LIBRARY
OF THE
UNIVERSITY
OF ILLINOIS
Q
547
Il6s
1955/56

Return this book on or before the
Latest Date stamped below.

University of Illinois Library

L161—H41

Digitized by the Internet Archive
in 2012 with funding from
University of Illinois Urbana-Champaign

http://archive.org/details/organicsemi195556univ

UNIVERSITY OF ILLINOIS

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING

ORGANIC SEMINARS

1955-1956

47
.6s
55/56

SEMINAR TOPICS

CHEMISTRY 435 I SEMESTER 1955-56

Nitration With Cyanohydrin Nitrates
S. J. Strycker, September 23..... 1

Some Rearrangement Reactions of Organic Phosphites
J. C. Little, September 23..... 4

The Biosynthesis of Cholesterol
R. G. Schultz, September 30..... 7

The Chemistry of Pyrrocoline
Donald S. Matteson, September 30..... 11

Acetylenic Ethers
Albert J. Lauck, October 7..... 15

Cylic Diarsines
A. J. Reedy, October 7..... 19

The Tropolone Benzoic Acid Rearrangement
L. M. Werbel, October 14..... 23

Reduction of Aromatic Systems With Dissolved Metals
B. M. Vittimberga, October 14..... 26

Theoretical Aspects of Nuclear Magnetic Resonance
E. W. Cantrall, October 21..... 30

Nuclear Magnetic Resonance: Applications to Organic Chemistry
Louis R. Haefele, October 21..... 34

Organic Fluorine Compounds
R. J. Crawford, October 28..... 37

Organic Reactions Effected by Ionizing Radiation
Part One: Non Aqueous Systems
R. A. Scherrer, October 28..... 40

Organic Reactions Effected by Ionizing Radiations
Part Two: Aqueous Systems
W. DeJarlais, November 4..... 43

Transannular Reactions and Interactions
Kenneth Conrow, November 4..... 47

Stereochemistry of Reserpine and Deserpidine
Ralph J. Leary, November 11..... 50

The Ivanoff Reagent
Norman Shachat, November 18..... 55

JUN 28 1956
HOLMES

Steric Effects in Unimolecular Olefin-Forming Elimination Reactions
Joe A. Adamcik, November 18..... 58

A New Route to Tertiary α-Keto Alcohols
H. S. Killam, December 2..... 62

Acid Hydrolysis of Reissert Compounds
J. S. Dix, December 2..... 65

Mechanisms for the Hydrolysis of Organic Phosphates
John F. Zack, Jr., December 9..... 71

Epoxyethers
Willis E. Cupery, December 9..... 74

Reductions With Formic Acid
C. W. Schimelpfenig, December 9..... 78

Quaterenes
G. W. Griffin, December 16..... 81

New Cyclobutane Derivatives: Preparation and Reactions
J. H. Rassweiler, December 16..... 85

Isomerization of 5-Aminotetrazoles
M. E. Peterson, January 6..... 88

Structure Determination by Raman Spectroscopy
W. A. Remers, January 6..... 91

Anodic Synthesis of Long Chain Unsaturated Fatty Acids
Thet San, January 6..... 95

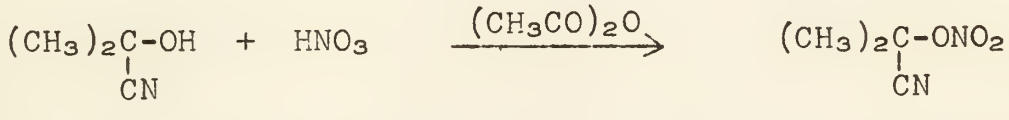
Polyacetylenic Compounds From Plants of the Compositae Family
Philip N. James, January 13..... 99

Kinetic Conformational Analysis of Cyclohexane Derivatives
Carol K. Sauers, January 13..... 103

NITRATION WITH CYANOHYDRIN NITRATES

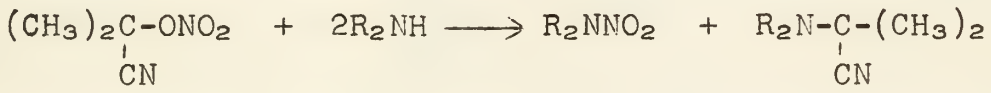
Reported by S. J. Strycker September 23, 1955

The nitrate esters of ketone cyanohydrins, I, are unique reagents for effecting nitration under alkaline conditions.[1-3] Previous nitration attempts involving the use of nitrate esters have either led to poor yields of the nitrate,[4-7] except in the case of certain active methylene compounds,[8,9] or to alkylation.[10,11] This type of compound, heretofore unknown, fulfills the structural requirements found to be necessary from a preliminary study on the nitration of amines:[12] (1) the nitrate ester should possess no α-hydrogen atoms; (2) it should contain bulky groups around the α-carbon atom to hinder bimolecular displacement reactions; and, (3) it should contain an electronegative group to weaken the oxygen-nitrogen bond.



I

Both primary and secondary amines are converted to the corresponding nitramines in excellent yields by the use of I.

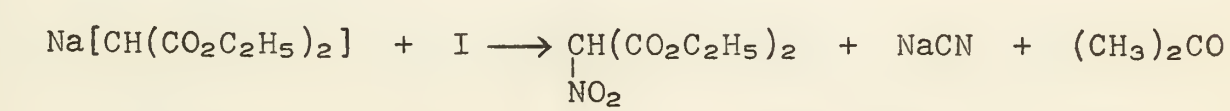


Primary amines require a solvent such as acetonitrile or tetrahydrofuran but the secondary amines serve as their own solvent. Aromatic amines and aliphatic amines with branching on the α-carbon atom are unaffected by nitrate esters.

The unique reactivity of I appears to be due to three factors:

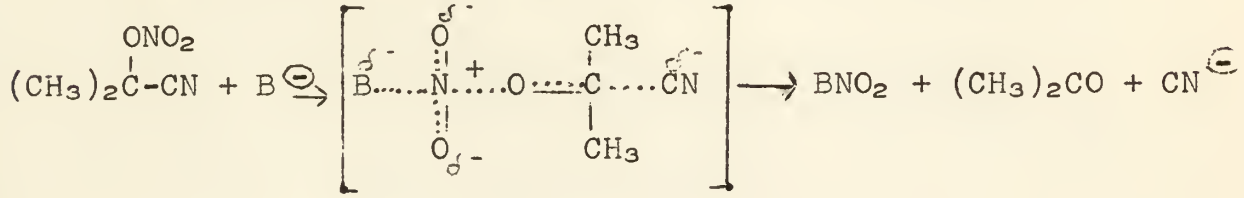
(1) the tertiary nature of the nitrate ester reduces the possibility of a simple alkylation reaction;
(2) the presence of the electronegative nitrile group weakens the oxygen-nitrogen bond, thereby favoring attack at the nitro group; and
(3) the cyanohydrin structure is easily decomposed upon attack by a nucleophilic reagent.

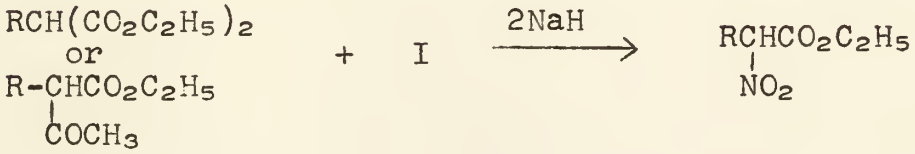
Several active methylene compounds have been nitrated effectively by means of I.[2] The solvent used was of necessity non-hydroxylic since it was found that metal alkoxides readily destroyed the nitrate ester.[3] Typical conditions are the use of a threefold excess of sodiomalonic ester in tetrahydrofuran with sodium hydride as the base.



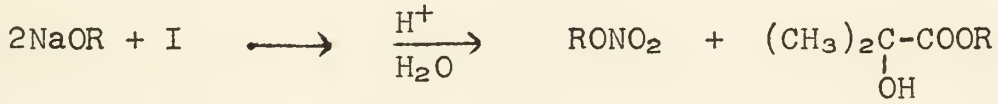
The fact that an excess of sodium hydride degraded the nitromalonic ester to ethyl nitroacetate led to the discovery that a general synthesis of α-nitroesters could be realized by means of this reagent. This method is more general and more efficient than previous ones.[13-15]

The proposed mechanism is:

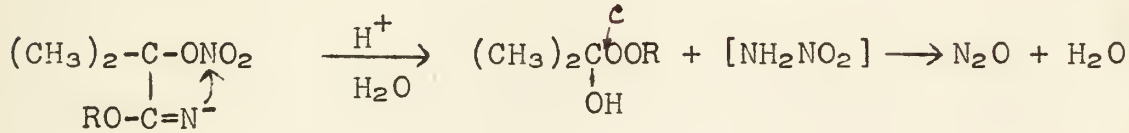




Metal alkoxides react with I to produce a nitrate ester plus the corresponding ester of α-hydroxyisobutyric acid.[3] Although the yields are low the reaction is a general one.



An intramolecular denitration step initiated by the strongly nucleophilic imide ion is proposed.



Nitrous oxide was identified by means of an infrared spectrometer. The predominance of attack at the nitrile instead of at the nitro group by the alkoxide ion is attributed to the unique structural features of I and to the fact that the alkoxide ion is a more powerful nucleophile than either amines or active methylene anions.[16]

BIBLIOGRAPHY

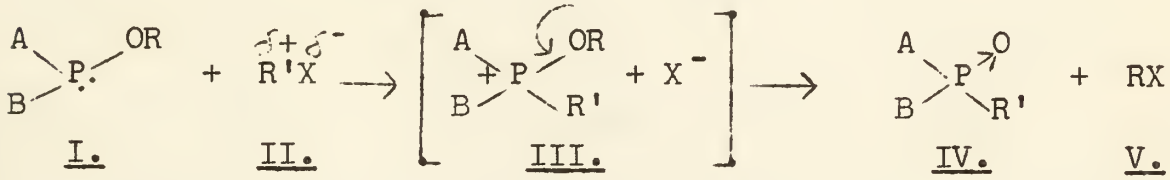
1. W. D. Emmons and J. P. Freeman, J. Am. Chem. Soc., 77, 4387 (1955).
2. W. D. Emmons and J. P. Freeman, ibid., 77, 4391 (1955).
3. W. D. Emmons and J. P. Freeman, ibid., 77, 4673 (1955).
4. H. J. Backer, Sammlung Chem. und Chem. Tech. Vortrage, 18, 365 (1912).
5. E. Bamberger, Ber., 53, 2321 (1920).
6. H. Wieland, P. Garbsch and J. J. Chavan, Ann., 461, 295 (1928).
7. R. L. Shriner and E. A. Parker, J. Am. Chem. Soc., 55, 766 (1933).

