen fluoride occurs as well as reaction at the difluorovinyl group to give the products (XLVII) and (XLVIII) whose structures were presumed on the basis of infrared data. The latter product could easily arise from the attack of ethoxide on the intermediate (XLIX) which is formed by the elimination of hydrogen fluoride from (XLII).

$CF_2=CHCH_2CF_2SC_6H_5$

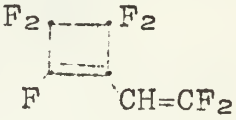
XLVI



XLVII



XLVIII



XLIX

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ACYL NITRATES

Reported by R. Carnighan May 1, 1961

Acyl nitrates in solution and mixtures thought to contain acyl nitrates as the principal constituents have been used to nitrate alcohol olefins, aromatic amines (both ring and N nitration), aromatic hydrocarbons and substituted benzenes. Aromatic nitrations are characteriz by unusually high ratios of ortho to para substitution. Mixtures of acetic anhydride and nitric acid have been used to nitrate acid sensitive compounds such as thiophene[1] and for the preparation of tetranitromethane.[2] This seminar will survey the information on acyl nitrates in an attempt to identify the active species and the mechanism of reaction. Three general kinds of data will be considered: the physical properties of the reactive solutions, the kinetics of reaction of the solutions and product studies.

Conventional Nitration

With one exception discussed below, the nitronium ion has been demonstrated to be the active species in aromatic nitration.[3] In a variety of solvent systems, the nitronium ion arises by "dehydration" of two molecules of nitric acid (1)(2). In sulfuric acid, the reaction

$$HNO_3 + HNO_3 \rightleftharpoons H_2NO_3^{\oplus} + NO_3^{\ominus} \qquad (1)$$

$$H_2NO_3^{\oplus} \rightleftharpoons NO_2^{\oplus} + H_2O \qquad (2)$$

$$HNO_3 + 2H_2SO_4 \longrightarrow NO_2^{\oplus} + H_3O + 2HSO_4^{\ominus} \qquad (3)$$

(3) proceeds to completion. The nitric acid is completely ionized; cryoscopic measurements give an i value of four. The Raman and infrared spectra of these solutions contain absorption bands found in salts of the nitronium ion.

Nitric acid in organic solvents is very slightly ionized. The Raman spectra show no nitronium ion absorption. Solutions of nitric acid in organic solvents have neglible conductivity indicating little ionization takes place. The active species in the organic solvents is the nitronium ion (1)(2). Nitration of aromatic compounds is second order in nitric acid and either first or zero order in substrate, depending upon whether the slow step is formation of the nitronium ion followed by more rapid substrate attack (4) giving zero order dependence on substrate or there is rapid formation of nitronium ion followed

$$NO_2^{\oplus} + ArH \longrightarrow ArHNO_2 \qquad (4)$$

by slower substrate attack which gives first order dependence on substrate. In acetic acid solutions of nitric acid, the substrate dependence can be varied from zero to first order by varying the extent of activation of the aromatic ring.

Nitration by Molecular N_2O_5

Pure N_2O_5 reacts violently with aromatic compounds, but dilute solutions of N_2O_5 in carbon tetrachloride nitrate at rates conveniently measured.[4] The rate is first order in substrate, first order in N_2O_5. Tetraethylammonium hydrogen sulfate and tetraethylammonium nitrate both

$$\text{rate} = k(ArH)(N_2O_5) \qquad (5)$$

show the normal salt effect of slight reaction rate acceleration. The absence of rate depression with the added nitrate ion rules out the free nitronium ion as the active agent. The Raman spectrum of N_2O_5 in carbon tetrachloride indicates the N_2O_5 is not ionized.[5]

Acyl Nitrates as Pure Compounds

Pure benzoyl nitrate was first isolated by Francis in 1906 by the reaction of benzoyl chloride with silver nitrate at low temperature.[6] This is a general method for the preparation of acyl nitrates from acid chlorides. Acyl nitrates prepared in this way in carbon tetrachloride are free from water and proton donors and are suitable for nor aqueous nitration. Acetyl nitrate was first isolated by Pictet and Khotinsky in 1907 by the reaction of N_2O_5 on acetic anhydride.[7] Acetyl nitrate can also be made by reaction of N_2O_5 on acetic acid, by treatin ketene with nitric acid[8] and by the reaction of acetyl chloride with silver nitrate. Acetyl nitrate has the undesirable property of exploding violently on heating to 60° and occasionally without apparent cause at lower temperatures. Several explosions with pure acetyl nitrate have been reported to result in loss of limbs, and consequently isolation of the pure compound is rare now.

Pure acyl nitrates in aprotic solvents such as carbon tetrachlorid and acetonitrile nitrate certain aromatic compounds to give nitro substitution products of high ortho content. The Raman spectra of acyl nitrates in carbon tetrachloride indicate the acyl nitrates are not ionized.[5] A priori acyl nitrates would be expected to be relatively weak nitrating agents. Ingold has formulated a series of "carriers" of the nitronium ion; the more strongly X in NO_2X attracts electrons,

$NO_2^{\oplus}$ $NO_2OH_2^{\oplus}$ N_2O_5 NO_2OBz NO_2OH decreasing activity

the more powerful the nitrating agent. On this basis, acyl nitrates would be expected to be weaker than N_2O_5 as nitrating agents. Attempts to demonstrate direct nitration by less active members of the above series are complicated by ionization to the nitronium ion. To prove that an agent is actually the active species, it must be demonstrated that ionization to a very small concentration of nitronium ion or other more active nitrating agent which served as the attacking species did not take place. Solvents of high dielectric constant would be expected to facilitate such ionization.

The kinetics of nitration of excess benzene by benzoyl nitrate in carbon tetrachloride have been examined.[4] Nitration rates were measured dilatometrically. An occasional chemical check by measuring product formed or change in acidity of the hydrolyzed reaction mixture showed general agreement. The rates of nitration by benzoyl nitrate are much slower than rates of nitration by carbon tetrachloride solutions of N_2O_5.

Nitration of excess benzene by benzoyl nitrate in carbon tetrachloride is first order in "nitrating agent". Addition of benzoic anhydride depresses the rate. The active species is N_2O_5 formed in a rapid equilibrium from benzoyl nitrate (6). The equilibrium lies far toward the left. The added benzoic anhydride drives the reaction to

$$2\ BzONO_2 \rightleftharpoons N_2O_5 + Bz_2O \qquad (6)$$

the left making less N_2O_5, the actual nitrating agent, available.

The effect of benzoic anhydride and benzoic acid on nitration of benzene by carbon tetrachloride solutions of N_2O_5 was investigated in an attempt to build up the benzoyl nitrate system.[4] If pure benzoic anhydride is added to N_2O_5 in carbon tetrachloride, the rate of benzene nitration is extremely fast at rates comparable to nitration by N_2O_5 with carbon tetrachloride, and the benzoic anhydride is nitrated also. If a very small amount of benzoic acid is added to the benzoic anhydride N_2O_5 mixture, the rate of nitration is much slower and comparable to the solution of benzoyl nitrate in carbon tetrachloride. Thus the equilibrium between benzoyl nitrate and N_2O_5 (6) is slowly attained in the absence of benzoic acid and rapidly attained in the presence of a

catalytic amount of benzoic acid. Traces of water are sufficient to provide the benzoic acid.

In the nitration of benzene by N_2O_5 in the presence of benzoic anhydride, the rate of nitration decreases with increasing benzoic acid concentration. The benzoic acid is reducing the N_2O_5 concentration by reacting with the N_2O_5 directly or indirectly by reaction with benzoyl nitrate. Since the presence of benzoic acid leads to nitric acid, the

$$N_2O_5 + BzOH \longrightarrow BzONO_2 + HNO_3 \tag{7}$$

$$BzONO_2 + BzOH \longrightarrow Bz_2O + HNO_3 \tag{8}$$

equilibrium (6) catalysis may not be specific for benzoic acid.

Nitration by Nitric Acid in Acetic Anhydride

In investigations by early workers, it was found that acetic anhydride was unique as a "solvent" in nitration of certain aromatic compounds by nitric acid. Much higher ortho to para substitution ratios were obtained. This was attributed to the formation of acetyl nitrate which was said to be the nitrating agent. In the nitration of anisole with nitric acid in excess acetic anhydride and with benzoyl nitrate in carbon tetrachloride and acetonitrile, identical isomer yields of high ortho content were produced.[11] A mixture of two moles of nitric acid and one mole of acetic anhydride give the same Raman spectrum as a mixture of two moles of acetic acid and one mole of N_2O_5.[5] This

$$\begin{tikzcd}
2\,HNO_3 + Ac_2O \arrow[r, dash] \arrow[d] \arrow[dr] & N_2O_5 + 2\,AcOH \arrow[d, shift left] \arrow[dl] \\
2\,AcONO_2 + H_2O \arrow[r, shift left] & AcONO_2 + AcOH + HNO_3 \arrow[l, shift left] \arrow[u, shift left]
\end{tikzcd}$$

suggests that nitration by nitric acid in acetic anhydride and by acyl nitrates proceeds through the same active species.

Nitric acid reacts completely with acetic anhydride at temperature above 0° to form acetyl nitrate. If nitric acid is added to acetic anhydride at -10°, the mixture resembles a solution of nitric acid in acetic anhydride and little or no nitration of alkenes occurs.[12] If nitric acid is added to acetic anhydride above 10°, an exothermic reaction occurs. If this solution is cooled to -10°, rapid addition to alkenes occurs.

Nitronium borofluoride in 99.2% nitric acid absorbs strongly at 2360 cm^{-1} in the infrared.[13] This absorption is due to the nitronium ion. Solutions of acetic anhydride in nitric acid were examined at this frequency. A is the absorbance of the solution relative to back-ground.

acetic anhydride mole %	A
0	0.056
8	0.252
18	0.152
31	0.00
47	0.01
81	0.00

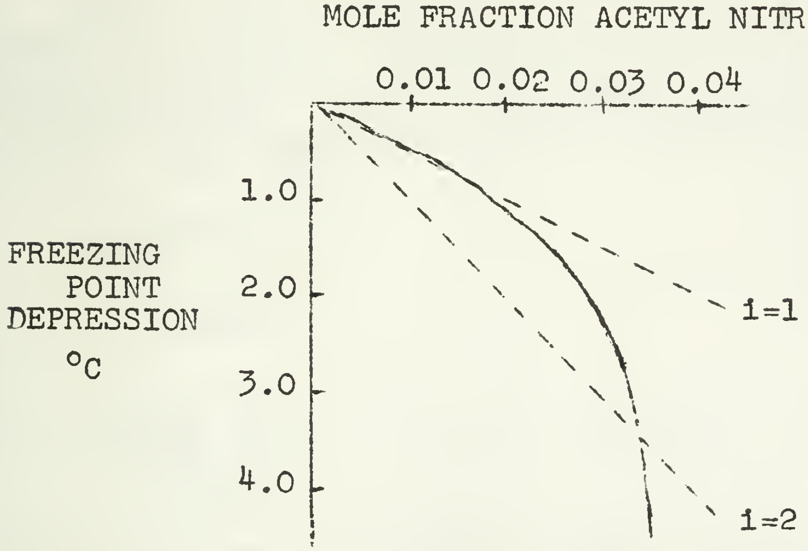
Nitronium ion concentration was a maximum at *ca.* 9 mole % acetic anhydride. No nitronium ion absorption was seen above 31 mole % acetic anhydride. Nitronium ion is seen in solutions of excess nitric acid. In nitric acid in excess acetic anhydride in which nitrations are customarily run, no free nitronium ion is seen.

These qualitative data suggest that since free nitronium is in sufficiently high concentration to be seen in the spectra of acetic anhydride solutions containing excess nitric acid, nitronium ion is the nitrating agent. Failure to detect the nitronium ion spectrally

in nitric acid solutions containing excess acetic anhydride does not eliminate nitronium ion as the active species. Raman spectra of nitri acid in nitromethane, acetic acid and chloroform show no nitronium ion absorption; however, nitronium ion is known to be the active agent in these solutions.[3]

The Raman spectra of mixtures of acetic anhydride and nitric acid have been examined.[5] In solutions of excess nitric acid, the acetic anhydride is transformed completely to acetyl nitrate; the spectral lines characteristic of acetic anhydride are not seen. The lines of nitrate and nitronium ion are seen. In solutions of excess acetic anhydride, the nitric acid is transformed to acetyl nitrate. The most intense lines are those of covalent acetyl nitrate; no nitronium or nitrate ions are seen. A small amount of covalent N_2O_5 is also seen. Since the solvent increases in dielectric constant in going from acetic anhydride to nitric acid, an increasing amount of ionized form of acetyl nitrate would be expected to be present. N_2O_5 in chloroform, carbon tetrachloride and acetyl nitrate shows lines correspondin to the covalent form. N_2O_5 in nitric acid shows the nitrate and nitronium ions.

Cryscopic measurements on nitric acid solutions of acetyl nitrate are unsatisfactory.[14] Nitric acid is self-dissociated more than sulfuric acid, making necessary larger concentrations of solutes and therefore larger freezing point depressions than in sulfuric acid. Self-dissociation obscures the region where linearity is expected. The addition of large concentrations of solutes produces heat of dilution which complicates the interpretation of the experimental results. If a solvent dissociates, addition of one of the dissociation products does not initially alter the freezing point. Larger concentrations of the dissociation products will suppress the solvent dissociation and ideal behavior will be observed, providing these dissociation products do not take part in further equilibria. Low concentrations of potassiu nitrate and ammonium nitrate each give an i value of 1 which approaches 2 as the concentration is increased. Acetyl nitrate gives a similar behavior. At low concentrations, the i value is 1 as would be expected



by a rapid formation of nitronium and acetate ion. The acetate ion would undoubtedly react with the acid to yield acetic acid and nitrate ion. Ionized N_2O_5 is produced, not ionized acetyl nitrate as suggested by Dunning and Nutt.[14] Ionized N_2O_5 and acetic acid formed in the reaction would give the observed i value of 1. The steep slope at higher concentration is unexplained.

Although acetyl nitrate is the major component other than solvent in acetic anhydride-nitric acid mixtures, N_2O_5 and nitric acid are also present in small amounts. Either nitric acid, acetyl nitrate, N_2O_5 or nitronium ion might be the active species in aromatic nitration. *A priori* we would expect the nitrating power to be in the order (9)

$$NO_2^{\oplus} > N_2O_5 > AcONO_2 > HNO_3 \; . \qquad (9)$$

2,4-Dinitrobenzyl alcohol has been nitrated in mixtures of nitric acid and acetic anhydride.[15] Over the range 0-10 mole % acetic anhydride, there is an increasing rate of conversion of the alcohol into

$$\O CH_2OH \; + \; NO_2^{\oplus} \longrightarrow \O CH_2ONO_2 \qquad (10)$$

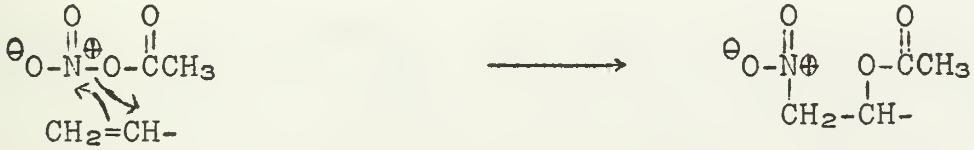
nitrate ester with increasing acetic anhydride concentration. At low anhydride concentrations, a maximum in the rate occurs at 7 mole % anhydride. At acetic anhydride concentrations above 40 mole %, the reaction is too fast to measure. At 0-10 mole % acetic anhydride, the reaction is first order in alcohol, second order in nitric acid. This nitration appears to take place through the nitronium ion. The rate of reaction in the 0-10 mole % anhydride range is in agreement with the concentration of nitronium ion as determined spectrophotometrically which showed a maximum concentration at *ca.* 9 mole % acetic anhydride[1]. With increasing anhydride content (7-10 mole %), the solvent dielectric constant becomes less and the concentration of free nitronium ion is lessened.