8. W. Wislicenus and A. Endres, Ber., 35, 1755 (1902).
9. W. Wislicenus and H. Wren, ibid., 38, 502 (1905).
10. E. S. Lane, J. Chem. Soc., 1172 (1953).
11. D. T. Gibson and A. K. Macbeth, ibid., 438 (1921).
12. W. D. Emmons, K. S. McCallum and J. P. Freeman, J. Org. Chem., 19, 1472 (1954).
13. W. Steinkopf and A. Supan, Ber., 43, 3248 (1910).
14. J. Schmidt and K. Widmann, ibid., 42, 1893 (1909).
15. H. Feuer, H. B. Hass and K. S. Warren, J. Am. Chem. Soc., 71, 3078 (1949).
16. G. S. Hammond, ibid., 77, 334 (1955).

SOME REARRANGEMENT REACTIONS OF ORGANIC PHOSPHITES

Reported by J. C. Little September 23, 1955

Michaelis[1a] and Arbusov[1b] have reported the reaction of trivalent phosphorus compounds having at least one ester grouping with compounds possessing a polarized covalent bond to form pentavalent phosphorus derivatives. The path of the reaction could conceivably involve two successive nucleophilic attacks, first by the phosphorus on the positive center and then by the resulting anion on the ester grouping[1c]:



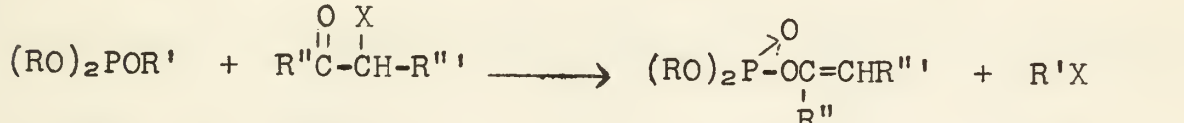
I. II. III. IV. V.

Several articles have been published recently describing preparations which utilize the Michaelis-Arbusov reaction. Table I lists a few of these applications and will serve to illustrate the versatility of the reaction.

Table I.

R	R'	X	A	B	Yield	Ref.
Et	$C_6H_5CCl_3$	Cl	EtO	EtO	94%	2
Et	Th-$(CH_2)_5$	I	EtO	EtO	61	3
Na	n-Bu	OTs	EtO	EtO	82	4
Et	$(CH_3)_2NC$	Cl	EtO	EtO	92	5
n-Pr	EtS	Cl	n-Pr	n-Pr	95	6
Et	$RCOCH_2CH_2$	$MeEt_2NI$	EtO	EtO	72	7

A reaction closely related to the Michaelis-Arbusov reaction involves the treatment of phosphites with carbonyl compounds. Prior to 1954, there had been reports that α-halo aldehydes, ketones, and esters underwent the normal Michaelis-Arbusov reaction with trialkyl phosphites[8]. However, Perkow[9] and later Allen and Johnson[10] showed that the product was a vinyl phosphate rather than the usual phosphonate:

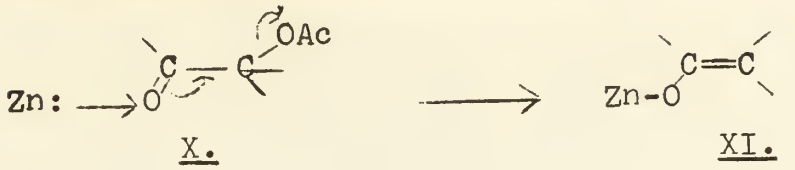


VI. R= Alkyl. VII. VIII. IX.

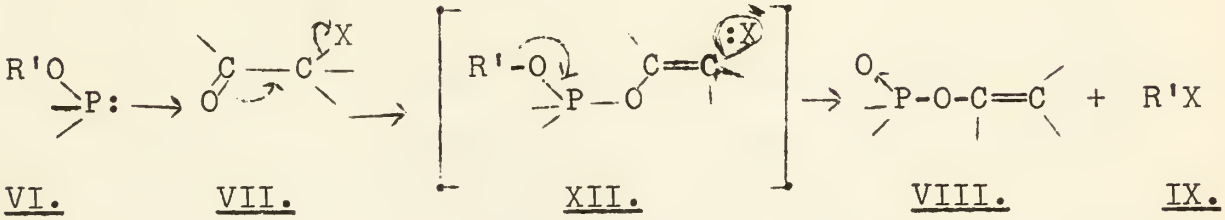
No readily acceptable reaction path has been proposed[9-11], but if we consider an initial nucleophilic attack by the phosphorus electrons, we have three alternatives: attack at the oxygen[10], carbonyl carbon[10], or at the α-carbon[9].

Initial attack on the carbonyl oxygen is not without analogy. The action of zinc on α-halo[12] and α-acetoxy[13] ketones possibly proceeds through attack on the carbonyl oxygen[13]. If we allow the phosphorus to play the same role as the zinc and

assume an additional nucleophilic attack on the ester group by the resulting anion, we have:

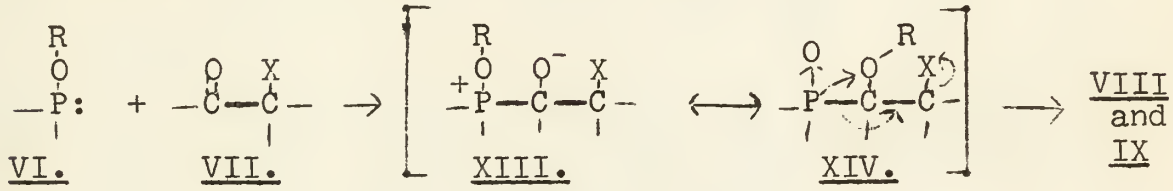


X. XI.



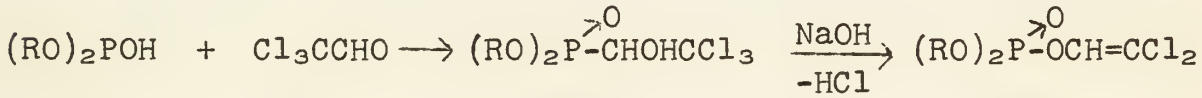
VI. VII. XII. VIII. IX.

Initial attack on the carbonyl carbon might be favored since this is the "normal" point of nucleophilic attack. In this case formation of the intermediate XIV followed by a 1,2-shift by the phosphorus from carbon to oxygen is conceivable:



VI. VII. XIII. XIV. VIII and IX

This approach draws support from observations made with a similar reaction with dialkyl hydrogen phosphites. Abramov[11,14] demonstrated the formation of hydroxyalkyl phosphonates similar to XIV from aldehydes and ketones using a basic catalyst. A striking parallel is to be found in the condensation of chloral with a series of dialkyl hydrogen phosphites in the absence of base[15]. The products in this case were O,O-dialkyl-1-hydroxyl-2,2,2-trichloroethyl phosphonates XVII whose structures were confirmed by physical data[16]. Mild treatment with alkali yielded the vinyl phosphates XVIII. These structures were confirmed independently by two groups[16,17].



XV. XVI. XVII. XVIII.

The third alternative attack by the phosphorus electrons at the α-carbon atom can be compared to the original Michaelis-Arbusov reaction described above. The observation by Perkow[9] that the chloroacetaldehydes react in the order: $Cl_3CCHO > Cl_2CHCHO > ClCH_2CHO$ seems somewhat contradictory, however.

Additional investigations have undoubtedly been already undertaken, and the final result should help clarify some of the confusion concerning the course of these reactions, particularly in the patent literature[18].

BIBLIOGRAPHY

1. (a) A. Michaelis et al., Berichte 30, 1003 (1897); 31, 1048 (1898). (b) A. E. Arbusov, Dissertation, Kazan (1905); Berichte 38, 1171 (1905); J. russ. physik-chem. Ges. 42, 395 (1910). (c) A. N. Pudovik, Dok. Akad. Nauk (SSSR) 84, 519 (1952).
2. See I. S. Bengelsdorf and L. B. Barron, J.A.C.S., 77, 2869 (1955).
3. J. P. Parikh and A. Burger, J.A.C.S., 77, 2386 (1955).
4. T. C. Myers, S. Preis and E. V. Jensen, J.A.C.S., 76, 4172 (1954).
5. T. Reetz, D. H. Chadwick, E. E. Hardy and S. Kaufman, J.A.C.S., 77, 3813 (1955).
6. D. C. Morrison, J.A.C.S., 77, 181 (1955).
7. T. C. Myers, R. G. Harvey and E. V. Jensen, J.A.C.S., 77, 3101 (1955).
8. See J. F. Allen and O. H. Johnson, J.A.C.S., 77, 2871 (1955) for various references.
9. W. Perkow et al., Naturwissenschaften 39, 353 (1952); Berichte 87, 755 (1954); 88, 662 (1955).
10. J. F. Allen and O. H. Johnson, loc. cit.
11. V. S. Abramov et al., Zhur. Obsch. Khim. USSR 22, 647 (1952).
12. C. K. Ingold and C. W. Shoppee, J. Chem. Soc., 1928, 401.
13. R. B. Woodward et al., J.A.C.S., 74, 4225 (1952).
14. V. S. Abramov et al., Dok. Akad. Nauk (SSSR) 73, 487 (1950); Zhur. Obsch. Khim. USSR 23, 257, 1013 (1953); 24, 123, 315 (1954); 25, 1141 (1955).
15. W. F. Barthel, P. A. Giang and S. A. Hall, J.A.C.S., 76, 4186 (1954).
16. W. Lorenz, A. Henglein and G. Schrader, J.A.C.S., 77, 2554 (1955); W. Lorenz, U. S. Pat. 2,701,225 (1954).
17. W. F. Barthel, B. H. Alexander, P. A. Giang and S. A. Hall, J.A.C.S., 77, 2424 (1955).
18. W. E. Craig and W. F. Hester, U. S. Pat. 2,485,573 (1949); E. K. Fields, U. S. Pat. 2,579,810 (1951); R. H. Wiley, U. S. Pat. 2,478,441 (1949). See also references 8 and 15.
19. G. M. Kosolapoff, "Organophosphorus Compounds", John Wiley and Sons, New York, 1950.
20. C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, New York, 1953.

THE BIOSYNTHESIS OF CHOLESTEROL

Reported by R. G. Schultz September 30, 1955

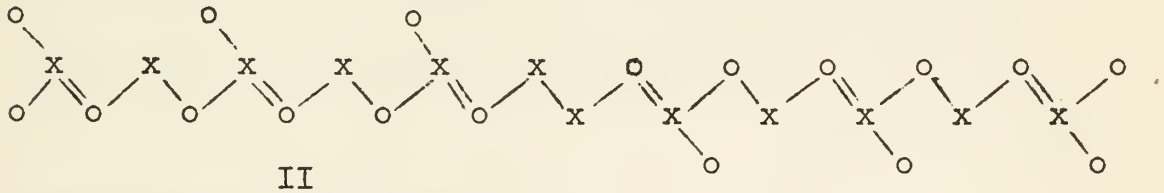
In 1934 Robinson[1] proposed that cholesterol (I) was formed by the cyclization of squalene; in 1935 Bryant[2] postulated carotene as a precursor; in 1938 Reichstein[3] suggested that nine moles of a triose condensed to form cholesterol.

It was noted as early as 1926 that the feeding of squalene (II) increased the production of cholesterol in rats by as much as 100%[4]. Squalene was known primarily as a constituent of shark livers, but it has since been found in rat liver and human fatty tissue[5].

It was shown using methyl C^{14} and carboxyl C^{14} labeled acetate that acetic acid was a precursor of cholesterol[6]. Labeled sterols were produced by several methods. Cholesterol was synthesized by feeding rats labeled acetate and then isolating the sterol from the liver[6]. Ergosterol was synthesized by incubating yeast preparations with labeled acetate[7].

Bloch[8] determined the ratio of methyl carbons to carboxyl carbons of acetate in cholesterol to be 15/12 (calc. 1.25, found 1.27). The isooctyl side chain of cholesterol was removed by well known reactions and the tetracyclic product subjected to Kuhn-Roth degradation to form two moles of acetic acid. From further degradations it was shown that carbons 18 and 19 and probably carbon 17 were from the methyl and that carbon 10 was from the carboxyl of acetate. Further systematic degradation was carried out on cholesterol. The arrangement of the isooctyl side chain was determined by Bloch[9]. Cornforth[10] degraded rings A and B of cholesterol and determined that carbons 1,3,5 and 18 came from methyl and carbons 2,4,6 and 10 from carboxyl of acetate.

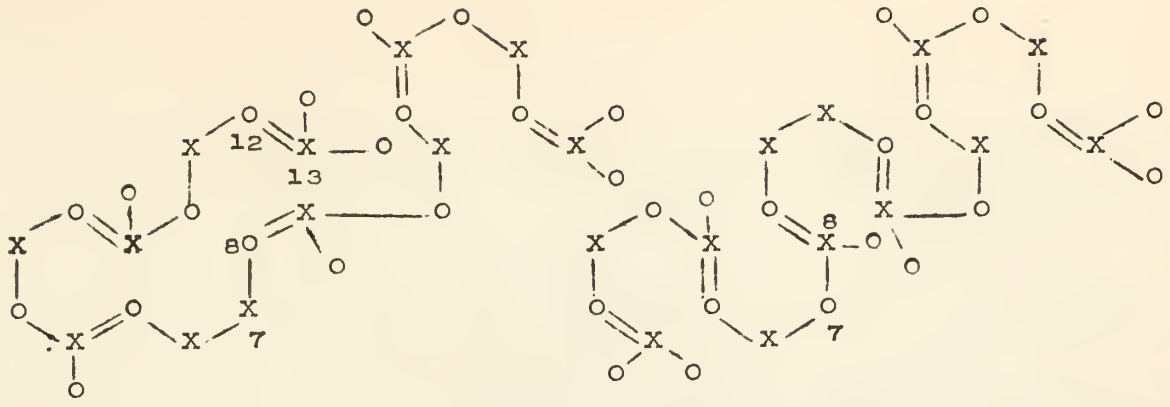
The proposal on the cyclization of squalene was re-examined. Labeled squalene was degraded and the source of each carbon atom determined.[11] The distribution of carbons in squalene (II) is shown.



II

x = from carboxyl of acetate
o = from methyl of acetate

In addition to the scheme of Robinson[1], A below, Woodward and Bloch[12] proposed an alternate method of cyclization, B below. The schemes differ in the source of carbon at C-7,8, 12 and 13 in cholesterol. To check the validity of their proposal, Bloch degraded cholesterol synthesized from methyl labeled acetate.[13] Carbon 7 was removed as CO_2 and shown to possess 75-80% of the activity as calculated from the Woodward and Bloch scheme.



A B

x = carbon from carboxyl of acetate
o = carbon from methyl of acetate

Search was now begun for other intermediates in the biosynthetic pathway. Isovaleric acid[14] and acetoacetate[15] were found to be more efficient than acetate in cholesterol formation. β-Hydroxyisovaleric acid[16], β-hydroxy-β-methylglutaric acid[17] and β,β-dimethylacrylic acid[18] were isolated as intermediates in the rat. The latter three compounds are all active in cholesterol biosynthesis.[18] Using acids labeled only at the β-carbon, radioactivity should be found only at carbons 4,8,10,14,20 and 25 and should be 4.5 times as great as the overall average for the molecule. Degradations determined[18] that the activity at carbons 10 and 25 had on the average 3.85 times the average activity. Similar labeling experiments on the gem dimethyl carbons of the five carbon acids are in agreement with the above data, but when the carboxyl carbon is labeled, complete randomization occurs.[19] This might be explained by decarboxylation and random recarboxylation. Work is currently in progress with C^{14} labeled farnesol to see whether this is an intermediate in the squalene synthesis.[19]

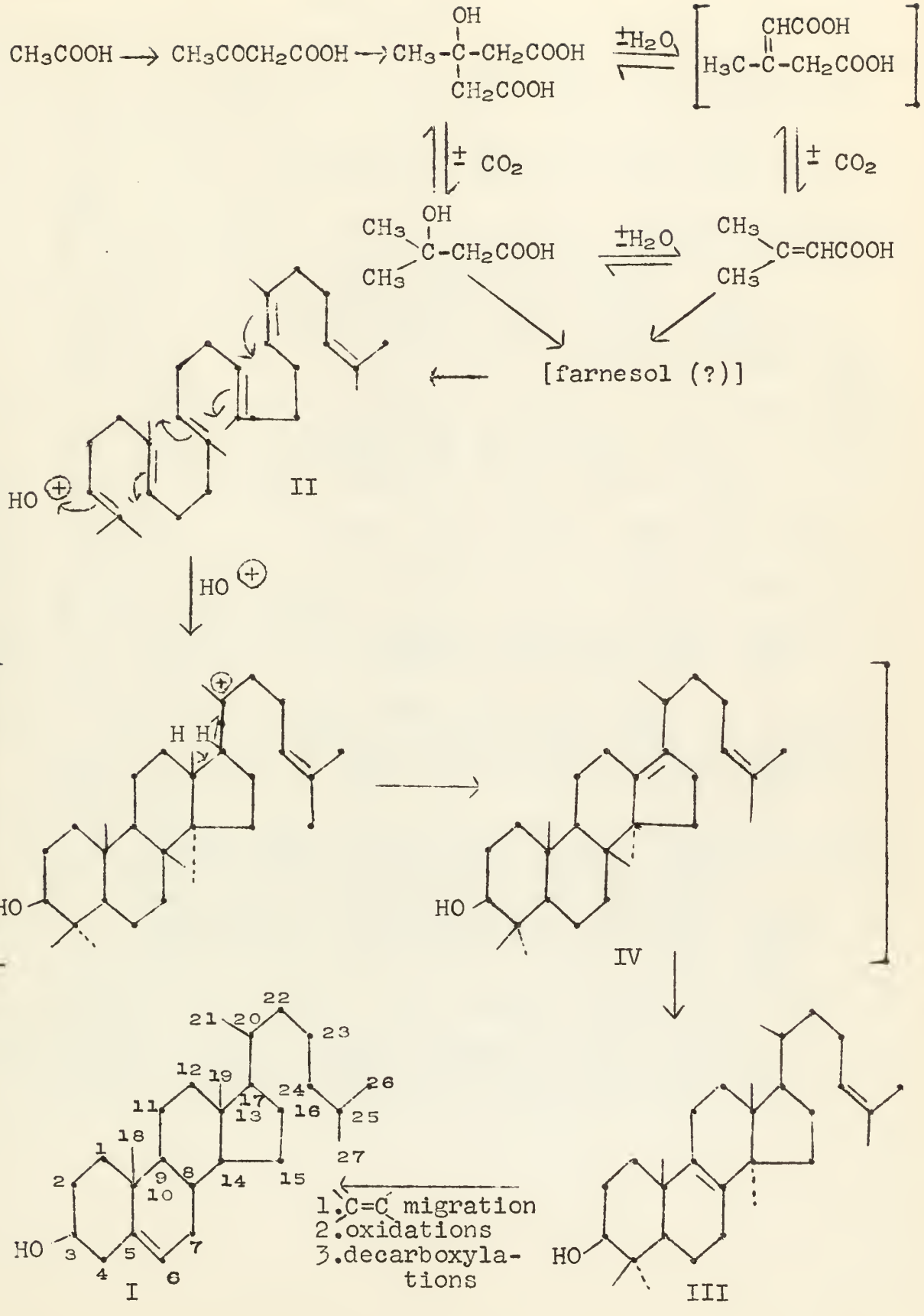
In the conversion of squalene to cholesterol the only intermediate isolated has been lanosterol (III). Bloch[19] has studied sterol synthesis in rat intestinal tissue for short time periods. After ten minutes and sixty minutes of synthesis before sacrificing the animal the relative activities of the fractions were measured. The results appear in Table I.