Nitration of benzene by acetic anhydride and nitric acid mixtures has been studied kinetically.[16] The nitration is approximately second order in nitric acid, first order in benzene (11). Addition of a small

$$\text{rate} = k(HNO_3)^2(\O H) \qquad (11)$$

amount of sodium nitrate decreases the rate by half. The nitration by nitronium ion is being suppressed while there would be no effect on nitration by molecular N_2O_5. If a catalytic amount of sulfuric acid is added, the rate is faster and first order in benzene, first order in nitric acid. The sulfuric acid presumably acts to supply a proton which is supplied by a nitric acid molecule in the absence of sulfuric acid.

Acetyl nitrate prepared from nitric acid in excess acetic anhydride[12] and N_2O_5 in methylene chloride[17] add to olefins to give *cis* addition products. The stereochemistry of addition suggests a concerted addition. Free nitronium ion addition would be expected to result in *cis*-*trans* mixtures. Ion pair addition might lead to *cis*



addition; however, the Raman spectra of these solutions show no nitroniom ion, indicating that the concentration of ion pair would have to be very small. In the acetyl nitrate addition, small amounts of nitronitrates are found, possibly from addition of the small concentration of N_2O_5.

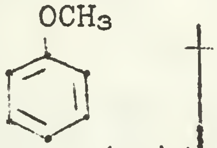
If in the N_2O_5 addition nitrate ion is added, no yield changes are observed. Less oxidized by-products are found. In competition experiments with 1-octene and benzene, considerable nitrobenzene is formed

along with olefin addition in nitration with N_2O_5. If nitrate ion is added, aromatic nitration is almost completely suppressed in favor of olefin addition. This work suggests that aromatic nitration through nitronium ion is being suppressed and addition of molecular N_2O_5 is mor rapid with olefins than with aromatics.

Almost without exception, aromatic nitration by nitric acid in acetic anhydride has been used with compounds with strongly activating groups such as anisole and anilides. With these compounds, high yields of ortho substitution are found. In the nitration of toluene, nitric acid in acetic anhydride gives the same ortho-para ratio as nitration by nitric acid in other solvents and without solvent.[18] The high ortho para ratio must depend on the nature of the substituent on the benzene ring.

In aromatic substitution there is no hydrogen isotope effect in nitration by acetyl nitrate.[11] Hydrogen and tritium are displaced at the same rate. This suggests that the carbon hydrogen bond is broken after the rate determining step and casts doubt on a concerted mechanis involving simultaneous nitro group entrance and hydrogen displacement. Ortho substitution involving a complex with the neighboring group and involving simultaneous nitro group entrance and hydrogen displacement is improbable. Two suggestions have been advanced to account for the high ortho ratios.

Paul reasoned that there is interaction between the positively charged nitronium ion and the overall molecular dipole on the ring substituent.[19] If the dipole moment is directed into the ring (12) as in anisole, the electrostatic interaction would favor ortho substitution. If the dipole moment is directed from the ring (13) as with the halobenzenes, ortho substitution is suppressed relative to para substitution. This effect would be enhanced in solvents of lower dielectric constants. Paul nitrated bromo and chlorobenzene with nitri acid in excess acetic anhydride. He found that high yields of para substituted products were obtained. Not mentioned in Paul's paper is the work of Bird and Ingold.[18] The latter workers nitrated chloro and bromobenzene with equal molar quantities of acetic anhydride and nitric acid and obtained isomer yields similar to heterogenous nitration with nitric acid without a solvent. Paul stated that a catalytic amount of sulfuric acid was necessary for the reaction to proceed. Bird and Ingold did not find this addition necessary. If the ortho-para substitution ratio is sensitive to the dielectric constant of the solvent, then the isomer ratio should vary with solvent, and solvents with dielectric constants lower than acetic anhydride should produce higher ortho substitution. This is not found to be the case. Benzoyl nitrate in carbon tetrachloride and acetonitrile and nitric acid in acetic anhydride give almost identical isomer yields in the nitration of anisole.[11] Until Paul's work can be repeated, conclusions must be made



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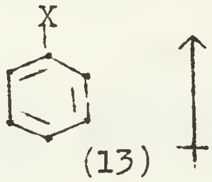


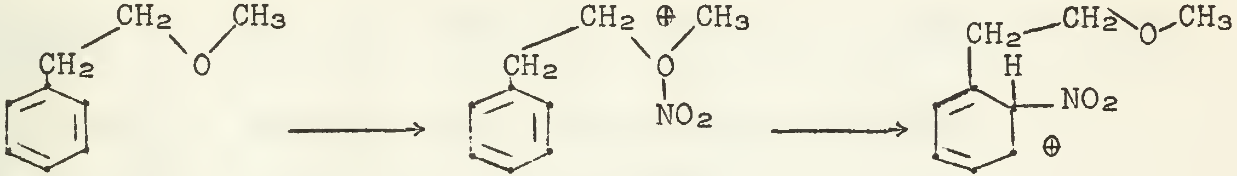
(13)

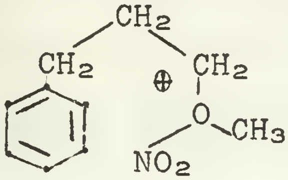
	HNO_3-no solvent	HNO_3 in acetic anhydride	
chlorobenzene	Holleman[20]	Paul	Bird, Ingold
ortho	30.1%	10%	29.0%
para	69.1	90	71.2
bromobenzene			
ortho	37.6	25	38.5
para	62.4	75	61.5

nitrating agent	nitro anisoles ortho	para
HNO_3 in Ac_2O	71%	28%
$BzONO_2$ in CCl_4	71	29
$BzONO_2$ in CH_3CN	75	25

with reserve.

Norman and Radda investigated the nitration of aromatic ethers.[21] They propose that nitration by nitric acid in acetic anhydride takes place through two simultaneous paths: direct ring attack by the nitronium ion and direct displacement of nitrate ion from covalent N_2O_5 by the ether oxygen which gives an intermediate (15) which rearranges through a six membered cyclic transition state to the usual sigma-bonded intermediate (16). If compound (14) is nitrated, ortho substitution is increased by 20% over that obtained by nitric acid or nitric acid-sulfuric acid mixtures if nitric acid in acetic anhydride is used as the nitrating solution. If compound (17) is nitrated, isomer yields are independent of ntrating agent. This is attributed to the increased strain required to form the required seven membered transition state and this path is blocked. The proposal of Norman and Radda would attribute the ortho enhancement with anisole to a four membered cyclic transition state (18).

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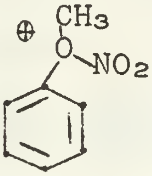
(18)

It is difficult to decide between these two explanations accountin for the high ortho ratios because sufficient experimental work has not been reported. Nitration of the halobenzenes should provide a method of distinguishing the two suggestions. Norman and Radda's proposal predicts that there would be no substituent assisted ring attack and consequently isomer yields should be independent of nitration agent. As stated above, Paul expects and claims increased para substitution with halo benzenes with nitric acid in excess acetic anhydride.

Nitration by nitric acid in acetic anhydride is clearly more complicated than nitration by nitric acid in other solvents. The nitric acid reacts with the acetic anhydride to produce acetyl nitrate along with small amounts of N_2O_5. The molecular N_2O_5 and acetyl nitrate migh form ion pairs more easily in acetic anhydride than pure acetyl nitrate and N_2O_5 do in the less polar carbon tetrachloride. This ionization of acetyl nitrate and N_2O_5 in acetic anhydride, while spectroscopically not observable, may furnish the active species in small quantities through rapid equilibria. Although the nature of the active species in aromatic nitration with nitric acid in acetic anhydride is at present poorly defined, there appears to be nitration both by nitronium ion and, since N_2O_5 has been shown to be present and sufficiently reactive, there is probably nitration by it also. In view of the intrinsic and extrinsic value of this solvent system, the problem deserves more attention.

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NUCLEAR MAGNETIC RESONANCE INVOLVING THE CARBON-13 NUCLEUS

Reported by T. Koenig May 15, 1961

Introduction

Transitions between nuclear quantum states induced by an external magnetic field and a r. f. oscillator are possible only for those nuclei which have a non-zero nuclear magnetic moment. Nuclei with nuclear spins of one half yield the simplest spectra since those with spins greater than one half also have quadrupole moments which complicate the spectra, although they can give useful information. Carbon-12, the most abundant (98.9%) isotope of carbon, has zero spin. Therefore, carbon containing compounds are usually thought of as giving spectra which are uncomplicated by resonance of the carbon nuclei. Carbon-13, which has a natural abundance of 1.1%, has a nuclear spin of one half and should give rise to spectra of its own. The low natural abundance prohibits this with ordinary techniques and; together with the observed long spin-lattice relaxation time (of the order of minutes), has inhibited its investigation. The long relaxation time implies saturation effects which can be overcome by observation of the spectra in the dispersion mode (1,2). Recently, application of a flowing sample technique and the Overhauser effect have been successful in improving the resolution of the spectra of the carbon-13 nucleus itself (3,4). It is also possible to obtain isotopically enriched compounds if the natural abundance is too low for a given experiment.

The original measurements of carbon-13 n.m.r. spectra were made by Lauterbur (1) and by Holm (2) and reports of these experiments have been extensively reviewed (5,6,7,8). There have been attempts at correlation of the carbon-13 chemical shifts with fluorine-19 shifts in substituted toluenes and benzenes respectively. There is a rough correlation between carbon-13 chemical shifts and electronegativity of substituents and some other observations have been made, but as yet, no really conclusive information has been obtained from these measurements.

The major field of investigation utilizing the carbon-13 nucleus involves spin-spin coupling constants. This seminar will be concerned with the information gained from these constants, which were obtained from the satellite lines produced by carbon-13 in natural abundance unless it is specified that use was made of isotopically enriched compounds.

Determination of Coupling Constants of Equivalent Nuclei

It is well known that equivalent protons do not split each other but rather give rise to single peaks. This can be demonstrated for a simple set of two equivalent protons with the aid of two of the several rules for the analysis of n.m.r. spectra given by Pople et. al. (5).

1. Only transitions with $\Delta F_z = \pm 1$ are allowed where F_z is the spin component in the z direction.
2. The only allowed transitions are those between states of the same symmetry.

Table I

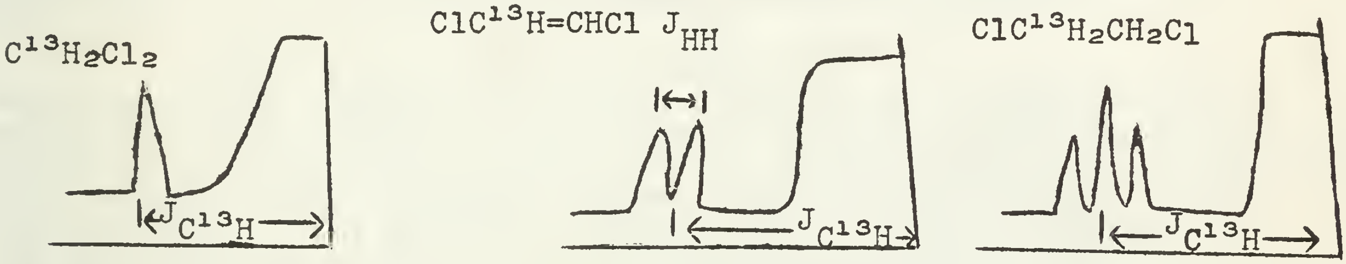
Spin Function	Spin Component (F_z)	Symmetry	Energy
1. $\alpha\alpha$	1	s	$\gamma H/2\pi + 1/4\ J$
2. $\alpha\beta + \beta\alpha$	0	s	$1/4$
3. $\alpha\beta - \beta\alpha$	0	a	$-1/4$
4. $\beta\beta$	-1	s	$-\gamma H/2\pi\ +1/4\ J$

Table I gives the values for the energy states obtained by the use of perturbation theory using the spin-spin coupling as the perturbing energy. The terms α and β are the usual spin functions and

the symmetry is classified as symmetric (s) or anti-symmetric (a). The above stated rules allow transitions between states 1 and 2, and 2 and 4 since these are the only ones of the same symmetry with $\Delta F_z = \pm 1$. Simple subtraction gives the energy of the transitions which are seen to be degenerate and independent of the coupling constant. This is in way of demonstration and not a proof. However any set of equivalent nuclei have molecular symmetry associated with them so that the same results might be qualitativly expected.

The property of carbon-13 which is usually utilized in the determination of coupling constants between equivalent nuclei is its ability to split protons directly bonded to it (10). These splittings appear as satellite lines symmetrically spaced around the main proton resonance line. (The stipulation of symmetrical spacing is an oversimplification which neglects isotope effects which will be discussed further.) Coupling constants between carbon-13 nuclei and protons directly bonded to them are of fairly large magnitude (120-200cps). The satellite lines are thus easily discernable if the main resonance is not too broad. Typical spectra exhibiting these lines are given in fig. 1(10).

Figure 1



Disubstituted Ethylenes (9,10)

Since the natural abundance of carbon-13 is so low (1.1%) the probability of two such nuclei occurring in one small molecule is vanishingly small. Therefore the spectra observed are uncomplicated by such splittings as would arise from such an isotopic molecule. The large coupling constant has the same effect on the carbon-13 bonded proton as a chemical shift of $\pm 1/2 J_{C^{13}-H}$cps. The relative intensity would of course be divided equally between the high field and low field components of the doublet contrary to the intensity of a line caused

Table II

Compound	J_{H-H}(10)	$J_{calc.}$(9)	J_g(11,12)	calc.(9)	J_t(11,12)	calc.(9)
1. trans-dichloroethylene	12.2±.2	11.9				
2. cis-dichloroethylene	5.0±.2	6.1				
3. p-xylene (ortho H's)	8.0±.3					
4. 1,2-dichloroethane			-1.2±1.5	1.7	18±4	9.2
5. 1,2dibromoethane			3.4±1.0* 2.5±1.5 (13.1±1.0)		15.3±1* 16.5±2.5 (1.3±.8)	
6. 1,1,2,2tetrachloroethane			2.5±1		14 ±7	
7. Dioxane			2.7± .2 (6.1± .2)		9.4±.2 (-0.6±.2)	

*From five line spectrum. Bracketed values arise from uncertainty in sign.

by a real chemical shift. The carbon-13 bonded proton(s), now being magnetically nonequivalent to the carbon-12 bonded one(s), can be split further by the latter. For example, 1,2-dichloroethylene (spectrum given in fig. 1) can be analyzed by ABX theory, in the notation of Pople et. al. (5). As a consequence of this analysis or of the simple qualitative argument above, the J_{H-H} can be taken directly from the spectrum as the spacing of the outer two lines which in this case are the satellite doublet. Table II lists coupling constants determined in this way.