	% Total Activity	
	10 min.	60 min.
Unsaponifiable fraction	13	--
Squalene	60.5	1
Lanosterol	20	1.8
Cholesterol	6.3	83

Table I. Sterol Synthesis in the Intestine[19]

It can be seen that squalene and lanosterol fulfill the requirements as intermediates. Bloch[19] proposed isoeuphol (IV), as yet unisolated, in the sequence squalene → lanosterol. The overall biosynthetic pathway for cholesterol is summarized

below:


CH3COOH
CH3COCH2COOH
CH3-C(OH)-CH2COOH
CH2COOH
±H2O
CHCOOH
H3C-C-CH2COOH
± CO2
± CO2
CH3 C(OH) CH3
CH2COOH
±H2O
CH3 C=CHCOOH CH3
[farnesol (?)]
HO
II
HO
H H
HO
IV
III
HO
22
21 20 23
12 19 24 26
11 17 16 25
13
18 1 27
2 9 8 14 15
10
HO 3 5 7
4 6
I
1.C=C migration
2.oxidations
3.decarboxyla-
tions

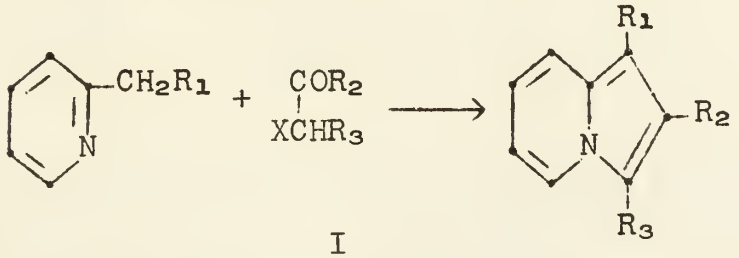
BIBLIOGRAPHY

1. R. Robinson, J. Soc. Chem. Ind., 53, 1062 (1934).
2. W. M. D. Bryant, Chem. and Ind., 1935, 907, 1082; C.A., 30, 1064^{1}, 1826^{9}.
3. T. Reichstein, Helv. Chim. Acta, 20, 978 (1937).
4. H. J. Channon, Biochem. J., 20, 400 (1926); 31, 738 (1937); R. G. Langdon and K. Bloch, J. Biol. Chem., 200, 135 (1953).
5. E. Calandra and P. Cattanet, Rev. soc. Argentina Biol. 24, 275 (1948); C.A., 43, 8494d; R. G. Langdon and K. Bloch, J. Biol. Chem., 200, 129 (1953).
6. K. Bloch and D. Rittenberg, J. Biol. Chem., 145, 625 (1942); D. Rittenberg and K. Bloch, ibid., 160, 417 (1945); K. Bloch, E. Borek and D. Rittenberg, ibid., 162, 441 (1946).
7. I. S. MacLean and D. Hoffert, Biochem. J., 20, 343 (1926); E. Schwenk, G. J. Alexander, T. H. Stoudt and C. A. Fish, Arch. Biochem. Biophys., 55, 274 (1955).
8. H. N. Little and K. Bloch, J. Biol. Chem., 183, 33 (1950).
9. J. Wuersch, R. L. Huang and K. Bloch, ibid., 195, 439 (1952).
10. J. W. Cornforth, G. D. Hunter and G. Popjak, Biochem. J., 54, 590, 597 (1953).
11. J. W. Cornforth and G. Popjak, ibid., 58, 403 (1954).
12. R. B. Woodward and K. Bloch, J. Am. Chem. Soc., 75, 2023 (1953).
13. K. Bloch, Helv. Chim. Acta, 36, 1611 (1953).
14. I. Zabin and K. Bloch, J. Biol. Chem., 185, 131 (1950); R. C. Ottke, E. L. Tatum, I. Zabin and K. Bloch, ibid., 189, 429 (1951); I. Zabin and K. Bloch, ibid., 192, 267 (1951).
15. G. L. Curran, ibid., 191, 775 (1951); R. W. Chen, D. D. Chapman and I. L. Chaikoff, ibid., 205, 383 (1953); M. Blecher and S. Gurin, ibid., 209, 953 (1954); R. O. Brady, et.al., ibid., 193, 137 (1951).
16. J. L. Rabinowitz, J. Am. Chem. Soc., 77, 1295 (1955).
17. J. L. Rabinowitz and S. Gurin, J. Biol. Chem., 208, 307 (1954).
18. K. Bloch, L. C. Clark and I. Harary, ibid., 211, 687 (1954).
19. K. Bloch, Seventh Summer Seminar in the Chemistry of Natural Products, University of New Brunswick, 1955.

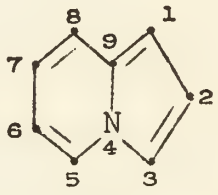
THE CHEMISTRY OF PYRROCOLINE

Reported by Donald S. Matteson September 30, 1955

Substituted pyrrocolines have been prepared from α-alkylpyridines and α-haloketones(I)[1,2,3]. Pyrrocoline(II) is best prepared by decarboxylation of 2-pyrrocolinecarboxylic acid, which is obtained from ethyl bromopyruvate and α-picoline[4].



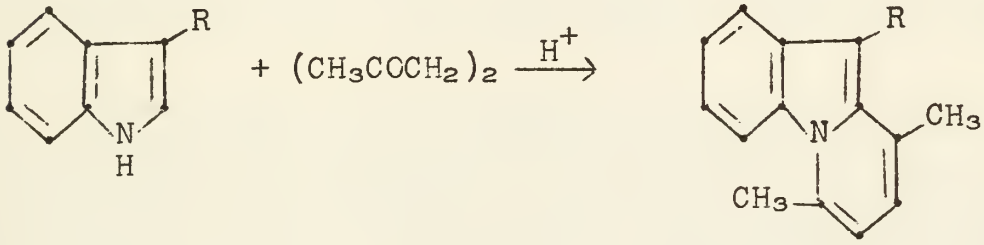
I



II

R_1 and R_3 = H or CH_3 R_2 = alkyl, aryl or -COOEt

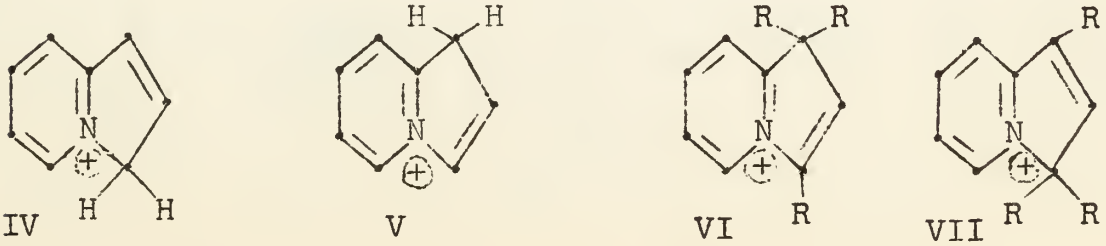
Acid catalyzed condensation of acetonylacetone with 3-substituted indoles leads to benzopyrrocolines (III)[5].



III

Molecular orbital calculations for pyrrocoline indicate a high electron density on carbon atoms 1 and 3, the higher density being on 3 [6]. By a similar calculation, the resonance energy is about 62 kcal./mole.[16]

Although the calculated electron density on the nitrogen atom is lower for pyrrocoline than for pyrrole, pyrrocoline is a base of moderate strength[5,7]. Salt formation is sometimes slow; 1% aqueous hydrochloric acid will not extract benzopyrrocolines from ether, but ether will not extract benzopyrrocolines from a 1% hydrochloric acid solution. The transformation is easily observed, since pyrrocolines are fluorescent but their salts are not. This behavior has been clarified by ultraviolet spectra, which indicate that the salts are mixtures of pyridinium compounds (IV) and (V)[7,8,15].



IV V VI VII

On alkylation with alkyl iodides, an alkyl group enters the 3-position first, followed by the 1-position[2]. On prolonged treatment, another alkyl group enters the 1- or 3-position to give a mixture of quaternary salts (VI) and (VII)[2,7].

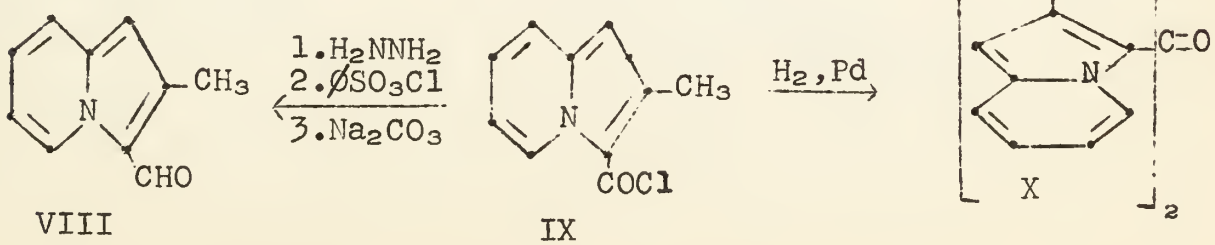
Hydrogenation over platinum or copper chromite catalysts converts pyrrocolines to their 5,6,7,8-tetrahydro derivatives; hydrogen with Raney nickel catalyst gives octahydro derivatives[9]. Zinc and acid do not attack the pyrrocoline nucleus[9]. Oxidation of pyrrocolines with hydrogen peroxide, useful in structure work, gives picolinic acid N-oxide[10].

Pyrrocoline has no acidic hydrogen. Pyrrole can be ethylated with ethanol and sodium ethoxide at 200°, a reaction in which the anion may be an intermediate; 2-phenylpyrrocoline is not ethylated under these conditions[9]. Attempts to prepare Grignard reagents analogous to the indole Grignard reagent have failed[11].

Several studies of electrophilic substitution in the pyrrocoline series have been made [2,3,11,12,13,14]. The reactions are often similar to those encountered with indole and pyrrole. Most of the work has been done on 2-methyl- or 2-phenylpyrrocoline, which are easier to make than pyrrocoline itself.

Pyrrocolines are acetylated in excellent yield by heating with acetic anhydride and sodium acetate[3,12]. The acetyl group enters the 3-position, or if this is blocked, the 1-position. Diacetylation occurs only in moderate yield on prolonged heating. Acetylation is reversible; 3-acetyl-2-phenylpyrrocoline is hydrolyzed by hydrochloric acid at room temperature[3]. Iodination also causes cleavage of the acetyl group; the hydriodic acid generated is a sufficient catalyst, and 1,3-di-iodo-2-phenylpyrrocoline is the product unless sodium acetate is added to prevent hydrolysis[11].

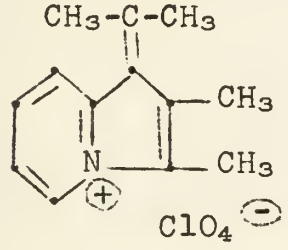
Rossiter and Saxton[2] claimed an 8% yield of 3-formyl-2-methylpyrrocoline (VIII) from the reaction of 2-methylpyrrocoline with N-methylformanilide and phosphorus oxychloride. Holland and Nayler[12] attempted to duplicate this, but obtained only 1,3-diformylpyrrocoline. They[12] prepared 2-methylpyrrocolinecarbonyl chloride (IX) by the reaction of 2-methylpyrrocoline with phosgene, and reduced it to the aldehyde by the procedure of McFadyen and Stevens. An attempted Rosenmund reduction gave di-2-methyl-3-pyrrocolinyl ketone (X).