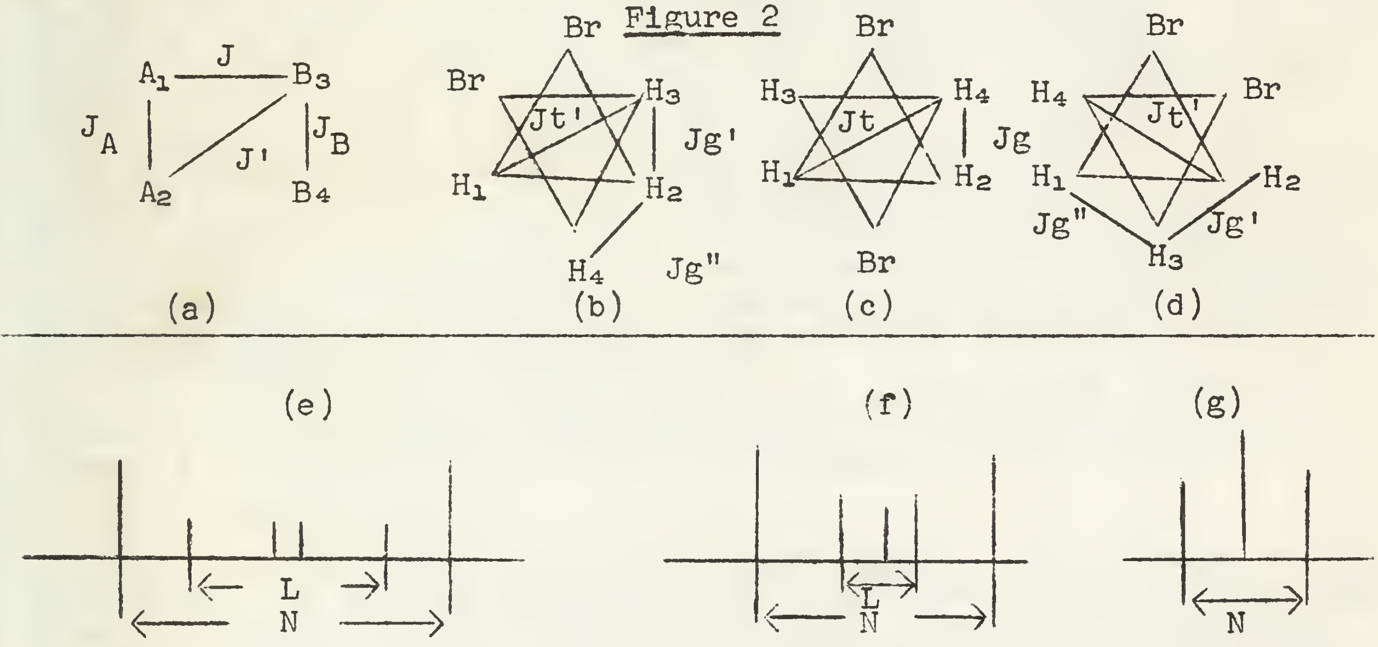
Substituted Ethanes (9,11,12,13)

In the case of substituted ethanes the situation is substantially more complicated. As an example, 1,2-dibromoethane can be used to demonstrate the method of analysis. The coupling constants which are ultimately determined are J_t and J_g illustrated in fig. 2c. The spectrum observed from $BrC^{13}H_2C^{12}H_2Br$ can be calculated using A_2B_2 or approximately A_2X_2 in the notation of Pople et. al. (5). The same type of qualitative argument as was given above for the ABX system, of "psuedo" chemical shift of $\pm 1/2 J_{C-H}$, applies in this case. Figure 2a represents the four coupling constants pertinent to A_2B_2 systems. These may be conveniently parameterized by the equations:

$$K=J_A+J_B \;;\; L= J-J'; \; M= J_A-J_B; \; N=J+J'.$$

These parameters simplify the matrix elements of the Hamiltonian of the system. The solution of the secular equation gives the energy levels as was illustrated above for the case of equivalent nuclei. These energy levels together with the selection rules give rise to the positions of the lines in the calculated spectrum. Schematic representations for the A_2 part of the spectra obtained from such a calculation are given in fig. 2e-g. The number of lines in the spectrum depends on the values of the parameters K,L,M,N.

Figure 2



(e) When L is small (f) When L is large (g) J=J'

For all the compounds treated $J_A = J_B$ which implies M = 0 from eqns. (1). Because the energy barrier to rotation is sufficiently low the spectra obtained from these compounds give directly only average values of the coupling constants operating in the various isomers (J_t's and J_g's of fig. 2 b-d). In order to obtain the values of J_t and J_g specifically it is necessary to analyze the weighted average popula-

tions of the rotationally isomeric states. To do this J and J' are written in terms of the J's of the *trans* and *gauche* rotational isomers *ie*., the J_t's and J_g's of fig. 2b-d. This is done in the following equations:

(2) $$J=J_{13}=J_{24}=N_tJ_g + (1/2)N_g(J_t' + J_g''); \quad J'= N_tJ_t+(1/2)N_g(J_g'+J_g')$$
$$J'= J_{14}=J_{23}.$$

(3) $N_g/N_t = 2\exp\Delta E/RT$ (ref. 21.)

Here N_t and N_g are the mole fractions of the *trans* and *gauche* isomers respectively and $\Delta E = (E_t-E_g)$. If it is assumed that $J_g=J_g'=J_g''$ and $J_t=J_t'$ then equations (2) are simplified.

(4) $J = (1/2)N_gJ_t + (N_t + (1/2)N_g)J_g \; ; \quad J' = N_tJ_t + N_gJ_g$

From these equations together with the values of J and J' obtained from the n.m.r. spectrum and the value of ΔE obtained from the literature the values of J_t and J_g can be calculated if the value of L (eqn. 1) is not zero. Such is the case with the dibromoethane being considered. The values of the coupling constants obtained in this way are given in table II above.

If the value of ΔE is approximately zero then, if our assumptions are correct, the spectrum should approximate the three line one in fig. 2g. The value of $\Delta E = 0 \pm .2$ (21) for 1,2 dichloroethane and indeed the three line spectrum is observed. This is confirmation of the approximation ahat $J_g= J_g' = J_g''$ and $J_t = J_t'$. In such cases the values of J_t and J_g cannot be obtained from a single spectrum. Therefore an alternative method was used which in principle is as follows.

The n.m.r. spectra were observed in several different solvents of varying dielectric constant. The *trans* isomer has a zero dipole moment and the *gauche* isomer has one of appreciable magnitude. Thus the value of the ratio N_g/N_t will change with change in solvent *ie*. ΔE depends on the dielectric constant of the medium. To determine the extent of the change in N_g/N_t the intensities of bands attributed to these isomers in the infra red were measured. The ratio of these intensities was taken to be the ratio of N_g to N_t which is clearly in error unless the ratio of the extinction coefficients is equal to one in all solvents used. It is not clear whether this was verified by the authors. Therefore there is some uncertainty in the reliability of the values of coupling constants obtained in this manner. However uncertain they may be, the values thus obtained are given in table II for dibromoethane and dichloroethane.

For symmetrical tetrachloroethane the group is ABX, similar to that of the disubstituted ethylenes above. The equation for the observed J in terms of J_t and J_g is as follows:

(5) $J=N_tJ_t + N_gJ_g$

In this case the solvent variation method *must* be used. These values are subject to the same uncertainty as mentioned for the dichloroethane case above and are also listed in table II. They agree with those found by Lemieux *et. al*. (22) for acetylated sugars and their ratio agrees with that calculated by Karplus (9) though they are individually somewhat lower than the latter values.

The normal dioxane spectrum (no C^{13}) gives a single sharp line. The *trans* isomer cannot exist here, *i.e.* $N_t = 0$. The single sharp peak shows rapid equilibrium between the two chair forms. As pointed out in an earlier seminar, the equilibrium in analogous compounds possessing axial and equatorial bonds has been studied by use of temperature dependent chemical shifts as well as by other methods (41).

If $N_t = 0$ the equations for J and J' have the form,

$$(6)\ J = 1/2(J_t + J_g); \quad J' = J_g \quad \text{where } J_t = J_{aa} \text{ and}$$

$J_g = J_{ae} = J_{ee}$. (a = axial, e = equatorial.)

Dioxane gives the desired five line satellite spectrum. It should be noted that the values obtained from a single five line spectrum, such as those of dioxane and dibromoethane, are somewhat ambiguous due to the uncertainty in the sign of J and J'. (bracketed values in table II) In the light of the solvent variation experiments this ambiguity is removed. This method of analysis has been applied to the complicated spectrum of liquid propane with results in good agreement with those of an independent method (12,19).

Case of Accidental Degeneracy-Methyl acetylene

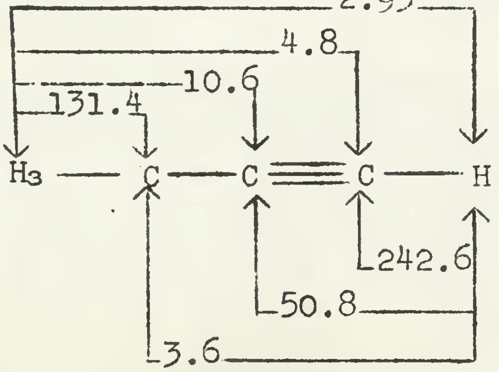
Preliminary determination of the proton magnetic resonance spectrum of methyl acetylene showed one unresolved peak. From the obvious non-equivalence of the methyl and acetylenic protons two possible explanations were considered. Either liquid methyl acetylene is in rapid equilibrium with allene or the spectrum observed arises from the accidental situation of nearly equivalent shielding arising from different sources. Acetylenic protons are known to show resonances at higher fields than expected from extrapolation of the resonances of ethane and ethylene. This has been explained by Pople (23). The chance of equality is small. To discern any small differences in the shifts the spectrum was run at extremely high field strength (14,092 gauss at 60Mc). The spectrum of methyl acetylene can be calculated by AB_3 theory in the notation of Pople. The first-approximation chemical shifts were found by assuming the satellite lines of the various isotopically substituted compounds were symmetrically spaced about the position of the main resonance, disregarding isotope effects. The positions of these satellite lines were then averaged to give the calculated positions of the proton chemical shifts. These numbers are listed in table III. The calculated spectrum depends on the value of the ratio $J_{H-H}/\delta\nu$ where $\delta\nu$ is the difference in ν of transition for the types of H's. There are an infinite number of values for this ratio and in order to find in what range of values to vary it the carbon-13 data are useful. The best fit for the observed spectrum is given for $J_{H-H}/\delta\nu = 1.33$. This is indeed very close to the observed one from the satellite measurement.

The value of J_{H-H} agrees very well with that obtained by Goldstein (15) by direct gas phase as well as solution measurement

$CH_3\text{-}C{\equiv}C\text{-}H$
(I)

$CH_3\text{-}C{\equiv}C\text{-}D$
(II)

$CD_3\text{-}C{\equiv}C\text{-}H$
(III)



Coupling in methylacetylene cps (14)

Vaughn and Taylor (31) determined the spectra of compounds I, II and III. Compound I, the normal methyl acetylene, gave the reported unresolved multiplet, compound II gave a triplet due to coupling with the single deuterium and III gave a 10 line multiplet due to the three deuteriums in the proton n.m.r. This eliminates the allene equilibrium possibility.

Table III

Compound *=13	cps (.1)	J_{H-H}	av.
$C^*\underline{H}_3C\equiv C-H$	172.9; 170.0, 41.5, 38.6	2.9	105.75 .07
$CH_{\underline{3}}-C^*\equiv C-H$	99.1, 102.0, 109.7, 112.6	2.9	105.85 .07
$CH_3C^*\equiv C-\underline{H}$	129.0, 131.9, 134.8, 137.6	2.9	107.90 .05
	78.0, 81.0, 83.9, 86.9	2.9	
$CH_3-C\equiv C^*\underline{H}$	227.3, 230.3, 233.2, 236.1	2.9	107.86 .05
	-20.5, -17.5, -14.5, -11.6	3.0	
$C\underline{H}_3-C\equiv C^*H$	102.0, c , c , 109.7	--	
$C^*H_3-C\equiv C-\underline{H}$	101.3, c , c , c ,	--	107.45 .02(d)
	c , 107.8, 110.7, 113.6	2.9	

(c Not observed due to interference with main resonance)
(d Enriched sample)

Theory of Spin-Spin Coupling

Before introducing the work involving the mechanism of spin-spin interactions it is appropriate to consider some of the theory of the mechanism which is found in Pople, et. al. (5). The energy of a nuclear quantum state is given by the solution of a secular equation whose matrix elements are found by operation on appropriate wave functions by a Hamiltonian operator. The Hamiltonian may be broken down crudely as follows,

$$(7) \qquad H = H_{en} + H_{mm'} + H_c + H'.$$

Here H_{en} depends on electron orbital motion and the nuclear magnetic moment, $H_{mm'}$ depends on the dipole-dipole interaction of the nuclear and electron magnetic moments and H' depends on the electrostatic potential and the electron orbital-orbital and spin-orbital interactions. The remaining term, H_c, is called the contact term and is not easily interpreted in a physical sense. It turns out to be the most important term and involves the ground state- triplet excitation energy for all the excited states of the molecule so that, in its complete form, it is too complicated to be of use. If approximations are made limiting the number of contributing electrons and a mean excitation energy is used the expression is simplified to a practical form and is then dependent on the probability of the electrons being found simultaneously at their nuclei. Thus certain types of wave functions or their orbitals give larger contributions to the coupling constant than others.

Direct Spin-Spin Coupling Constants

The dependence of the contact term on the probability of the electrons being at their nuclei immediately suggests a correlation between the amount of s character in the hybridized carbon-13 atom bonded to the proton and the coupling constant observed between the two nuclei. This correlation has been studied by Mueller and Pritchard (24,25) and by Shoolery (26). Shoolery's work is summarized by the graph (fig. 4) of the measured coupling constants versus fraction s character of the hybridized atomic orbital. The result is a good straight line which passes through the origin. Shoolery's interpretation of this result was that it confirmed the operation of a contact

mechanism.

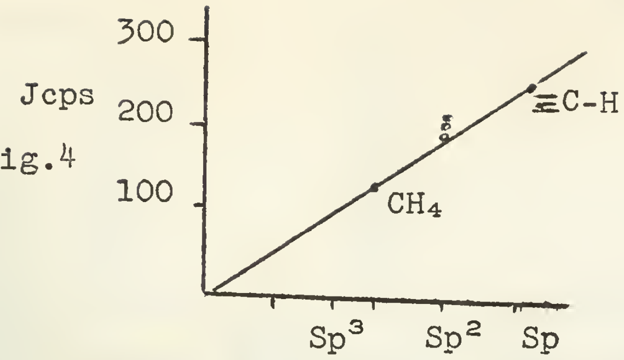


Fig.4

Mueller and Pritchard have made more extensive calculations based on more extensive assumptions which allow the construction of a semi-empirical scheme of analysis. The assumptions are the following:

1. The contact term dominates the coupling expression. (Converse of Shooler's treatment.)
2. Only one pair of electrons makes a significant contribution to the direct coupling constant; i.e., perfect pairing is assumed. (Converse of the long range mechanism)
3. The molecular orbital for this electron pair may be represented by $\psi_{m.o.} = a(1s_H) + b(2s_C) + c(2p_{\sigma}C)$. where $1s_H$ is the 1s atomic orbital on the hydrogen etc.
4. The excitation energy is assumed to be the average energy difference between the ground and triplet states and is constant from molecule to molecule.
5. The important term in the expanded Hamiltonian is a^2b^2. This implies $J_{C-H} = J^{o}a^2b^2$ where J^{o} is to be determined empirically.
6. The overlap integrals are neglected and normalization gives, $a^2 + b^2 + c^2 = 1$ sp^n hybridization implies $b^2 = c^2/n$.

A pure calculation using these relationships shows a^2b^2 is relatively insensitive to changes in $a^2/(b^2+c^2)$ has its maximum value for $a^2 = 0.5$. Thus the value of a^2 is assumed to be constant for all the compounds and equal to 0.5. The coupling constant for methane of 125 cps was used to determine J^{o}. The equation for coupling constants in general then becomes

$$J_{C-H} = (2.00 \times 10^3)\, a^2b^2 \text{ assuming } sp^3 \text{ for methane.}$$

The per cent s character is given by

$$\rho_{C-H} = (b^2/b^2+c^2) \times 100 = (b^2/1-a^2) \times 100$$

Substituting for b^2 gives $\rho_{C-H} = 0.05J_{C-H}/a^2(1-a^2)$.

But $a^2 = 0.5$ $\rho_{C-H} = 0.20\, J_{C-H}$

where ρ_{C-H} is the symbol for the per cent s character.

The case of cycloalkanes is interesting in that the hybridization for cyclopropane obtained from its J_{C-H} coupling constant gives a value close to sp^2. This is in agreement with the theory that increase in H-C-H angles produces increases in s character (45). Various other discussions of cyclopropane agree that it should be close to sp^2.

s-Character Among Non-equivalent Bonds

Since the $CH_3^{\oplus}$ ion would most likely have sp^2 hybridization, the coupling constant should reflect the change in the C-X bond polarity by higher values with increasing electronegativities of substituents (X) in a series of methane derivatives. This order is observed in the first four members of table V where r_{C-X} is the carbon-substituent bond distance and Ex is the Huggins electronegativity of the X group.

A quandary arises when the monohalogenated methanes are viewed. To explain the constancy of this series it was assumed that ρ_{C-H} depends on a second factor which was concluded to be the C-X bond distance (r_{C-X}). An increase in ρ_{C-H} due to the electronegativity effect ($CH_3^{\oplus}X^{\ominus}$ forms) implies an increase in the p character of the C-X bond. However, it seems reasonable that an increase in the s character in the C-X bond would be favored by the increase in directionality accompanying it. A measure of the tendency of the halogen

Table V

Compound	J_{C-H} obs.	r_{C-X}	E_X	J_{C-H} calc.
1. CH_3CH_3	126	1.543	2.60	126
2. CH_3NH_2	133	1.474	3.05	134
3. CH_3OH	141	1.428	3.50	142
4. CH_3F	149	1.385	3.90	149
5. CH_3Cl	150	1.781	3.15	148
6. CH_3Br	152	1.939	2.95	150
7. CH_3I	151	2.139	2.65	151

to increase ρ_{C-X} would be the bond energy increase of the C-X bond for a given increment in ρ_{C-X}. A smaller atom like fluorine would have a greater increase in this bond energy for a given increment in ρ_{C-X} and thus would have a greater cancellation of the ρ_{C-H} predicted from the electronegativity and the series of monohalogenated methanes could give the observed nearly constant coupling constants. The functional dependence of J_{C-H} on E_X and r_{C-X} cannot be deduced from this qualitative reasoning. An empiricle equation was tested.

$$J_{C-H} = AE_X + Br_{C-X} + C$$

With the Huggins (43) electronegativities and literature values (43, 44) for r_{C-X} for compounds 1,4 and 7 of table V, the values of A, B and C were determined. The resulting equation is

$$J_{C-H} = 22.6\ E_X + 40.1\ r_{C-X} + 5.5$$

This equation reproduced the values of the other coupling constants in table V (J_{C-H} calc.). This equation has been used to calculate the electronegativities of the substituents in a large number of substituted methanes using observed coupling constants and literature values for the radii and the results are in agreement generally with other estimates (43,45).

Correlation of J_{C-H} with r_{C-H}

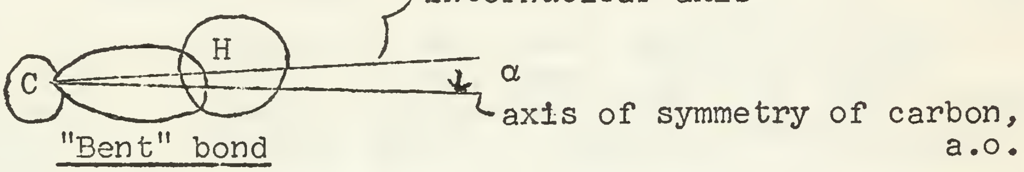
Originally Mueller and Pritchard used the radii and coupling constants of propyne and methane as parameters to assign a linear relationship between J_{C-H} and r_{C-H} (24). The resulting equation gave good results for benzene and ethylene [calc. 1.083; obs. benzene 1.084± .006 (36), ethylene - 1.086 (37)]. In a later paper (25) these authors considered this an unfortunate choice since there is considerable uncertainty in the values of bond distance in methane. The equation resulting from the use of methane r_{C-H} gives poor results for the substituted methanes. As a partial remedy for this they finally utilized some parametric radii from microwave spectroscopy which were derived and calculated by Costain (38). These can be thought of as effective radii. The values used to evaluate the slope and intercept parameters of the assumed linear dependence of J_{C-H} on these r_s's were those for the methyl and acetylenic protons in propyne. The resulting equation is $r_{C-H} = (1.1597\text{-}4.17 \times 10^{-4}\ J_{C-H})$ Å.

This equation gives reasonable values for other substituted methanes for which either a Costain r_s or a measured equilibrium radius is known. The values for benzene, ethylene and methane calculated from this equation are not good. However, those for benzene and ethylene are not much outside experimental error. The case of methane is more serious and caused the authors to postulate it to have anomalously short C-H bonds due to lack of repulsive forces present in substituted methanes. It seemes that there should not necessarily be an agreement with the measured bond distances and the calculated ones however, since the equation was set up to give r_s's and not equilibrium radii.

To the extent that the equation relating J_{C-H} to ρ_{C-H} gives a

reliable measure of the hybrididation, it is possible to calculate the bond angles for the chlorinated methanes, if the atomic orbitals are assumed to be orthogonal (39). The main support for this validity was the "good" agreement of observed and calculated C-H bond distances. The calculated bond angles do not agree with the experimentally determined ones. To explain this the authors proposed bent bonds and supported this by the observation that the overlap integral does not change much for small deviations (change in overlap = 1% for α (fig.6) equal to 11°). The reason for assuming collinearity of carbon atomic orbital symmetry axis and internuclear axis is to obtain maximum overlap. Thus it seems that small deviations are allowed. In view of the many assumptions made it appears that there are other factors operating in these systems and the results can not be accepted as conclusive. Schneider and Spiescke (46) have reported a similar correlation of coupling constants and bond hybridization in a series of substituted benzenes.

Fig. 6

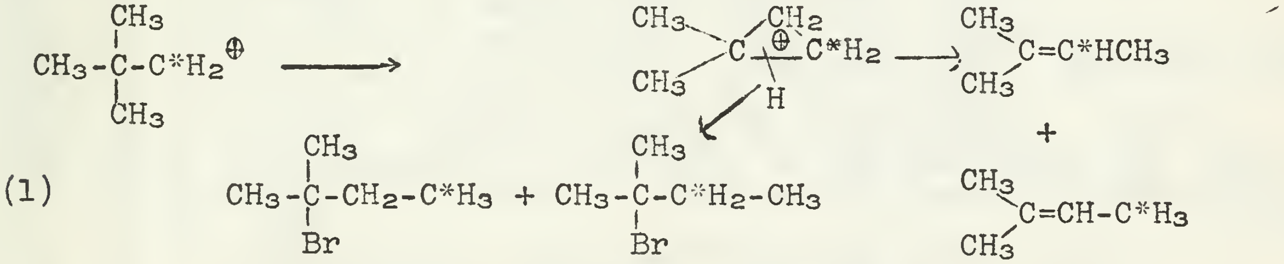


Isotope Effects

Isotope effects in the n.m.r. were observed first in deuterium compounds (34). The result of such an isotope effect is to displace chemical shift from its normal position. In the case of carbon-13 this means the center of the multiplet formed by the protons directly bonded to the carbon-13 nucleus is not exactly the chemical shift of the normal compound. Such effects have been observed in acetaldehyde (32). Tiers measured tentative isotope effects in a series of substituted methanes and found the order of magnitude to be $\Delta\tau = +.001-+.006$ (35). He also observed a long range isotope effect in the fluorine-19 resonance of carbon-13 containing fluoro-olefins of the type $F_2C = C^{13}Cl_2$ (33). Explanations are pending in near future publications of Tiers, Gutowsky and Lauterbur which are based on vibrational changes with isotopic substitution. The magnitudes of these effects are not large enough to effect seriously the preceeding discussion.

Labeling Experiments

The large coupling constants between carbon-13 and protons directly bonded to it make this nucleus a valuable tool for labeling and following a particular atom of a compound involved in a reaction. Karabatsos (41) has used 30% isotopically enriched neopentyl alcohol in which the carbon-13 is in the 1-position to study the carbonium ion rearrangement in the acid dehydration of this alcohol. It has been proposed that the protonated cyclopropane ring might be an important intermediate in Wagner-Meerwein rearrangements (49).



If the protonated cyclopropane intermediate were the precurser then a 1:1 mixture of products with carbon-13 in the 3 and 4 positions would be expected. There is no splitting of the protons in the 4 position and the per cent excess carbon-13 in the 3 position of the product is the same as the excess in the 1 position of the starting alcohol. An enrichment of 30% implies that carbon-13 in the 4 position would be detectable if the reaction went by path (1) to the extent of 20%.

This experiment is good evidence against the protonated cyclopropane as an intermediate in the neopentyl carbonium ion rearrangement in particular and are discouraging to its application in the general case of Wagner-Meerwein rearrangements.

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THE CHEMISTRY OF AZETIDINES

Reported by P. Tschampel May 22, 1961

Although azetidine (trimethylenimine) and its derivatives have been known since the latter part of the nineteenth century (1), comparatively little work has been done on methods of preparation until recently. The lack of interest in these compounds was undoubtedly due to an inherent difficulty of preparation and to the fact that the substances were of no obvious utility. With the advent of chemotherapy, their possible use as alkylating agents, analogous to ethylenimines (2), to inhibit mitosis in neoplastic tissue, has given impetus to the development of several effective syntheses and consequent chemical studies of these compounds. This report will deal with the syntheses and properties of azetidines, stressing the developments which have occurred since the last review (3) on the subject.

There are two general synthetic routes: A) cyclization of 3-substituted amines, and B) reduction of 2-azetidinones (β-lactams).

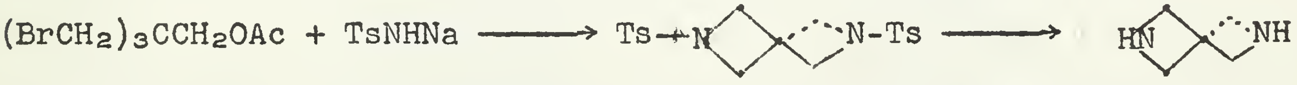
Cyclization procedures

Acyclic compounds have been cyclized to azetidine derivatives by a number of methods, none of which however, can be considered a genera synthesis. Until recently, yields have usually been low, with the azetidine derivative often being isolated as a minor constituent of th products. These preparative methods may be categorized in the following manner: a) dehydrohalogenation of 3-haloalkylamines by base, b) reaction of dihalides with amide, c) reaction of 3-aminoalkyl hydrogen sulfates with base, and d) pyrolysis of diamines and related compounds

a). Gabriel and Weiner (1) first prepared azetidine in low yield by reacting KOH with 3-bromopropylamine hydrobromide. Others (4,5) have used this method with reported yields ranging from 6 to 26%. Although ring closure does not take place readily when only the halogen is secondary, if both functional groups are on secondary carbon atoms, cyclization is more likely (6). This is illustrated by the preparation of 1,2-dimethyl-4-isobutyl- and 1,2-dimethyl-4-isopropyl-derivatives in yields of 79 and 50%, respectively (7,8). Functionally substituted trimethylenimines prepared in this manner are azetidine-3-sulfonic acid (9), 3,3-diaminomethylazetidine (10), azetidine-2-carboxylic acid (11), and 3-hydroxymethyl-3-aminomethylazetidine (12), the last compound being the only one not requiring a strong base at refluxing temperatures. Azetidine-2-carboxylic acid, a constituent of Convallaria majalis L. (13,14,15), is the only naturally occurring derivative thus far isolated, although the existence of several others has been postulated (16).

b). *p*-Toluenesulfonazetidide may be prepared from 1,3-dibromopropane (17) or from the bromochloro compound (18). Sulfonamides are used when incorporating the azetidine ring into spiro compounds such as 6-sulfanilyl-2-oxa-6-azaspiro [3.3] heptane (I) (19). By reacting the sodium salt of *p*-toluenesulfonamide with pentaerythrityl tribromide acetate, one obtains 2,6-diazaspiro [3.3] heptane (II) (10). Although

I

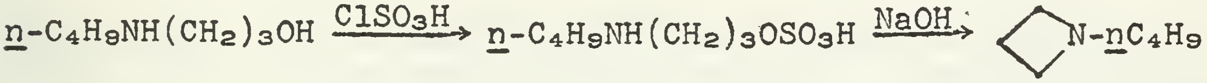


I

the first report (20) of reduction of *p*-toluenesulfonazetidide with Na in *n*-pentanol claimed an almost quantitative yield of azetidine, subsequent workers (5,18, 21-24) have reported yields of zero to 36%. The poor results are now understandable in view of the fact that amyl

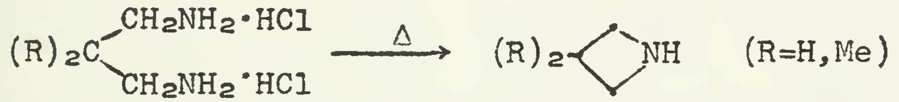
alcohol boils almost 80° higher than trimethylenamine, causing the latter to be lost during the course of the reduction (25). Sodium in liquid NH_3 (26) is not very effective in detosylation, and treatment with CH_3I gives but a 17% yield of the N,N-dimethylazetidinium salt(27

c). The Wenker synthesis (28) of aziridine (ethylenimine) has bee successfully adapted to produce 1-(*n*-butyl)azetidine (III) from 3-butylaminopropanol hydrochloride (29). An 8% yield of 1-methylazetidine can be had this way (18), while the 1-ethyl- and 1-*t*-butyl- compounds (30) are prepared in yields of 13 and 47%, respectively. Under the same conditions which produce aziridine in 83% yield from ethanolamine (31), however, 3-aminopropanol affords but 1.7% of azetidine (32



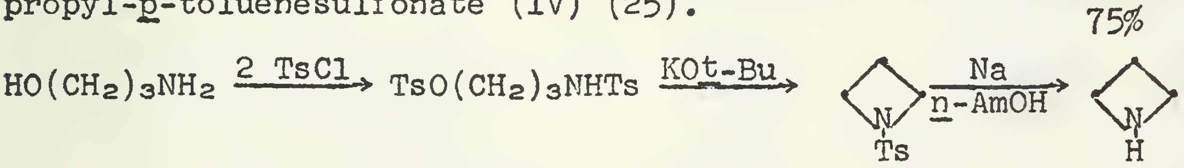
II

d). The syntheses of trimethylenimine (33) and its 3,3-dimethyl derivative (34) by the dry distillation of the appropriate trimethylenediamine hydrochloride are characterized by low yields.



The analogous preparation of 1-phenylazetidine (35,36) has been reported, but gives poor results also. The pyrolysis of pentaerythrityl tetramine (36) is a second method for synthesizing II.

Very recently it has been found that the best features for constructing the azetidine ring system present in methods a) and b) can be combined by cyclizing a ditosylate such as 3-(*p*-toluenesulfonamido)-propyl-*p*-toluenesulfonate (IV) (25).



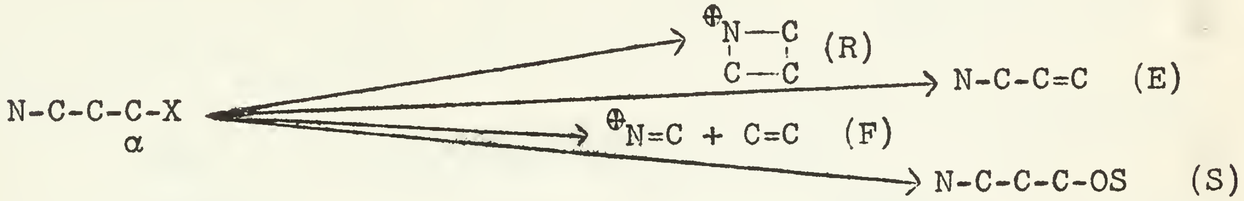
IV

The difficulty with which the azetidine ring is formed from acyclic reagents has been interpreted by King (38) in terms of the general principles of ring formation brought out by Ruzicka and coworkers (39). According to Ruzicka two factors determine the formation of a ring system of this type. The first is the strain (in terms of deviation from the tetrahedral angle) which operates against the formation of three- and, to a lesser extent, four-membered rings. The second is a probability factor; this is related to the distance between the two atoms which will close to form the ring and the probability that they will come close enough to one another to be joined by a valence bond. The first-order cyclization rate constants of Table I (40) show that these factors combine to give the four-membered ring the least propensity toward formation; competing reactions therefore have the best chance in this system.