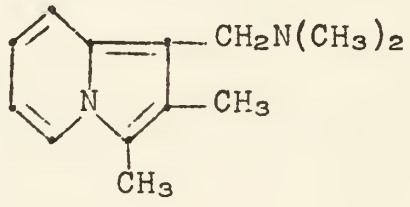
VIII IX

Pyrrocoline aldehydes and ketones show a lack of reactivity similar to pyrrole aldehydes and ketones. They do nc not give a positive Tollens test, and most do not form semicarbazones.[2] Oximes and 2,4-dinitrophenylhydrazones have been prepared, but only one carbonyl group of 1,3-diacylpyrrocolines will react with these reagents.[12] Reduction of these carbonyl groups with lithium aluminum hydride leads to alkylpyrrocolines, and is a better preparative metho than Wolff-Kishner or Clemmensen reduction.[9] Also analogous to the pyrrole series, 2-methylpyrrocolinecarboxylic acid is weaker than acetic acid and is easily decarboxylated.

Reactive aldehydes and ketones will add reversibly to pyrrocolines. Acetone and 2,3-dimethylpyrrocoline form an addition product (XI) in the presence of perchloric acid.[2] Ehrlich's reagent, p-dimethylaminobenzaldehyde, adds to pyrrocolines having a free 1- or 3-position to form blue dyes.[7] A Mannich base (XII) has been prepared from formaldehyde, dimethylamine and 2,3-dimethylpyrrocoline. Reverse aldol condensation occurs upon addition of water to the magnesium alcoholate formed from 3-acetyl-2-phenylpyrrocoline and ethylmagnesium bromide, the only products being methyl ethyl ketone and 2-phenylpyrrocoline.[11]



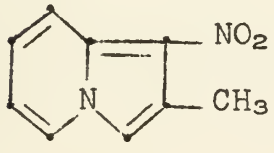
XI



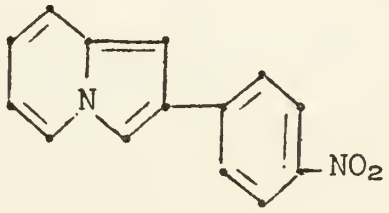
XII

Pyrrocolines are nitrosated by nitrous acid,[13] and couple with diazonium salts,[12] both in good yield.

In contrast to all the substitution reactions mentioned above, in which the 3-position is attacked in preference to the 1-position, treatment of 2-methylpyrrocoline with nitric and sulfuric acids gives 1-nitro-2-methylpyrrocoline (XIII) in 62% yield, with a 1.5% yield of the 3-isomer.[14] Under the same conditions, 2-phenylpyrrocoline is nitrated at the <u>para</u> position in the benzene ring (XIV); excess nitric acid attacks the 1-position in the pyrrocoline ring.[14]



XIII



XIV

An additional example of anomalous electrophilic substitution is the reaction of 2-phenylpyrrocoline with acetyl chloride and aluminum chloride, which leads to a mixture of 2-(p-acetylphenyl)-pyrrocoline and 1,3-diacetyl-2-phenyl-pyrrocoline.[3]

BIBLIOGRAPHY

1. A. E. Tschitschibabin, Ber. 60, 1607 (1927).
2. E. D. Rossiter and J. E. Saxton, J.C.S., 3654 (1953).
3. E. T. Borrows, D. O. Holland and J. Kenyon, J.C.S., 1069 (1946).
4. E. T. Borrows and D. O. Holland, J.C.S., 672 (1947).
5. R. Robinson and J. E. Saxton, J.C.S., 3136 (1950).
6. H. C. Longuet-Higgins and C. A. Coulson, Trans. Faraday Soc., 43, 87 (1947).
7. D. O. Holland and J. H. C. Nayler, J.C.S., 1657 (1955).
8. J. E. Saxton, J.C.S., 3239 (1951).
9. E. T. Borrows, D. O. Holland and J. Kenyon, J.C.S., 1083 (1946).
10. O. Diels and R. Meyer, Ann. 513, 129 (1934).
11. E. T. Borrows and D. O. Holland, J.C.S., 670 (1947).
12. D. O. Holland and J. H. C. Nayler, J.C.S., 1504 (1955).
13. E. T. Borrows, D. O. Holland and J. Kenyon, J.C.S., 1075 (1946).
14. E. T. Borrows, D. O. Holland and J. Kenyon, J.C.S., 1077 (1946).
15. R. Robinson and J. E. Saxton, J.C.S., 976 (1952).
16. Unpublished calculation.

ACETYLENIC ETHERS

Reported by Albert J. Lauck October 7, 1955

Introduction: Acetylenic ethers, compounds in which the triple-bond carbon is attached directly to oxygen, possess a rather unique structure. These ethers are derivatives of the "yne-ol" system which is related to the aldoketenes.

$$-C\equiv C-OH \longrightarrow -CH=C=O$$

Acetylenic ethers might be expected to show considerable reactivity since such carbonyl derivatives as ketene acetals are unusually reactive and enol ethers possess an active double-bond and are easily hydrolyzed by acids. The structurally similar acetylenic halides might be compared since in both cases the carbon-carbon triple-bond is attached directly to an atom containing unshared pairs of electrons.

Acetylenic ethers have been mentioned[1] in the early literature and also been postulated[2] as intermediates in organic reactions. The first isolation was made by Slimmer[3] when he prepared phenoxyacetylene which he described as an unstable oil which became a black, viscous mass in a few hours. It was not until 1940 when Jacobs and his coworkers[4] became interested in these compounds that a systematic investigation was begun.

Preparations:

1. $RC(Br)=CHOR' \xrightarrow{\text{Powdered KOH}} RC\equiv COR'$

R=H, R'=Me, Et, Pr, iso-Pr, Bu, Ø

R=Me, Et, C_5H_{11}, R'=Et ; R=Bu, R'=Ø

This method[3,4,5,6,7,8,9,10] involves the preparation of the β-bromo- or β-chlorovinyl ether. These vinyl ethers polymerize readily and only the trans isomer reacts smoothly with the powdered potassium hydroxide to form the desired product.

2. $ClCH_2CH(OR)_2 \xrightarrow[\text{in } NH_3]{NaNH_2} NaC\equiv COR \xrightarrow{HOH} HC\equiv COR + NaOH$

R=Me, Et, Bu

This recently developed method[11,12] affords a 60% yield from the commercially available α-chloroacetals and is practical on a large scale. The use of the bromoacetals offers no advantage. The reaction does not proceed with higher homologs. The sodium alkoxyacetylenes are extremely pyrophoric. The use of sodamide as a dehydrohalogenation agent has also been successful with β-halovinyl ethers and α,β-dihaloethyl ethers.[11]

3. $ØOC\equiv CH + HOBr \xrightarrow{\text{KOH solution}} ØOC\equiv CBr$

Bromophenoxyacetylene was prepared[13] after several attempts. The reaction mixture polymerized very readily, sometimes explosively.

Phenoxyacetylene polymerizes[3,4,14] at room temperature and must be stored at -7°, while the alkoxyacetylenes are stable at 0° for several weeks and are safe to handle. These low boiling ethers show some anesthetic properties but are toxic.[5]

Reactions: Acetylenic ethers show the usual addition reactions of the triple bond and form metallic acetylide ethers.

1. $RC{\equiv}COEt \xrightarrow[H^+]{H_2O} \left[RCH{=}C(OH){-}OEt \right] \longrightarrow RCH_2CO_2Et$

Water adds to the triple-bond when catalyzed by mineral acids to yield esters.[5,9,10,15] The inverse addition product was not found. The rate of hydrolysis of the acetylenic ethers is faster than the corresponding vinyl ethers and slower than the ketene acetals. The reaction is first order with respect to the ether and hydrogen ion concentration.[15]

2. $RC{\equiv}C{-}O{-}CH_2CH_3 \xrightarrow{120^\circ} CH_2{=}CH_2 + [RC{\equiv}C{-}OH]$

$[RC{\equiv}C{-}OH] \xrightarrow{RC{\equiv}COEt} RCH(C{\equiv}CR){-}CO_2Et$

$[RCH{=}C{=}O] \xrightarrow{R'NH_2} RCH_2C(=O){-}NHR'$

3. $CH{\equiv}COEt \xrightarrow[\text{in Ether}]{EtMgBr} BrMgC{\equiv}COEt \xrightarrow{(CH_3)_2CO} CH_3{-}C(CH_3)(OH){-}C{\equiv}COEt$

$CH_3{-}C(CH_3)(OH){-}C{\equiv}COEt \xrightarrow[Pd\cdot BaSO_4]{H_2} CH_3{-}C(CH_3)(OH){-}CH{=}CHOEt$

$CH_3{-}C(CH_3)(OH){-}CH{=}CHOEt \xrightarrow[H_2O]{H^+} (CH_3)_2C{=}CH{-}CH{=}O$

$CH_3{-}C(CH_3)(OH){-}C{\equiv}COEt \xrightarrow{10\%\ H_2SO_4} (CH_3)_2C{=}C(CH_3){-}C(=O){-}OEt$

Acetylenic ethers as Grignard reagents react with aldehydes and ketones.[5,11,16] The reaction provides an alternative to the Reformatsky reaction for the synthesis of α,β-unsaturated acids or α,β-unsaturated aldehydes when an intermediate hydrogenation stage is employed. The reactions have been applied to the systhesis of vitamin A aldehyde[17], terpene analogs[18] and

a total systhesis of cortisone.[19]

4. $2RCOOH + HC{\equiv}COEt \longrightarrow (RCO)_2O + CH_3COOEt$

This method[9,11,20] seems to be the mildest yet devised for converting a carboxylic acid into its anhydride. The reaction has also been applied to a sulfonic acid[11] and diethyl phosphate.[21]

5. $RCOOH + R'NH_2 + CH{=}COEt \longrightarrow RC(=O)-NHR' + CH_3CO_2Et$

In the presence of ethoxy- or methoxyacetylene an acid and an amine condense very smoothly to yield an amide. The reaction has also been applied to syntheses of peptides.[22]

6. $\begin{matrix} CH_2-NH_2 \\ | \\ CH_2-NH_2 \end{matrix} + EtOC{\equiv}CR \xrightarrow{HgO} \begin{matrix} CH_2-NH \\ | \quad \diagdown \\ CH_2-N \quad = \end{matrix} C-CH_2R + EtOH$

Ethoxyacetylene reacts with 1,2-diaminoethane to form the 2-substituted imidazoline. Ethoxypropyne reacts smoothly only when mercuric oxide is used as a catalyst.

BIBLIOGRAPHY

1. A. Sabanejeff and P. Dworkowitsh, Ann., 216, 279 (1883); J. U. Nef, ibid., 298, 337 (1897); J. W. Lawrie, Am. Chem. J., 36, 487 (1906); V. Grignard and H. Perrichon, Ann., 465, 84 (1928).
2. H. S. Rhinesmith, Abstracts of Papers 94th Meeting of ACS, Division of Organic Chemistry, p. 11 (1937).
3. M. Slimmer, Ber., 36, 289 (1903).
4. T. L. Jacobs, R. Cramer and F. T. Weiss, J. Am. Chem. Soc., 62, 1849 (1940).
5. T. L. Jacobs, R. Cramer and J. E. Hanson, ibid., 64, 223 (1942).
6. A. E. Favorkii and M. N. Shchukina, J. Gen. Chem. Russia, 15, 394 (1945); C.A., 40, 4347 (1946).
7. M. N. Shchukina, ibid., 18, 1350 (1948); C.A., 43, 2158 (1949).
8. D. A. Dorp, J. F. Arens and O. Stephenson, Rec. Trav. chim., 70, 289 (1951).
9. Miss J. Ficini, Bull. soc. chim., [5], 21, 1367 (1954).
10. J. F. Arens, Rec. Trav. chim., 74, 271 (1955).
11. G. Eglinton, E. R. H. Jones, B. L. Shaw and M. C. Whiting, J. Chem. Soc., 1860 (1954).
12. W. S. Johnson, "Organic Synthesis", John Wiley and Sons, Inc., New York, N. Y., 1954, Vol. 34, p. 46.
13. T. L. Jacobs and W. J. Whitcher, J. Am. Chem. Soc., 64, 2635 (1942).

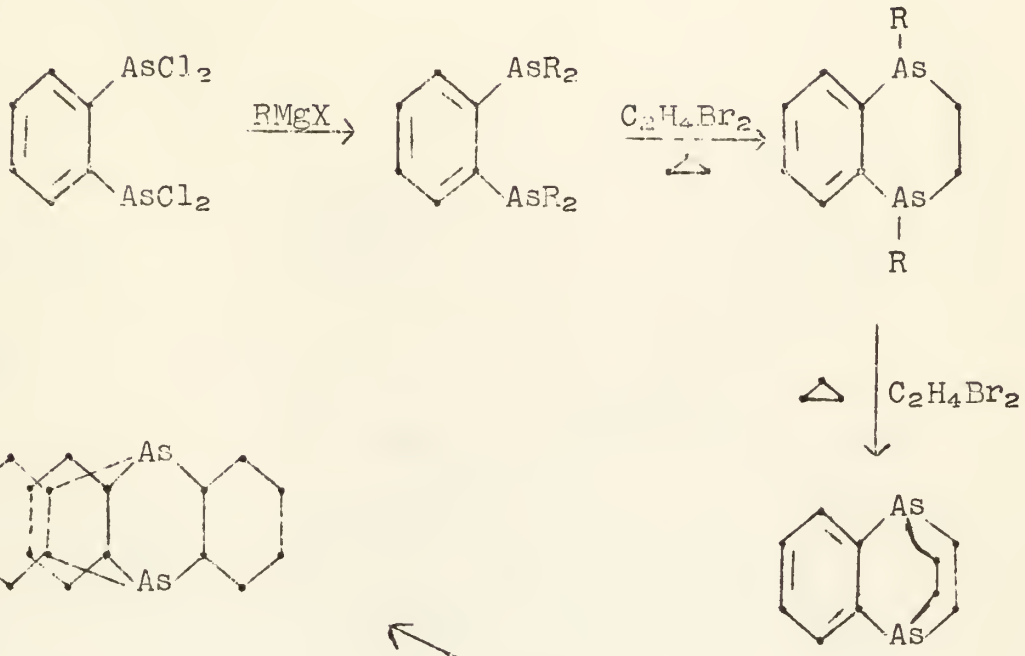
14. P. Tuttle, Jr. and T. L. Jacobs, Abstracts of Papers 104th Meeting of ACS, 13M, (1942).
15. T. L. Jacobs and S. Searles, Jr., J. Am. Chem. Soc., 66, 686 (1944).
16. I. Heilbron, E. R. H. Jones, M. Julia and B. C. L. Weedon, J. Chem. Soc., 1823 (1949).
17. D. A. Dorp and J. F. Arens, Nature, 160, 189 (1947).
18. G. R. Clemo and B. K. Davison, J. Chem. Soc., 447 (1951).
19. L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. E. Johns and J. M. Constantin, J. Am. Chem. Soc., 74, 4974 (1952).
20. J. F. Arens and P. Modderman, Nederland. Akad. Wetenschap, 53, 1163 (1950); C.A., 45, 6152 (1951).
21. J. F. Arens and T. Doornbos, Rec. Trav. chim., 74, 79 (1955).
22. J. F. Arens, ibid., 74, 769 (1955).

CYLIC DIARSINES

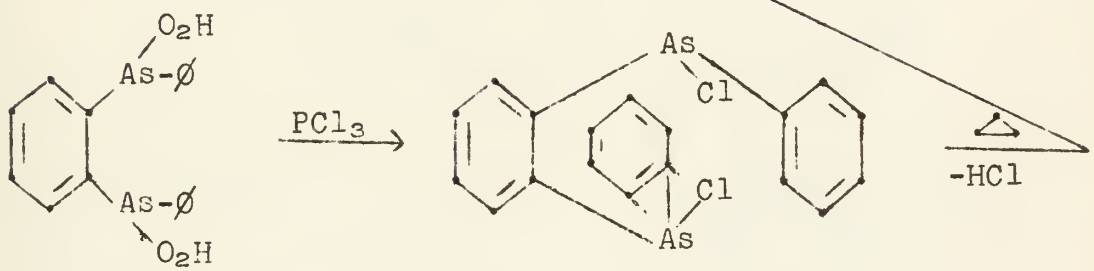
Reported by A. J. Reedy October 7, 1955

SYNTHESES

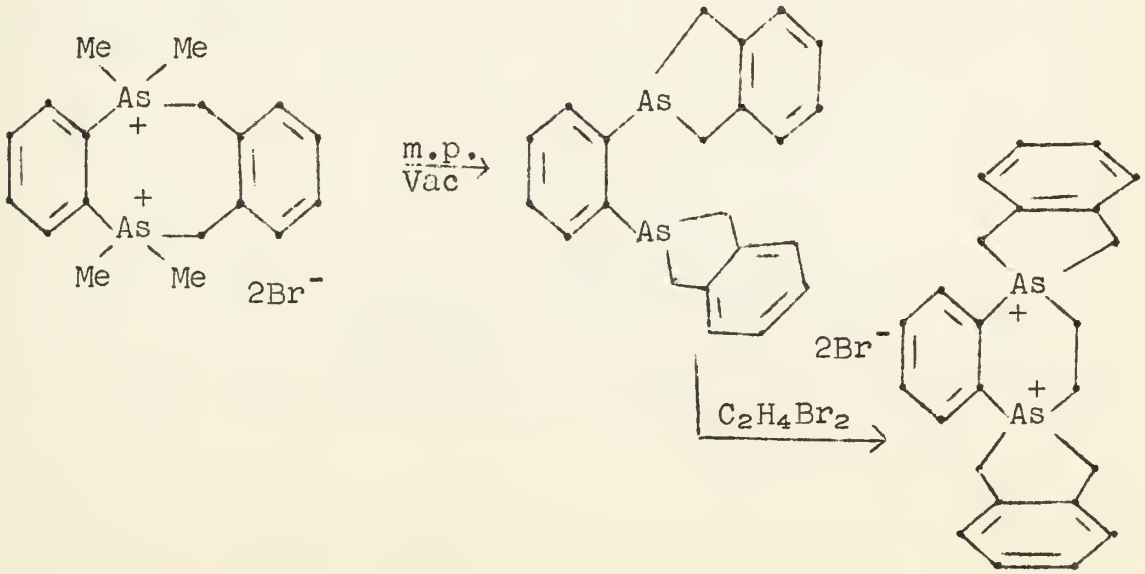
(1,2,3,4)

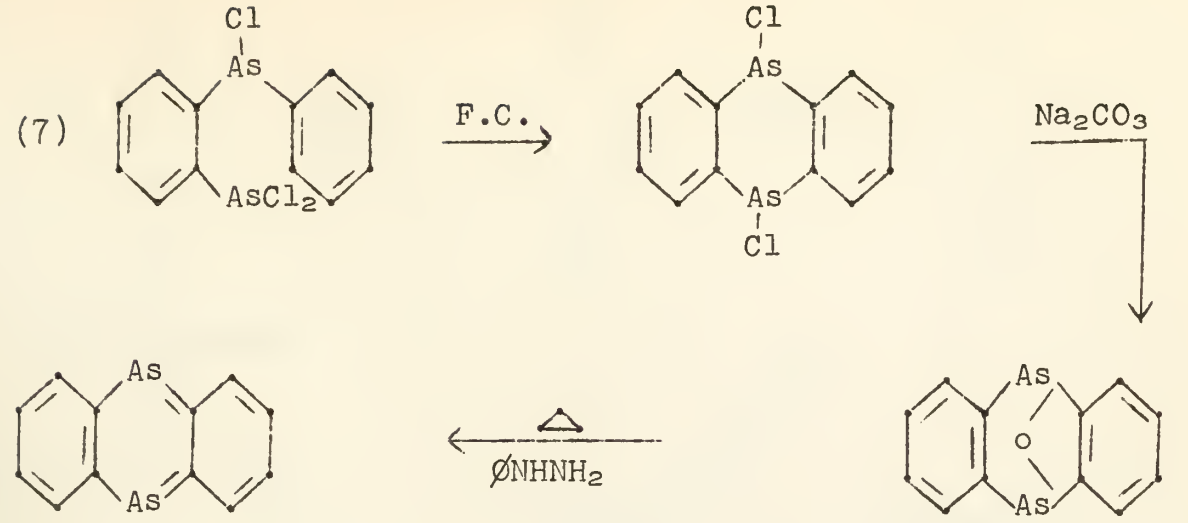


(5)