Table I. Rates of intramolecular condensations of bromoalkylamines.

Amine	$k_{25°}$
2-bromoethyl	0.036
3-bromopropyl	0.0005
4-bromobutyl	30.
5-bromopentyl	0.5
6-bromohexyl	0.001

Studies by Grob (41) on the solvolysis of γ-amino halides show the effect of substitution on ring closure. In these solvolyses, there are four possible reactions to consider: ring closure (R), fragmentation (F), elimination (E), and substitution by solvent (S):

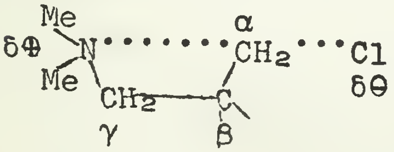


The extent of each of these reactions depends on the degree of alkyl substitution in the α and β positions, as shown by comparative examination of the γ-aminochlorides in Table II. The first order rate constants (k_1) are obtained under the same conditions (80% EtOH, 56°) as the k_{RCl} constants, the latter in each case however being for the corresponding chloride having a carbon atom in place of the nitrogen (Me_2CH- instead of Me_2N-). Of these three pairs of prim-, sec-, and tert- aminopropyl chlorides, the one member is unsubstituted on the β-carbon, while the other is dimethylated. The solvolytic rate constants of these amines show that they do not have reactivity in the usual order tert>sec>prim, and that with one exception, the amines are considerably more reactive than the corresponding alkyl halides, indicating anchimeric assistance by the nitrogen atom.

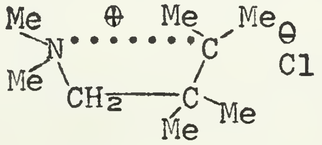
Table II.

	Compound	10^5k_1 (sec^{-1})	10^5k_{RCl}	Product,%
(1)	$(Me)_2N(CH_2)_3Cl$	10.8	1.8×10^{-3}	100R
(2)	$(Me)_2NCH_2C(Me)_2CH_2Cl$	98.	2.0×10^{-5}	100R
(3)	$(Me)_2NCH_2CH_2CHMeCl$	1.87	8.3×10^{-3}	100R
(4)	$(Me)_2NCH_2C(Me)_2CHMeCl$	28.2	8.3×10^{-3}	72R,19F
(5)	$(Me)_2NCH_2CH_2C(Me)_2Cl$	35.5	47	44F,38S,9E
(6)	$(Me)_2NCH_2C(Me)_2C(Me)_2Cl$	14500.	120	72,F20E

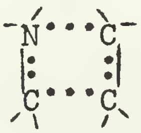
In the case of the prim-amino chlorides (1) and (2), the high k_1/k_{RCl} ratios as well as the exclusiveness of ring closure indicate an internal nucleophilic substitution (V). This mechanism should also be true for the sec-chloride (3) in view of the nature of the product. For amino chlorides (4) and (6), fragmentation and elimination occur, and the amino group enhances the solvolytic rate without necessarily being accompanied by a ring closure (i.e., by a covalent bonding of the nitrogen atom to the α-carbon atom). These results can be interpreted by the postulation of an internally solvated carbonium ion as an intermediate. This ion can undergo ring closure, fragmentation, or elimination. For the carbonium ion VI resulting from haloamine (6) [which is more hindered to nucleophilic attack on the α-carbon atom than the cation from haloamine (4)], the formation of an aminoolefin would be expected as a subsequent reaction. The elongation of the C_β-C_γ bond for (4) or (6) leads to a transition state (VII) required for fragmentation. The tertiary chloride (5) ionizes without any



V



VI



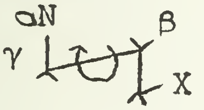
VII

assistance from the amino group (39) to form a classical tert-carboniu ion, which is then free to fragment, solvolyze, or lose a proton. The participation of the amino group in the ionization process is enhanced by the gem-methyl groups present on the β-carbon atoms of the three even-numbered chloroamines, since these groups further quasi-ring formation by decreasing the C_α-C_β-C_γ angle (41). Gem-substitution also has a profound effect in the formation of pyrrolidine rings, as is illustrated by Table III.

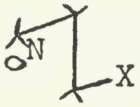
Table III. Gem-alkyl effect on rate of ring closure of bromobutylamines in acetate buffer at 30° (42).

Compound	k_{rel}
4-bromobutylamine	1.00
4-bromo-1,1-dimethylamine	2.19
4-bromo-2,2-dimethylamine	158.
4-bromo-2,2-diethylamine	594.
4-bromo-2,2-diisopropylamine	9190.
4-bromo-3,3-dimethylamine	0.158

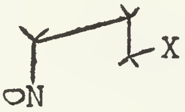
Fragmentation, the most serious competitor to cyclization, may be expected when electron release from the nitrogen atom is sufficient to cause bond breaking. This process should occur most readily if all the bonds involved and the lone pair of electrons on the nitrogen atom lie in one plane (VIII), and overlap of the developing p-orbitals in the transition state would be at a maximum as indicated by IX. However, other stereochemically favorable conformations for fragmentation may be derived by rotating the C_γ-N bond around the C_β-C_γ bond, and two particular conformations obtained this way are the skew form (X) and the eclipsed form (XI), the latter also being the one required for cyclization.



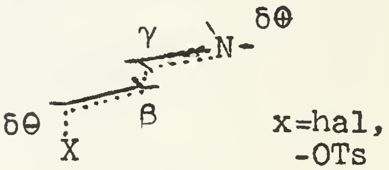
VIII



X

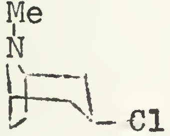


XI

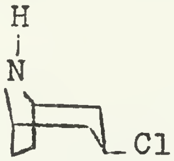


IX

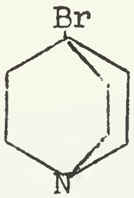
Examples of the skew form leading to fragmentation are provided by the solvolyses of 3-β tropanyl chloride (XII) and 3-β nortropanyl chloride, (XIII) whose respective rate constants (80%EtOH, 62°) are 2.5×10^4 and 1.4×10^3 times larger than that of the non-fragmentable cyclohexyl chloride under the same conditions (43,44). 4-Bromoquinuclidine (XIV) contains a coplanar, eclipsed γ-amino halide system and its rate of solvolysis is $>10^4$ that of the corresponding carbocycle 1-bromo bicyclo [2.2.2] octane (XV), under the same conditions.



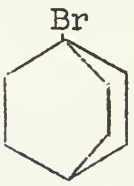
XII



XIII



XIV



XV

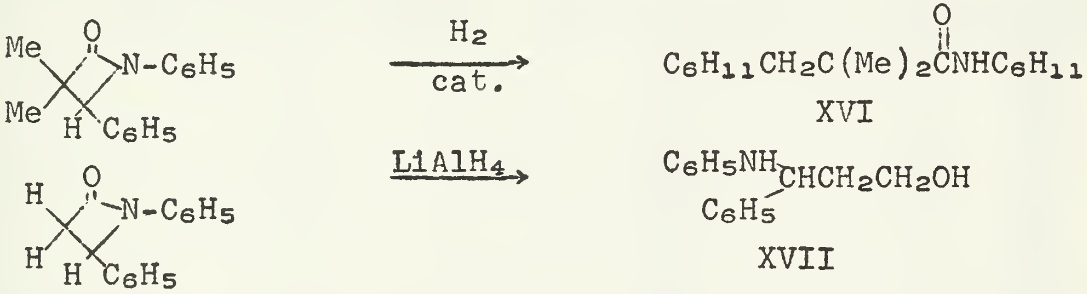
It can be seen then that no really well-defined requirements exis for fragmentation, and that for this reason one can expect this process to proceed more readily than ring closure unless steric effects are important, as is illustrated by the six γ-amino chlorides (Table II). Table IV shows some of the effects of C- and N-substitution upon azetidine yield.

Table IV.

Compound	Azetidine,%	Ref.
3-halopropylamines		
$Br(CH_2)_3NH_2$	6-26	5
$Cl(CH_2)_3NH_2$	poor	6
3-bromo-N-methylpropylamines		
$BrCH_2C(Me)_2CH_2NHMe$	80	6
$BrCHMeCH_2CH$*i*-PrNHMe	50	8
N-alkyl-3-propylsulfonate ions		
$^-OSO_3(CH_2)_3NH_2$	1.7	32
$^-OSO_3(CH_2)_3NHMe$	8	18
$^-OSO_3(CH_2)_3NHCH_2C_6H_5$	26	25
$^-OSO_3(CH_2)_3NH$*n*-Bu	30	29
$^-OSO_3(CH_2)_3NH$*t*-Bu	47	30
3-(4-toluenesulfonoxy)-propyl-N-sulfonamide ions		
$TsO(CH_2)_3\bar{N}Ts$	93	25
$TsOCHMeCH_2CH_2\bar{N}Ts$	68	25

Reduction of 2-Azetidinones

Preparation of azetidines by catalytic hydrogenation of β-lactams has not yet been reported. 1,4-Diphenyl-3,3-dimethyl-2-azetidinone, for example, yields quantitatively 2,2-dimethyl-3-N-dicyclohexyl propionamide (XVI) (25). Most attempts utilizing hydride reduction have also resulted in ring cleavage to aminoalcohols (45-47), the reduction of 1,4-diphenyl-β-lactam to 3-phenyl-3-N-anilinopropanol (XVII) being a typical example (45).

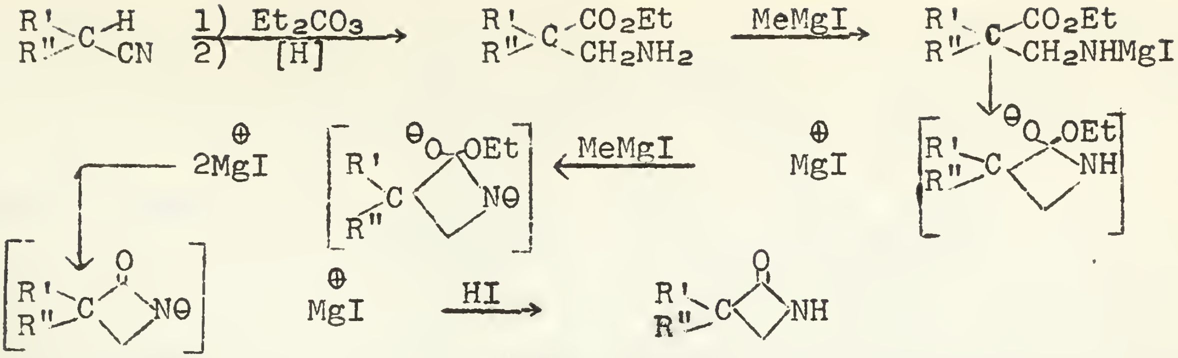


In the course of a recent investigation of new routes to 3,3-disubstituted β-lactams (48-55), Testa and Fontanella have found that reduction to azetidines by $LiAlH_4$ is possible if there is no substituent on the nitrogen atom (56). This is in contrast to the behavior of 2-pyrrolidones, since 1-methyl-3,3-diphenyl-2-pyrrolidone (XVIII) affords a 46% yield of the tri-substituted pyrrolidine (57).

XVIII

The stability of the N-unsubstituted β-lactam ring may be accounted for by postulating the formation of its aluminum salt, which would then be capable of reduction but immune to ring opening.

A most convenient method for the synthesis of 3,3-disubstituted β-lactams is the method of Breckpot (58), which utilized 3,3-disubstituted acetonitriles.



Other methods of synthesizing 2-azetidinones have been reviewed by Sheehan and Corey (59), and are also included in a recent seminar (60). The azetidines prepared by Testa and Fontanella are summarized in Table V. The only monosubstituted azetidine thus far reported as being produced by this method is 3-phenylazetidine (61,62). Hydride reduction of 2,4-azetidinones (malonimides) is feasible, but the cyclization step does not proceed readily, as evidenced by the production of 3,3-diisopropylazetidine from 2-isopropyl-2-carboxy-3-methylbutyramide (XIX) in a 9.5% yield (63).

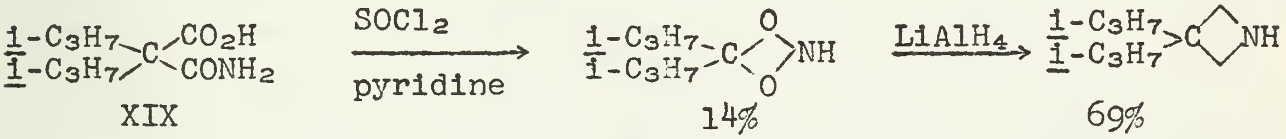


Table V. 3,3-disubstituted azetidines produced by $LiAlH_4$ reduction of 2-azetidinones (56).

R',R"	Azetidine yield,%	β-Lactam ref.	β-Laetam yield,%
Ø, Me	65	49	64
Ø, Et	70	52	86
Ø, n-Pr	73	49	56
Ø, i-Pr	75	52	78
Ø, n-Bu	73	52	92
Ø, CH₂Ø	85	52	87
Ø, C_6H_{11}	75	52	80
Me, Me	45	48	80
Et, Et	71	52	92
n-Pr, n-Pr	72	52	91
n-Bu, n-Bu	87	52	99

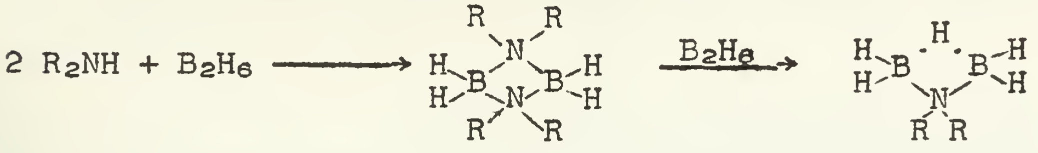
Properties and Reactions

The pK_a of azetidine, 11.3 at 25° (18), approximates that of pyrrolidine or piperidine, but is higher than that of ethylenimine. The stability of the trimethylboron compounds, however, gives ethylenimine ≪ piperidine < pyrrolidine < azetidine as the order of basicity (24), which is to be expected on the basis of F- and I-strain (64).

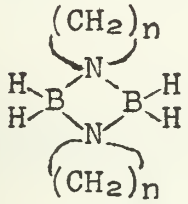
The NMR spectra of the last three bases, when substituted on the nitrogen atom, are temperature-independent down to -77°, indicating rapid inversion about the nitrogen even at this temperature (30). The spectra of N-substituted aziridine derivatives however are strongly temperature dependent, as would be expected if the nitrogen atom and attached groups do not lie in a plane and inversion occurs rather slowly.

Compounds of the types $(R_2NBH_2)_2$ (XX) and $R_2NB_2H_5$ (XXI) are fairly stable even though the B-N-B bond angle is about 76° for XXI (R=Me). (65). A study has shown that the N bonds are further strained when a ring-amino compound is incorporated into these boron hydrides, however (26). Compounds of type XXII can be made in quantitative yield for n=3,4,5, but this is true for XXXIII when n=4 and 5 only; when n=3,

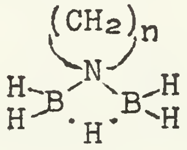
the dimer is obtained in only 40% yield, the rest being a glassy polymer incapable of absorbing any more diborane. The unusually high strain on the nitrogen atom in ethylenimine leads to opening of the C-N ring during attempts to make either XXII or XXIII, n=2.