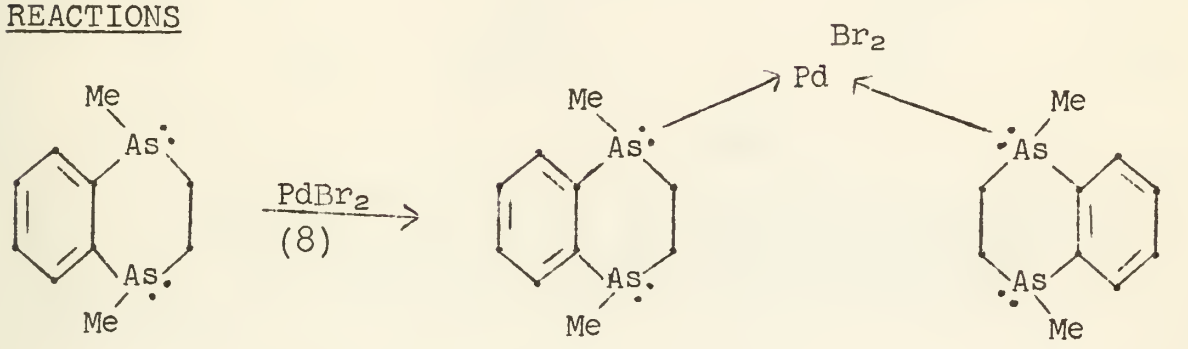


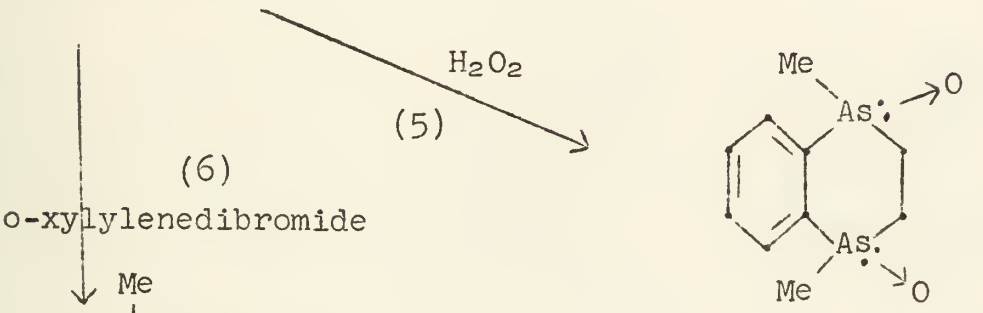
(6)



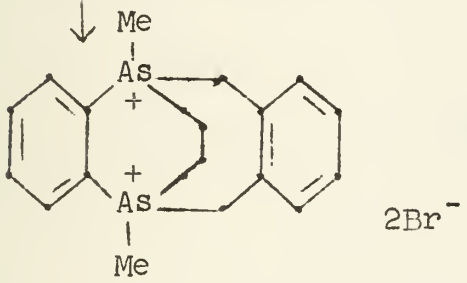


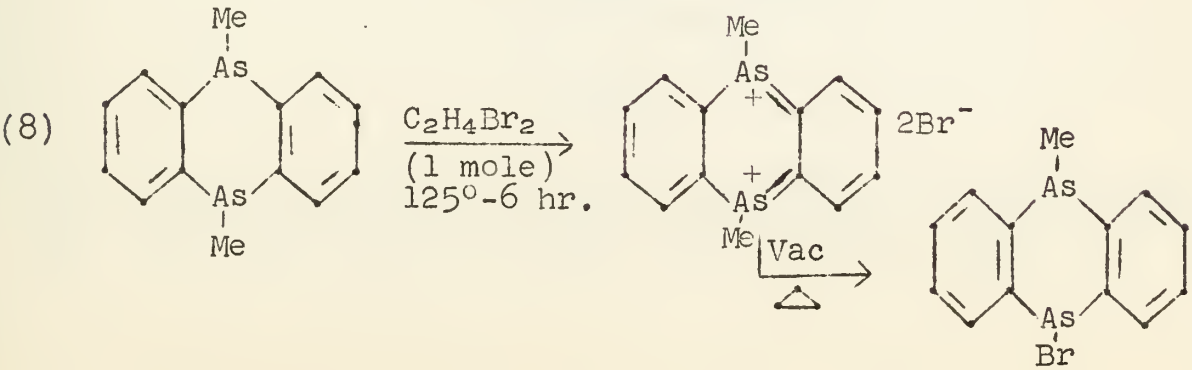
REACTIONS



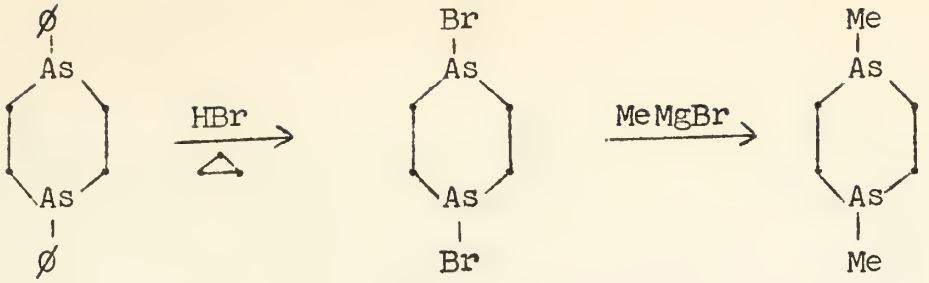


(6)
o-xylylenedibromide





(9)



STEREOCHEMISTRY

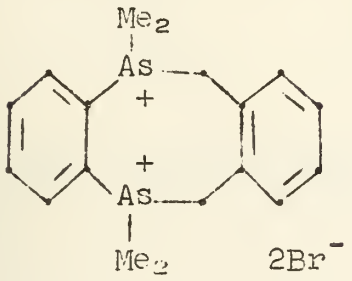


Fig. 1

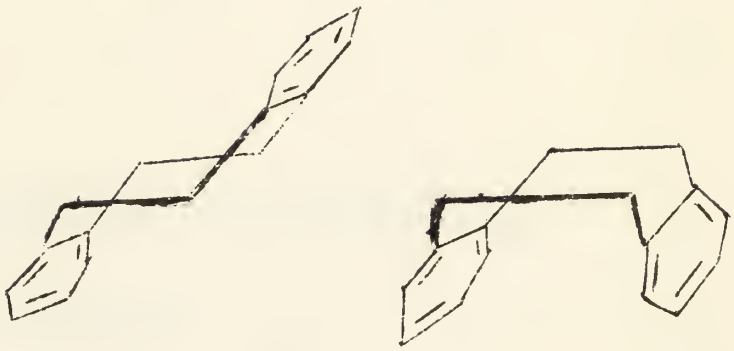
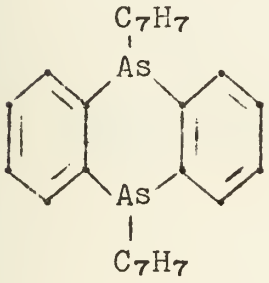
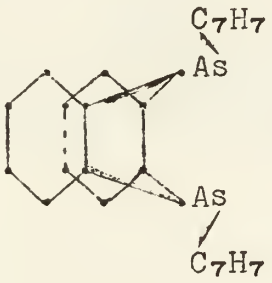


Fig. 2

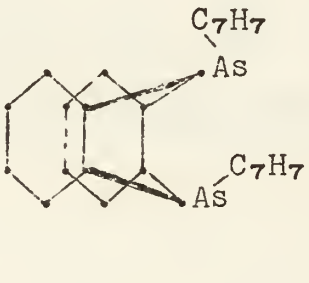
The horizontal plane in Fig. 2 corresponds to the plane of Fig. 1 comprised of the two As-CH_2- groups (substituents omitted). The benzene ring of the o-xylylene group tilts above or below this plane. This results in geometric isomerism.[6]



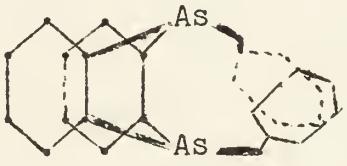
(II)



(IIa)

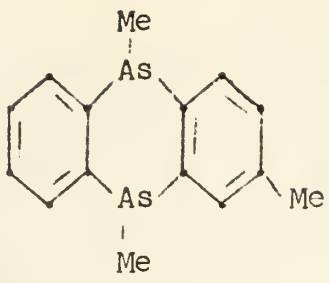


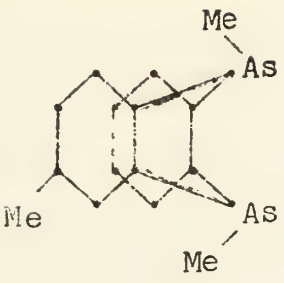
(IIb)

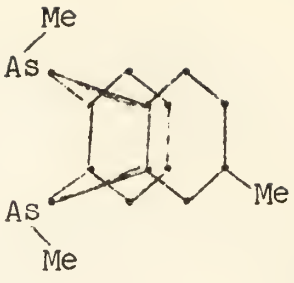


(IIc)

The triangular pyramidal structure of trivalent arsenic causes II to fold about the As-As axis, resulting in isomers IIa and IIb. The other possible isomer, IIc, could not exist.[8,10]







(III)

(III) exhibits optical activity.[8] The asymmetry of the molecule is due to the folding about the As-As axis.

BIBLIOGRAPHY

1. L. Kalb, Ann., 423, 72 (1921).
2. J. Chatt and F. G. Mann, J. Chem. Soc., 1939, 610.
3. F. G. Mann and F. C. Baker, J. Chem. Soc., 1952, 4142.
4. A. J. Quick and Roger Adams, J. A. C. S., 44, 805 (1922).
5. N. P. McCleland and J. B. Whitworth, J. Chem. Soc., 1927, 2753.
6. R. H. Jones and F. G. Mann, J. Chem. Soc., 1955, 405.
7. L. Kalb, Ann., 423, 39 (1921).
8. R. H. Jones and F. G. Mann, J. Chem. Soc., 1955, 411.
9. R. H. Jones and F. G. Mann, J. Chem. Soc., 1955, 401.
10. H. Gilman, ORGANIC CHEMISTRY I, 431 (1938).
11. H. S. Elins, Studies in the Synthesis of Some Arsenic Analogs of Fluorescein, Ph.D. Thesis, University of Illinois, (1949).