XX XXI

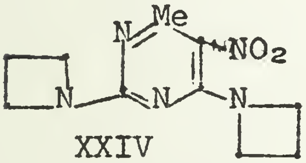


XXIII

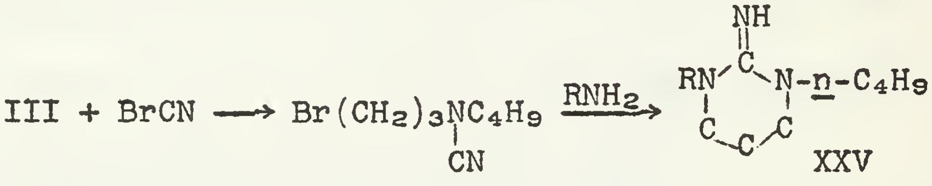


XXII

Since ring closure will not occur if the nitrogen atom is acylated (66), cyclization of a trimethylenimine must be effected before any attempt is made at N-acylation. An N-alkylated azetidine cannot be obtained in one step by reacting a β-lactam with an ester in the presence of $LiAlH_4$, but is produced by separate acylation of the azetidine followed by hydride reduction, or by the simultaneous process of reductive alkylation of the cyclic amine (67). N-Alkylation is also possible with ethylene oxide, yielding N-(β-hydroxyethyl) derivatives (68); these are used to make analogs of spasmolytics and anticholinergics in which the diethylamine group is replaced by azetidine. A recent report (69) describes the synthesis of a possible example of an antimetabolite with alkylating functions incorporated into it, <u>viz</u>., 2,4-bisazetidino-6-methyl-5-nitropyrimidine (XXIV). The heterocyclic nitrogen atom of azetidine derivatives can also be incorporated into six-membered cyclic guanidines (XXV) by means of the von Braun cyanogen bromide reaction (29).



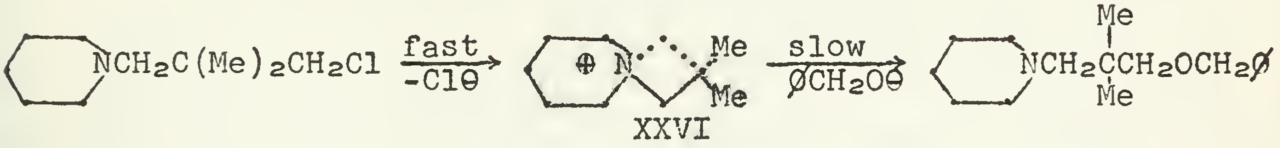
XXIV



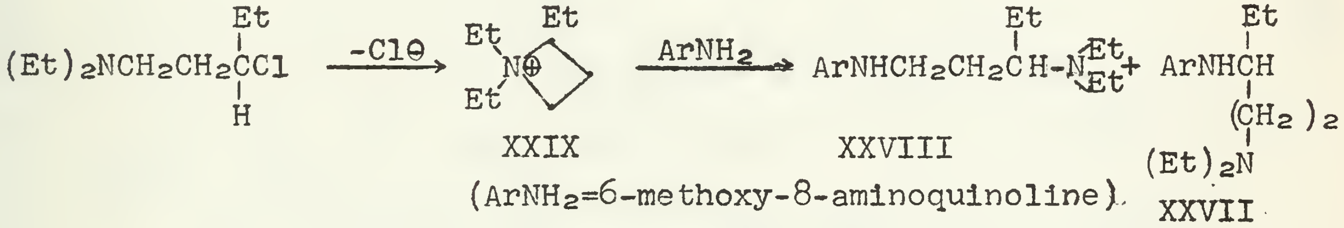
XXV

Despite the relatively slow rate at which they form, azetidinium structures are postulated in several reactions in which anchimeric assistance by the nitrogen atom is indicated. It has been reported that 3-N-piperidyl-2,2-dimethylpropyl chloride undergoes a displacement reaction with Na benzyloxide at a rate much faster than expected for a neopentyl-type chloride, and an azetidinium ion (XXVI) is thought to be an intermediate (70). The reaction of 6-methoxy-8-aminoquinoline with 1-diethylamino-3-chloropentane to give both 6-methoxy-8-(3-diethylamino-1-pentylamino)quinoline (XXVII) and 6-methoxy-8-(1-diethylamino-3-pentylamino)quinoline (XXVIII) appears to involve an unsymmetrical alkylating agent (XXIX) (71) also, since a rearranged (XXVII) and an unrearranged (XXVIII) product are obtained. Because the majority of the product of solvolysis in 80% EtOH is found to retain its configuration at the 3-position, the cyclic intermediate XXX has been proposed for this solvolysis of 3-α-tropanyl chloride (XXXI) (72). The most recent report on this effect of a nitrogen atom in the γ-position is found in the transannular interactions in the solvolysis of 4-chloropiperidines (73), the heterocyclic compounds being

solvolyzed by 80% EtOH 100 to 1400 times as fast as cyclohexyl chloride, to yield elimination and fragmentation products. To accoun for the nature of the products and the acceleration in rate, Grob has postulated an internally solvated carbonium ion (XXXII) in which the ionization is assisted by a transannular interaction in a boat-like conformation.

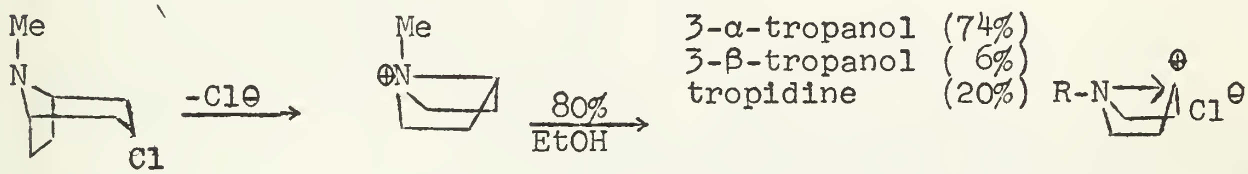


XXVI



XXIX XXVIII XXVII

(ArNH₂=6-methoxy-8-aminoquinoline).



XXXI XXX XXXII

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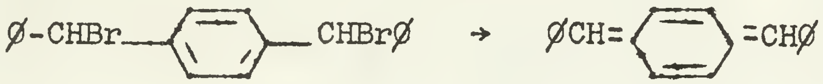
SOME ASPECTS OF THE CHEMISTRY OF XYLYLENES

K. R. Fountain May 29, 1961

Xylylenes are diamagnetic compounds which react under suitable conditions as diradicals. This seminar discusses the pyrolytic production of xylylenes, the preparation of solutions of xylylene monomer and interesting reactions of these compounds in solution. For a greater coverage of the properties of the polymers produced by gas phase and solution polymerization the reader may see reference 4. Szware and Errede have reviewed this subject extensively also (3).

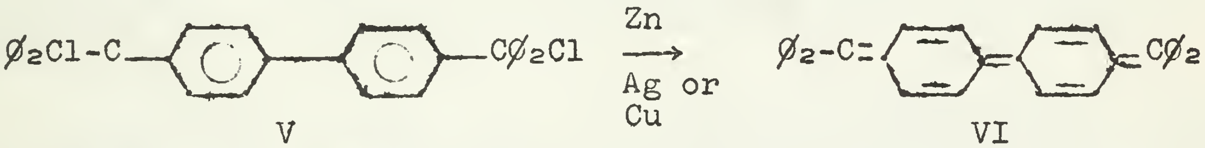
Gomberg's discovery of triphenylmethyl gave rise to much work on similar compounds. Thiele and Balhorn (5) attempted to make carbon analogs of quinones by cleaving p-xylylenedibromides I and II with zinc dust in acetic acid to produce III and IV. They obtained a fleeting, golden color with compound I but an intense colored solution similar to solutions of triphenylmethyl in the case of II. They attributed these results to the greater stability of IV relative to III. These same workers regarded a white insoluble powder produced from p-xylylene dibromide under these same conditions as the polymer of p-xylylene.



I III

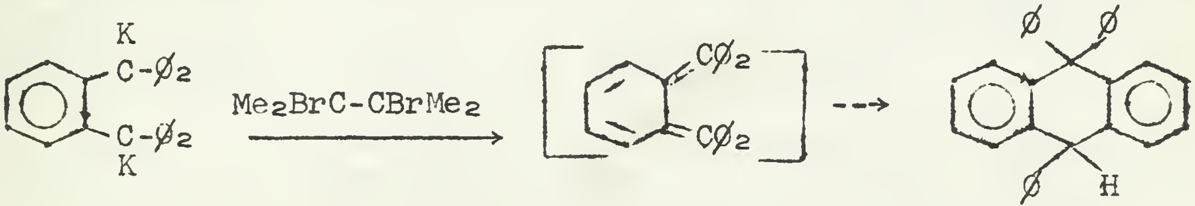
II IV

Tschitschibabin (2) prepared the compound corresponding to Heintshel's (6) proposed structure for triphenylmethyl by treating V with zinc, silver or copper. The compound VI was intense purple in solution; displaying some of the characteristics of triphenylmethyl.



V VI

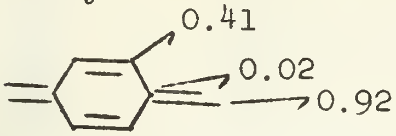
Wittig (8) as late as 1931 attempted to prepare tetra-phenyl-o-xylylene VII by the route shown, but isolated only the anthracene VIII.



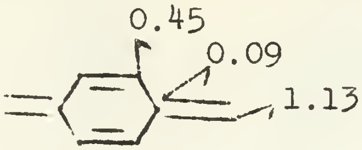
VII VIII

In every case the experimenters describe an extremely reactive species instable to atmospheric oxygen and rapidly decolorized by exposure to light.

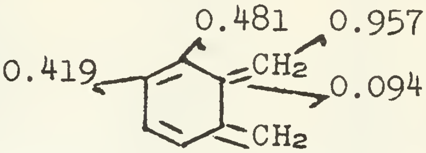
Several workers (7,9,10) have calculated free valences by molecular orbital and valence bond methods. The molecular orbital calculations of Coulson (7) and Pullman (10) are given here as a summary.



Ground state
p-xylylene



triplet state
p-xylylene



Ground state
o-xylylene

Comparing these free valence values with that of the benzyl radical, which is calculated by Coulson (7) to be 1.04 at the terminal positio one sees that the triplet state of p-xylylene does not differ greatly from the ground state, with the value of the benzyl radical between them. Ortho-xylylene is expected to be somewhat similar although triplet calculations were not available. The energy difference between ground and first triplet states for p-xylylene is estimated by many workers (7) to be from 6 (11) to 12 (9) Kcals. Using the latter value, Shaefgen calculated the percentage of molecules in the triplet state at 27° to be 2×10^{-9}; that at 900° to be 5.4×10^{-3}. From analogy of such compounds as tetra-phenyl-p-xylylene which are known to be diamagnetic (11), one expects the unsubstituted compound, p-xylylene, to be diamagnetic also. It is interesting, then, that these compounds, though they are indeed molecular species, behave in their reactions very much like radicals, being stable in the gas phase but polymerizing in a condensed phase.

Szwarc (12,13,14) obtained p-xylylene in the gas phase by pyrolysis of p-xylene at temperatures of about 800°. This method is widely used for the production of p-xylylene. His apparatus consisted of a furnace for pyrolysis, a U tube, fitted at the branch coming from the furnace with a capillary, which prevented diffusion from the U tube back into the furnace; a 0° trap formed from the bottom of the U tube to catch relatively non-volatile material from the pyrolysis, a trap after the U tube to collect poly-p-xylylene at -80°, and bulbs to contain any non-condensible gaseous products. Szwarc demonstrated the existence of p-xylylene by showing that the pyrolysate gases contained a species which reacted with iodine vapor in the tube to give only p-xylylenediiodide as iodine containing products.

The gas phase stability of p-xylylene was demonstrated by Farmer and coworkers (15) who pyrolysed o, m, and p-xylyliodides in a quartz tube connected to a mass spectrometer in such a way as to be able to determine the products of the pyrolysis as they were formed. They demonstrated by the appearence of a mass 105 peak at temperatures below 800° that the predominant species was the p-methylbenzyl radical At temperatures above 850° the mass 105 peak disappeared in favor of a mass 104 peak corresponding to p-xylylene. Above 1000° the mass 105 peak was entirely converted to the mass 104 peak.

Szwarc and Shaefgen have both elucidated the mechanism for the pyrolysis of p-xylene and formation of p-xylylene. Most of their work is in substantial agreement. Szwarc (13) showed that the reactio is first order by varying the pressure of p-xylene and time of contact (Table 1).

Table I Pyrolysis of p-Xylene

Temp°C	Press.(MMHg) p-Xylene	Contact time sec.	% Decomposition	$Kx10^2 sec^{-1}$	$\%H_2$^{b}	%CH
745	3.2	0.419	0.159	0.381	67	33
781	2.6	0.239	0.344	1.44	67	33
782	6.2	0.715	0.365	1.35	64	36
866	3.7	0.344	7.73	22.4	65	35
860^a	4.5	0.410	10.00	25.0	63	37

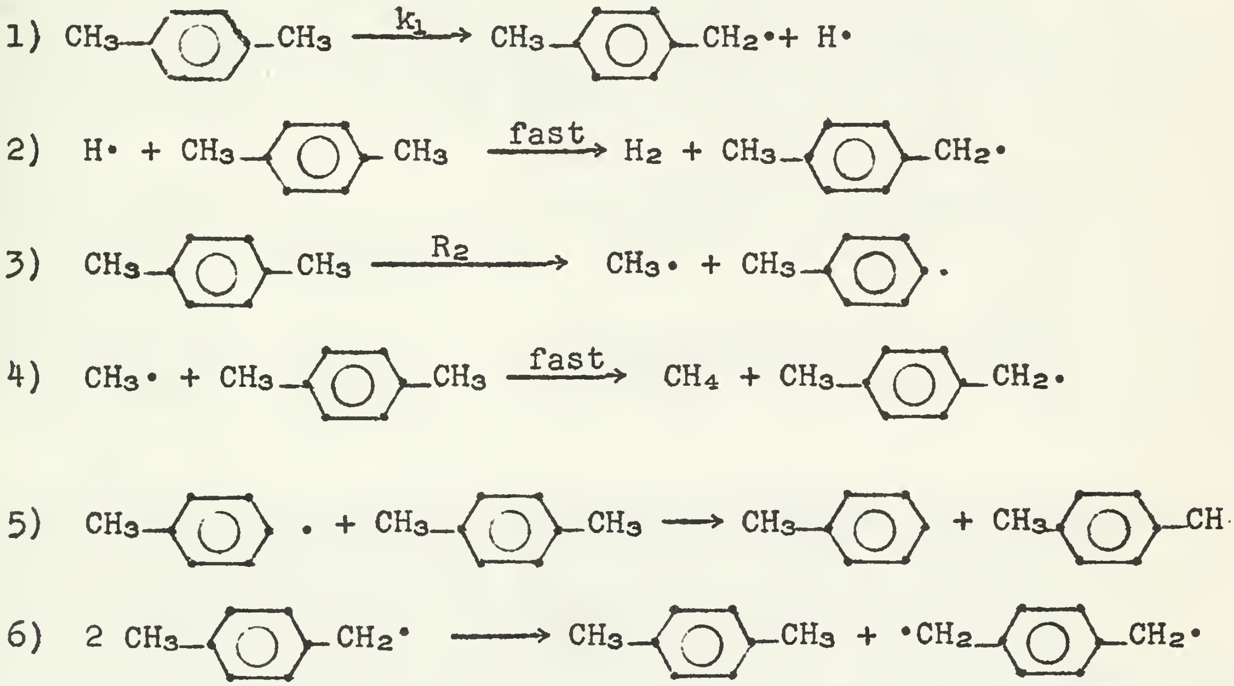
a) Surface area increased 15 times; b) Reaction followed by H_2 evolution. These data are typical of a number of experiments.

Products of Pyrolysis of p-Xylene

These products are the result of the passage of 57.3 moles of p-Xylene through the apparatus at 840°. The percentage of reaction was 3.52.

Material	Amount detected (moles)
poly-p-Xylylene	1.15
1,2-di-p-tolylethane	0.34
Toluene	0.52
Methane	0.57
ethylene	0.15
Propylene	0.04
Hydrogen	1.00
Other Hydrocarbons	0.001

The mechanism of Shaefgen (16) accounts best for these data and products.



By measuring the rate of methane formation Shaefgen determined k_2 as $k_2=4.7x10^{14} \exp(-81,800/KT)$, giving the C-$CH_3$ bond strength as 81.8 Kcals which is the order of magnitude of the C-H (methyl) bond strengt which Szwarc (13, 14) determined as 77 Kcals. An examination of table I shows toluene and methane formed in about equimolar amounts, white H_2 is formed in about a 2:1::H_2:CH_4 proportion consistant with this mechanism.

The number of p-methylbenzyl units accounted for by the production of polymer and dimer as tabulated in Table 2 is far insufficie

to account for all the p-methylbenzyl radicals produced in the pyrolys This leads to the belief that thermal dissociation of p-methylbenzyl-radicals to p-Xylylene and hydrogen is relatively of little importance in p-Xylylene production.

Table 2-Pyrolysis of P-Xylene - Variation of Products

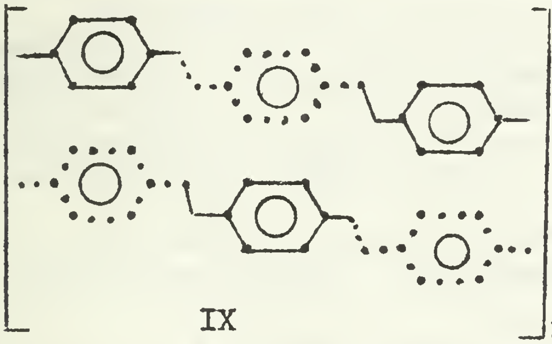
	Temperature C°					
	795	840	840	840	873	920
P-Xylene: Press. mmHg	7.1	2.6	7.2	12.2	6.8	7.0
P-$MeC_6H_4CH_2\cdot$: Units moles formed	3.32	3.09	3.06	3.25	3.11	3.01
P-$MeC_6H_4CH_2$: Units in dimer	0.86	0.34	0.34	0.50	0.26	0.24
Polymer: dimer	0.91	3.4	3.2	2.1	3.3	2.0

Shaefgen confirmed that the production of p-Xylylene was indeed due to a disproportionation, as in reaction 6, by pyrolysing the dimer 1,2-(di-p-tolyl)ethane under the reaction conditions and obtained p-Xylene and p-Xylylene in equimolar quantities (16).

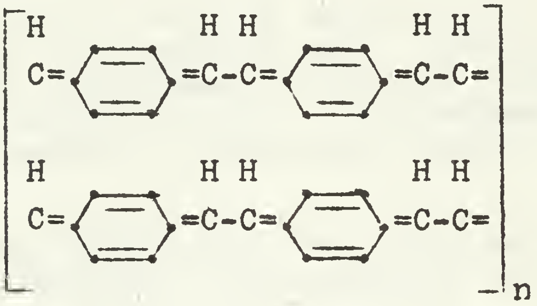
Table 3 - Pyrolysis of 1,2-(di-p-tolyl)ethane

Product	Moles x 10^4	Method of analysis
p-Xylene	11.2	Infrared
Poly-P-Xylylene:Units of-C_8H_8-	10.4	X ray
Hydrogen	2.5	Mass spectrometer
P-P'-dimethyl-trans-stilbene	1.8	U. V. Spectrum

Brown and coworkers (18) have demonstrated by xray analysis that polymeric p-Xylene exists in a low temperature, a form which the polyme takes when collected at -78° and β, the modification to which α is irreversibly changed when heated. The low temperature polymer is in the form of a staggered benzoid chain IX while the high temperature for is proposed to be quinoid X which would account for the irreversibility of the α→β transition. Xray data show no evidence of cross-linking.



IX



X

The most interesting vistas of xylylene chemistry were opened by Errede (19) when he discovered that p-Xylylene could be stabilized by quenching the pyrolysate gases in solvents such as toluene or hexane at -78°. His apparatus was a modification of Szwarc's. Warming solutions of pyrolysate gases to room temperature produced copious amounts of a precipitate in a highly swollen state, which xray analysis showed to be α-poly-p-Xylylene. Addition of these solutions to an excess of iodine produces p-Xylylene di-iodide in good yield. Hence it is shown that the solutions are truly monomeric p-Xylylene. Polymerization even at -78° is appreciable and is not prevented by the usual inhibitors, but the half life of the solutions is on the order of 20 hours, making study of the monomer convenient.

The concentration of monomer is somewhat dependant on the duration of pyrolysis. As pyrolysis continues the monomer concentration is a good solvent such as toluene increases to a maximum and then falls off

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

rapidly. This can be visualized as straight forward polymerization which accelerates as the reaction proceeds due to disappearance of an inhibitor in the solvent.

Bubbling oxygen or air through fresh monomer solutions produces an insoluble oxygen containing precipitate in which the percentage of oxygen is dependant upon the rate of O_2 throughput, degree of solutio agitation, and polarity of the solution (20). Under optimum conditio of precipitate formation the compound is formed by elemental analysis to be consistant with the unit $[C_8H_8O_2]_n$, which would be consistant with poly-p-xylylene peroxide. Decomposition of this product allowed isolation of terephthalaldehyde, p-hydroxymethylbenzaldehyde, p-xyxlyleneglycol and hydrogen. The use of oxygen as an initiator, however, generally failed to increase the rate of poly-p-Xylylene formation.

Monomer solutions also react with mono-radicals, halogens, and diphenylpicrylhydrazyl to give in all cases products from addition to the terminal CH_2 broups (21) XII. Radical reaction also leads to

XI XII

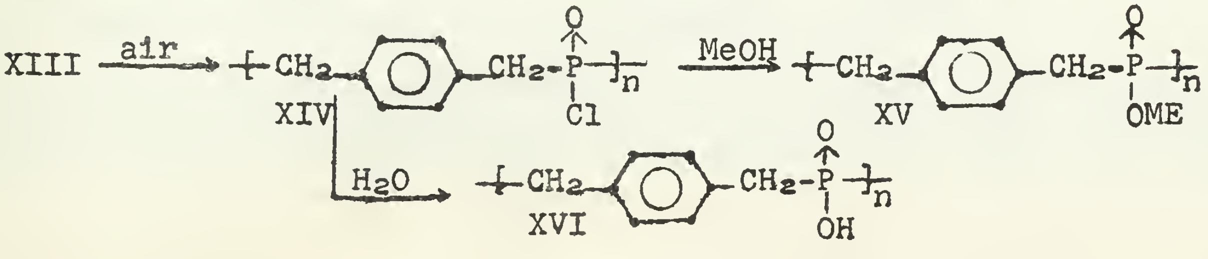
linear telomers whose degree of polymerization is dependant on the consentration of the radical used. Sulfur dioxide reacts with p-xylylene much after the manner of its addition to olefins (22) to form polymers. Chain transfer agents such as chloroform and carbon tetrachloride are not effective, but mercaptans are found effective in chain transfer with poly-p-xylene.

Copolymerization can not be effected at -78° with solutions of such monomers as vinyl-ethyl-ether, vinyl-acetate etc., but copolymerization occurs when solutions of p-xylylene at -78° are poured into solutions of the monomer in question at 100°. The properties of the resulting copolymers are intermediate in character between the corresponding homo-polymers.

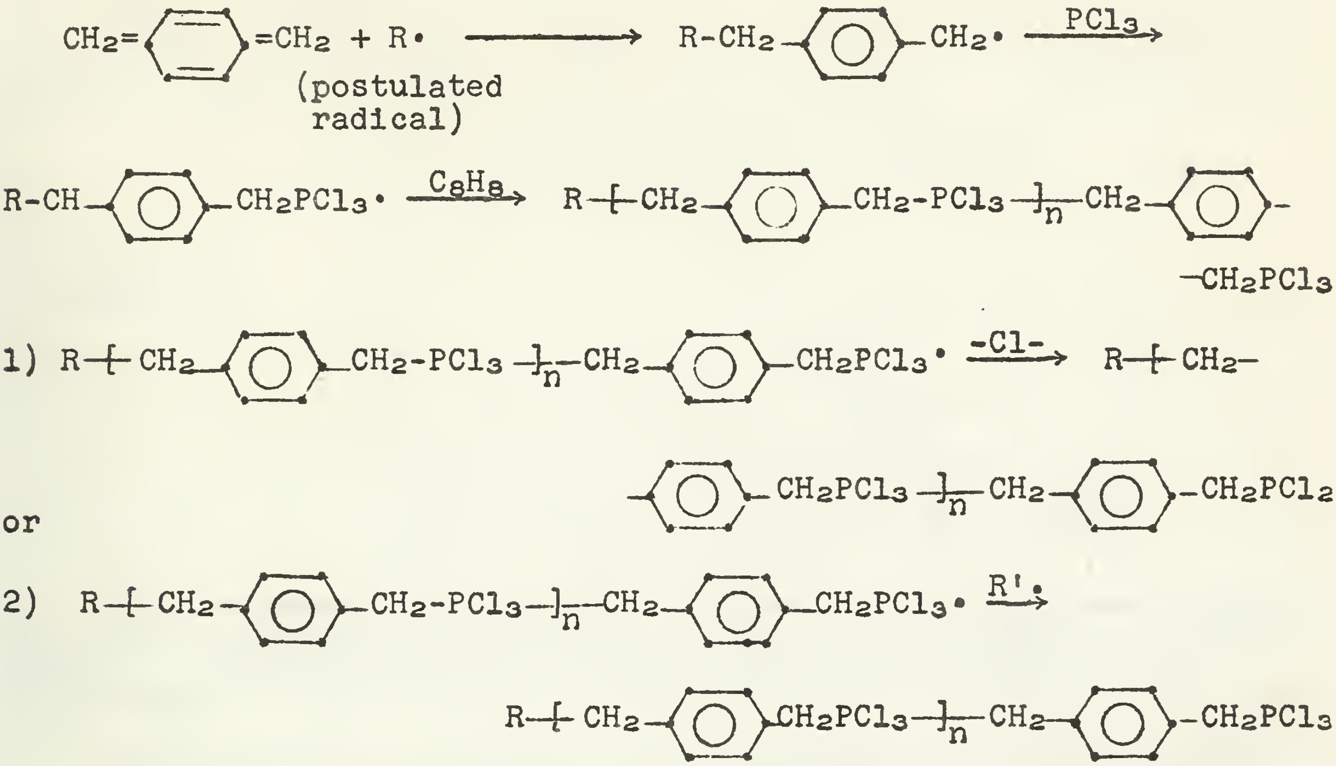
The addition of phosphorus trichloride (23) to p-xylylene solutio results in a linear Copolymer of composition corresponding to XIII.

XIII

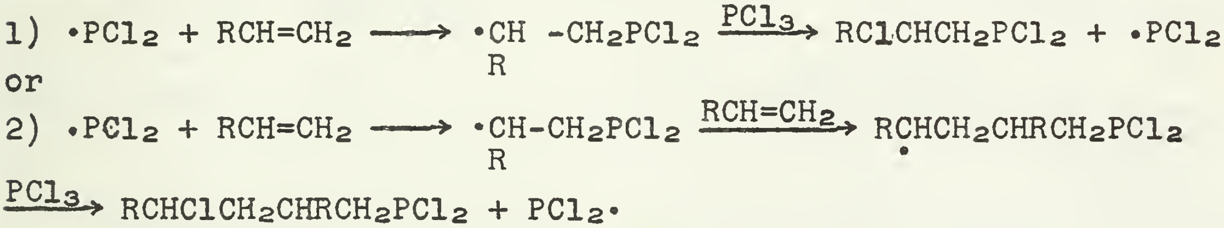
Simple addition of PCl_3 to olefins results in compounds of the type $RClCH-CH_2PCl_2$. Drying XIII in air produces XIV by displacement of two Cl atoms. This is probably not a hydrolysis as treatment of hydrocarbons with phosphorus trichloride followed by introduction of oxygen into the system yields alkylphosphonylchlorides (24).



Treatment of XIV with methanol or water gives XV and XVI the structur of which are determined from Xray and elemental analysis. The propo. mechanism is as shown:



The mechanism for the addition of phosphorus trichloride to olefins is postulated as follows: (23, 25)



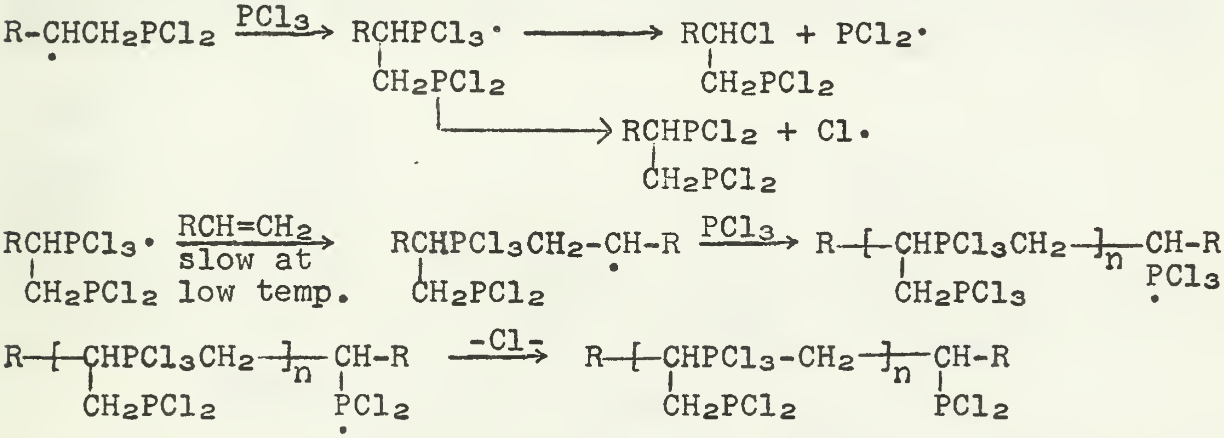
1) $\cdot PCl_2 + RCH{=}CH_2 \longrightarrow \underset{R}{\cdot CH}\ -CH_2PCl_2 \xrightarrow{PCl_3} RClCHCH_2PCl_2 + \cdot PCl_2$

or

2) $\cdot PCl_2 + RCH{=}CH_2 \longrightarrow \underset{R}{\cdot CH}-CH_2PCl_2 \xrightarrow{RCH=CH_2} R\underset{\bullet}{C}HCH_2CHRCH_2PCl_2$

$\xrightarrow{PCl_3} RCHClCH_2CHRCH_2PCl_2 + PCl_2\cdot$

One can envision in the present case the addition of PCl_3 to an alkyl radical followed by several modes of behavior.



$$R\text{-}\underset{\bullet}{C}HCH_2PCl_2 \xrightarrow{PCl_3} \underset{CH_2PCl_2}{RCHPCl_3\cdot} \longrightarrow \underset{CH_2PCl_2}{RCHCl} + PCl_2\cdot$$

$$\underset{CH_2PCl_2}{RCHPCl_3\cdot} \longrightarrow \underset{CH_2PCl_2}{RCHPCl_2} + Cl\cdot$$

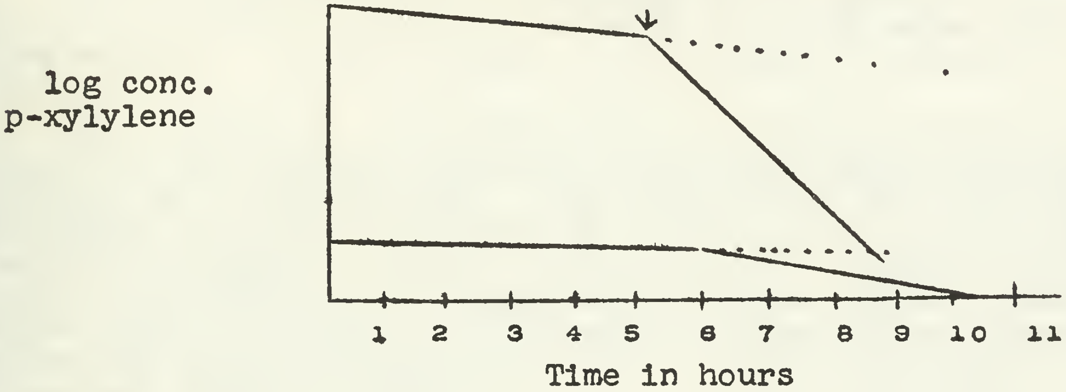
$$\underset{CH_2PCl_2}{RCHPCl_3\cdot} \xrightarrow[\text{slow at low temp.}]{RCH=CH_2} \underset{CH_2PCl_2}{RCHPCl_3}CH_2\text{-}\underset{\bullet}{CH}\text{-}R \xrightarrow{PCl_3} R\left[\underset{CH_2PCl_3}{CHPCl_3}CH_2\right]_n \underset{\underset{\bullet}{PCl_3}}{CH\text{-}R}$$

$$R\left[\underset{CH_2PCl_2}{CHPCl_3}CH_2\right]_n \underset{\underset{\bullet}{PCl_2}}{CH\text{-}R} \xrightarrow{-Cl-} R\left[\underset{CH_2PCl_2}{CHPCl_3}\text{-}CH_2\right]_n \underset{PCl_2}{CH\text{-}R}$$

The copolymerization of p-xylylene is attributable to the greater reactivity of the p-xylene relative to the olefin which allows copolymerization to compete with dissociation of the $PCl_3\cdot$ end group.

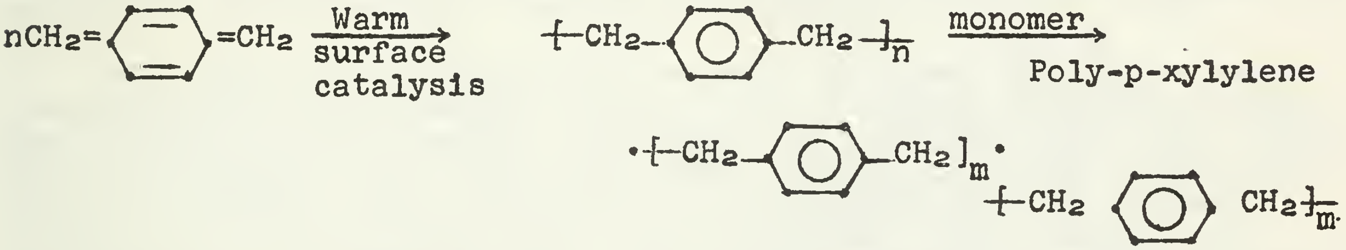
The homopolymerization of p-xylylene shows first order kinetics. The rate of monomer disappearance was followed by discharging samples of p-xylylene solution into a measured excess of iodine, and titratin the unreacted iodine. (19, 26) It was found that the reaction could be catalysed by brief introduction of a warm surface, i.e. drawing a bit of cold solution into a pipet and allowing it to fall back into the vessel which was kept at -78°. This behavior is demonstrated by figure 3, the arrow being the point of catalysis.

Figure 3 Polymerization of p-xylylene

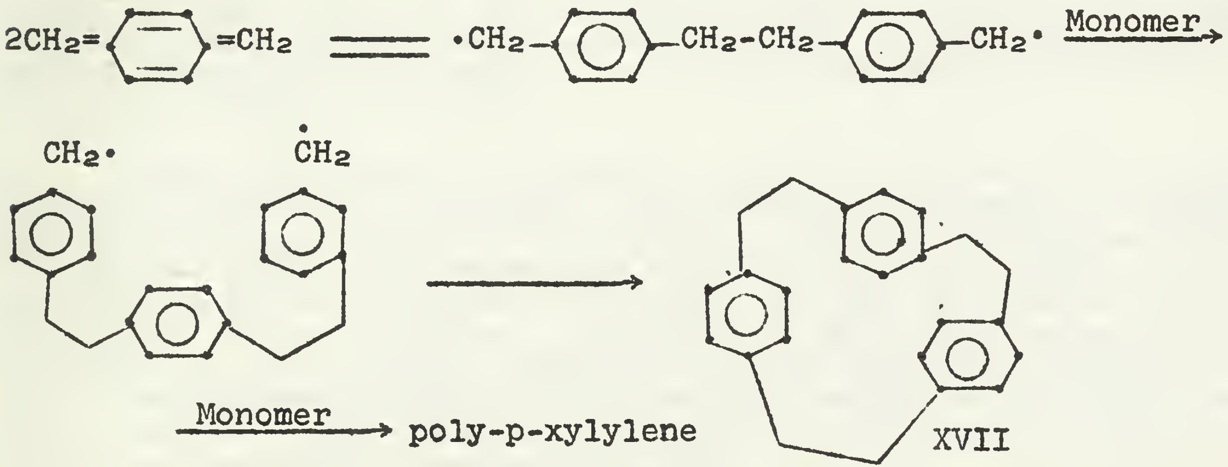


Products other than polymer are: cyclo-tri-p-xylylene, cyclo-di-xylylene, 1,4 bis-(2-p-tolyl)ethylbenzene and low molecular weight polymer. A mechanism which accounts for these products is the following:

Isothermal polymerization at -78° catalysed by a warm surface



Non isothermal conditions; solution is polymerized by warming to room temperature.



The most important reaction at low temperature is the polymerization, as Table 4 points out. As the solution warms to room temperature thermal randomization becomes a greater factor, allowing cyclization to become more important, giving a greater percentage of cyclic products.

Table 4 - Effect of temperature on Products of Polymerization

Material isolated	Experiment ⟶	A	B	C	D
cyclo-di-p-xylylene		2%	1%	1%	41%
cyclo-tri-p-xylylene		3%	15%	93%	58%
tetramer		-	0.05%	a	a
total polymer		95%	84.%	6	0.5

a) A mixture of low molecular weight products analysed by IR has cyclo-trimer as its major component.

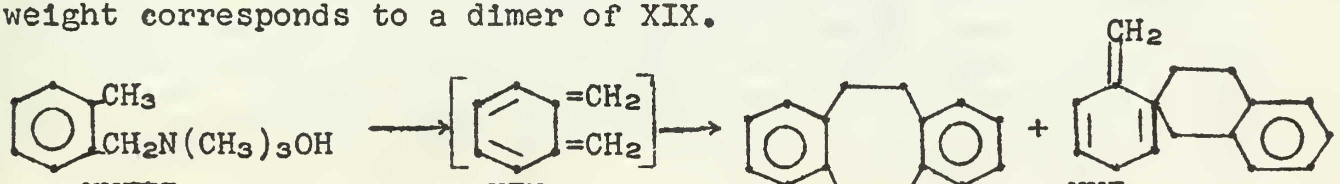
A - Polymerized at -78°; B - Polymerized by warming to room temperature; C - 0.08 molar solution diluted to 0.008 molar and warmed to toom temp.; D - dilute monomer solution added dropwise to toluene at 100°.

The initiation of polymerization depends upon the presence of sites for the reaction which are more effectively introduced into the solution by a warm surface. The introduction of such a surface cause adsorption of monomer units on to it in an end to end fashion simultaneously supplying energy of activation for polymerization to them. (27) This action causes formation of longer length, about 4 or 5 units, than is optimum for cyclization hence the sites go on to high molecular weight products with only a small percentage of two and three unit groups cyclizing.

Chain propagation is expressed by the rate law rate = -RP[M] where P is the concentration of polymerization sites M is the monomer concentration, and the product kP is an apparant rate constant for first order reaction. Plotting the various apparent rate constants versus the reciprocal of absolute temperature allowed the calculation of the activation energy, which was 8.7 Kcals.

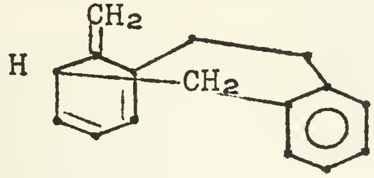
At long periods of time the reaction deviates from first order kinetics because of disappearance of polymer sites from the solution due to block polymerization. Plotting the variable 1/S=2.3/kP, where kP is the apparent rate constant stated above, gives the integrated plot of a second order rate law for the disappearance of polymer sites, 1/S-1/S,=4.6Kt/k, where K is the second order constant for coupling of benzyl-end groups (i.e., disappearance of polymer sites). The concentration of endgroups at a given time may be computed as P=Po/C1 + 2KPot), which when substituted into the rate expression leads by integration to $[Mo/M]^{2K/k}=1 + 2KPot$. The slope of ~~figure~~ such A PLOT ~~3~~ allows evaluation of 2K/k, which is 0.90. A plot of $[Mo/M]^{0.90}$ versus time gives a straight line showing the kinetics are consistant with the proposed mechanism.

Errede (28) has also isolated o-xylylene monomer in solvents. He used the pyrolytic 1,6 Hofmann elimination, the method of Winberg (29) and coworkers, to generate o-xylylene, which he quenched as before in toluene at -78°. The quaternary ammonium hydroxide (XVII) was pyrolysed in an evacuated flask at 200-250° and the pyrolysate collected in a stirred toluene container. When this solution was warmed to room temperature the products obtained were 20% cyclo-di-o-xylylene XX, 5% his co-methylbenzyl/ether, 4% esters, 12% methylbenzylacohol, and 61% of an unknown compound which by elemental analysis and molecular weight corresponds to a dimer of XIX.

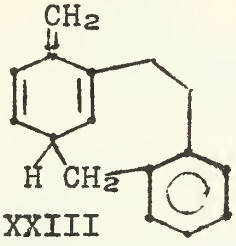


XVIII XIX XX XXI

The possible structures for this compound are XVI XXII and XXIII of which XXI is chosen as correct on the basis of the absence of NMR peaks at τ=6.3-7.0 which would correspond to a tertiary hydrogen. Similar compounds XXIV and XXV are reported from similar reactions by Gardner (30).



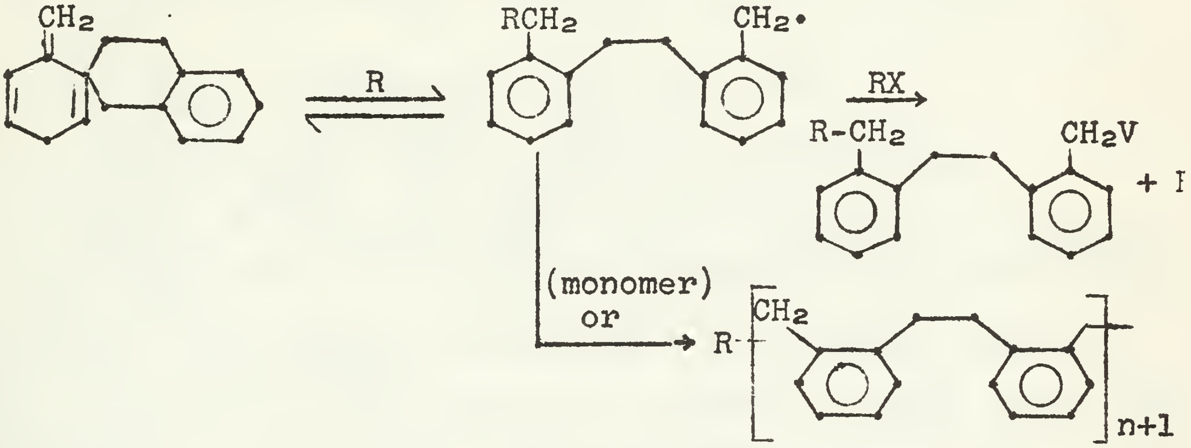
XXII



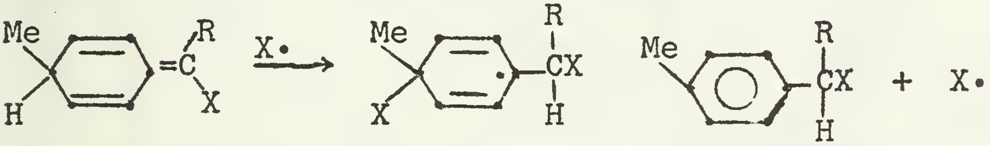
XXIII

Compound XXI is given the name spiro-o-xylylene by Errede. It is interesting in that its reactions by ionic and free radical mechanisms appear to be similar to several known reactions. The sequence (A) summarizes its free radical behavior.

(A)



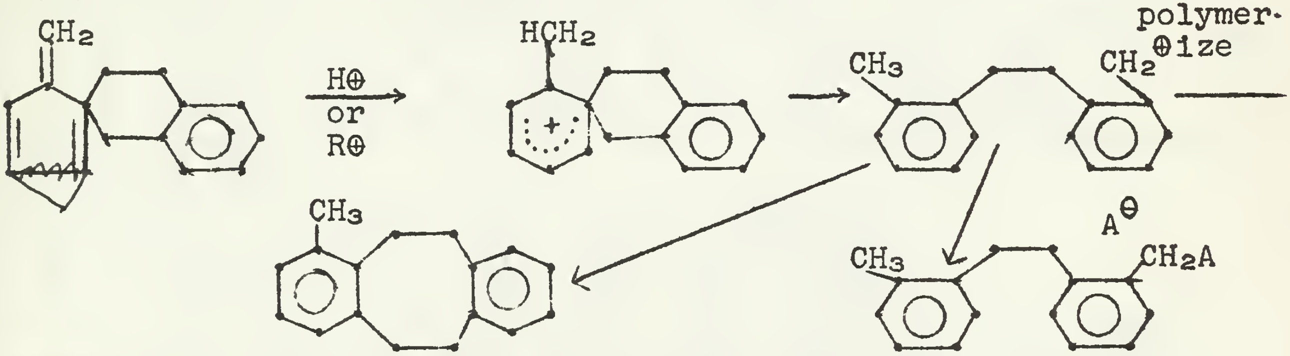
This is similar to the rearrangement of so called "semibenzenes,"(31),



The driving force being in both cases the rearomatization of the benzene nucleus.

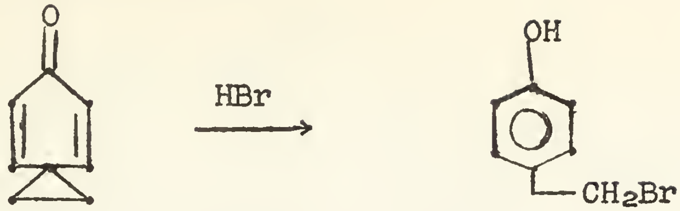
The cationic B sequence below summarizes the behavior of spiro-di-o-xylylene under acid conditions.

B)



The most probable place for the molecule to come apart is, as is shown, the methylene berdge as this leads to the most stable ionic intermediate. This cationic opening of a ring is analogous to that reported by Winstein (32) for XXVI in that it involves attack by a proton at the exomethylene group followed by rearomatizing of the

ring as a carbonium ion leaves.



XXVI

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