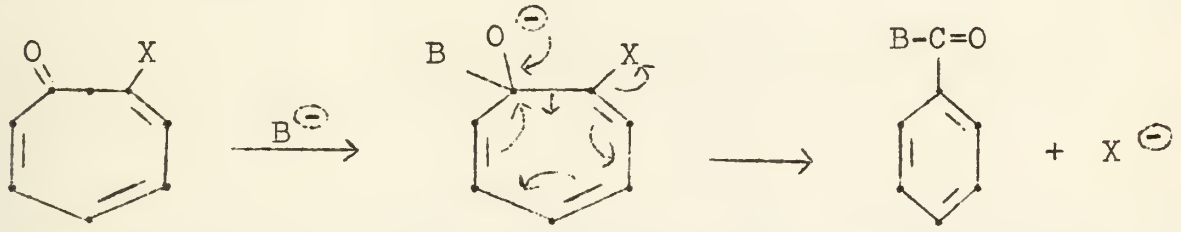
THE TROPOLONE BENZOIC ACID REARRANGEMENT

Reported by L. M. Werbel October 14, 1955

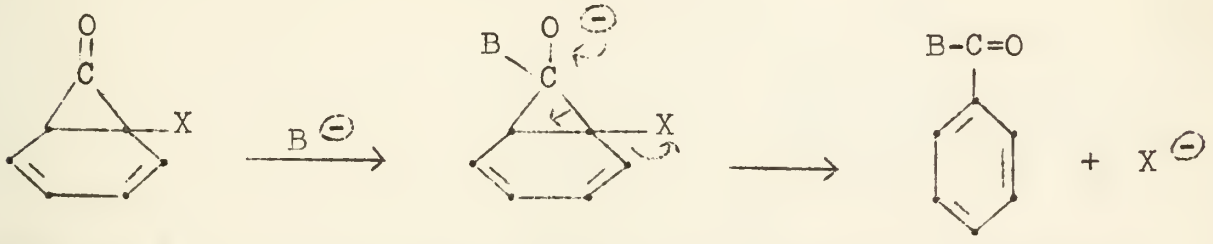
Perhaps the most important reaction of the tropolone system is its alkaline rearrangement to a benzenoid system. This is most valuable as a tool in structure proof of those natural products containing the ring system, and may also be significant in biogenesis of these materials.

Numerous mechanisms have been advanced to explain this phenomenon. The more noteworthy of these follow.

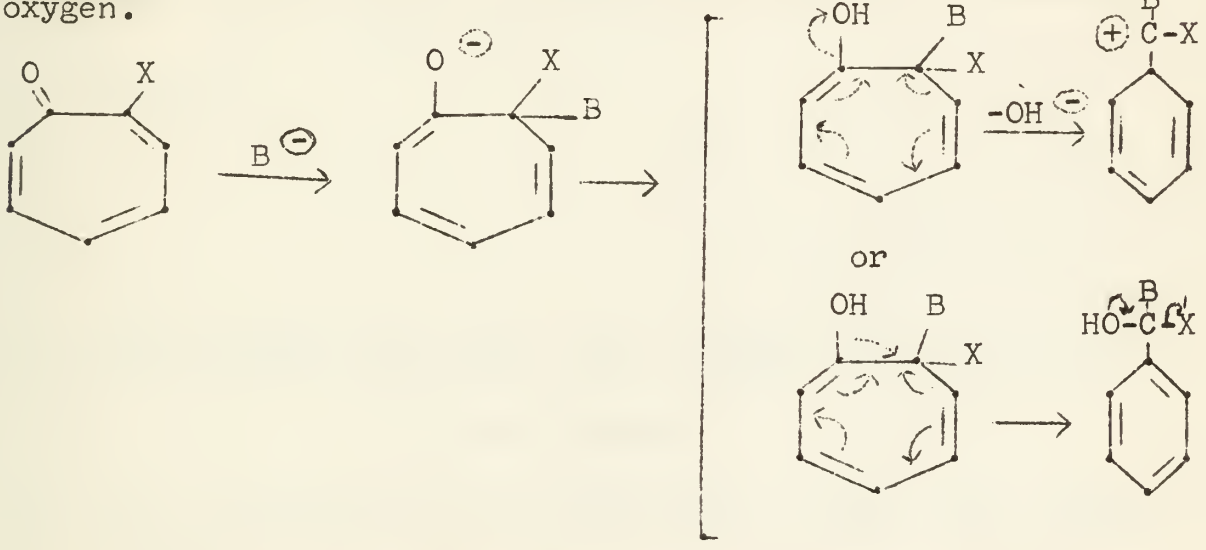
Mech. 1[1,2,7,8]--involving C_1 attack.



Mech. 1A[3,4]--a modification involving the Faworskii type norcaradienone intermediate.

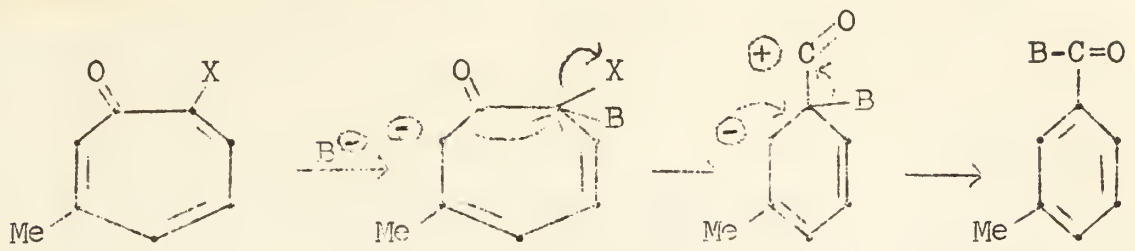


Mech. II[5]--involving C_2 attack and displacement of carbonyl oxygen.



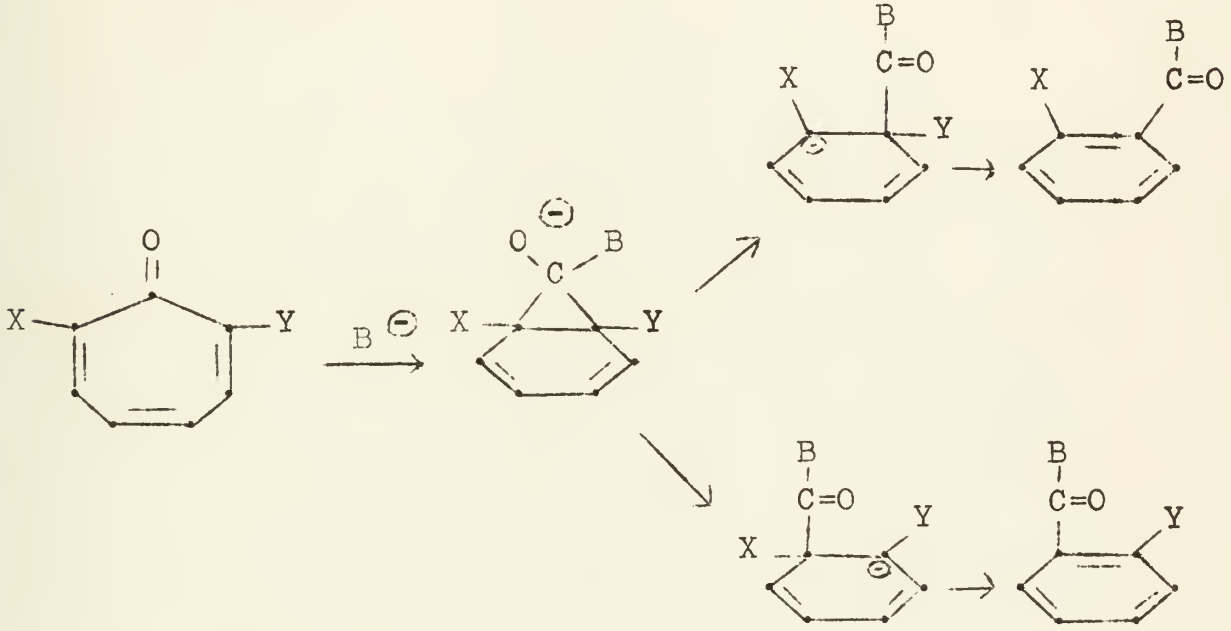
This is advanced to explain elimination of the stronger base, $OCH_3^{\ominus}$, in molecules such as 3,5,7-tribromo- or trichloro-tropolone methyl ether, by providing a situation where elimination of X is not a product determining factor.

Mech. IIA[6]--C2 attack without oxygen rearrangement.



Doering and Denney[9] using labelling studies have recently demonstrated that C_1 of the carbonyl group becomes the carbon of the carboxylic acid in the rearrangement product. This now excludes all mechanistic hypotheses wherein a carbon other than that of the carbonyl function emerges from the ring to become the carboxyl group. Mechanisms such as II can no longer be considered.

They propose a modification of Mech. IA including assignment of a separate transition state to the elimination step thus making the hypothesis compatible with the characteristic "insensitivity to base strength of leaving substituent".



Unfortunately an ideal pair of compounds with which to test this double transition state mechanism is not available.

BIBLIOGRAPHY

1. R. D. Haworth and P. R. Jeffries, J. Chem. Soc., 1951, 2067.
2. Nozoe, Kitahara and Masamune, Proc. Japan Acad, 27, 649 (1951).
3. W. von E. Doering and L. H. Knox, J. Am. Chem. Soc., 73, 828 (1951).

4. R. B. Loftfield, J. Am. Chem. Soc., 72, 633 (1950).
5. W. von E. Doering and L. H. Knox, J. Am. Chem. Soc., 74, 5683 (1952).
6. P. Akroyd, R. D. Haworth and P. R. Jeffries, J. Chem. Soc., 1954, 288.
7. J. W. Cook, R. A. Raphael and A. I. Scott, J. Chem. Soc., 1952, 4416.
8. A. W. Johnson, J. Chem. Soc., 1954, 1331.
9. W. von E. Doering and D. B. Denney, J. Am. Chem. Soc., 77, 4619 (1955).

REDUCTION OF AROMATIC SYSTEMS WITH DISSOLVED METALS

Reported by B. M. Vittimberga October 14, 1955

Alkali metals are readily dissolved by ammonia and lower primary amines. Such systems of dissolved metals are very powerful reducing agents for homogeneous phase reductions.[1] Reductions by these systems are thought to proceed by the addition of electrons resulting from the ionization of metal atoms.[2]

Unsaturated hydrocarbons are reduced by alkali metals to yield initially organo-metallic compounds which are either stable or ammonolysed in the presence of liquid ammonia depending on the acidity of the hydrocarbon involved.[3]

Diphenyl ethers are cleaved by sodium in liquid ammonia to form derivatives of benzene and sodium phenoxide.[4,5]

The proposed mechanism is:

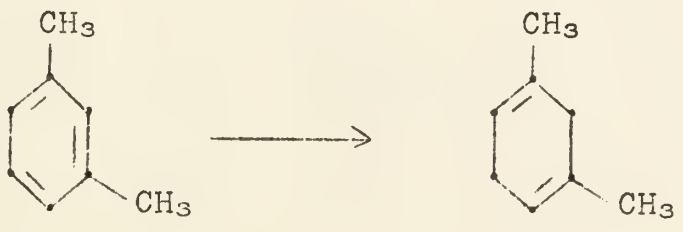
$$Ar\text{-}O\text{-}Ar + 2Na^+ + 2e^- \longrightarrow Are^- + Ar\text{-}Oe^- + 2Na^+$$

$$Are^- + NH_3 + Na^+ \longrightarrow ArH + NH_2^- + Na^+$$

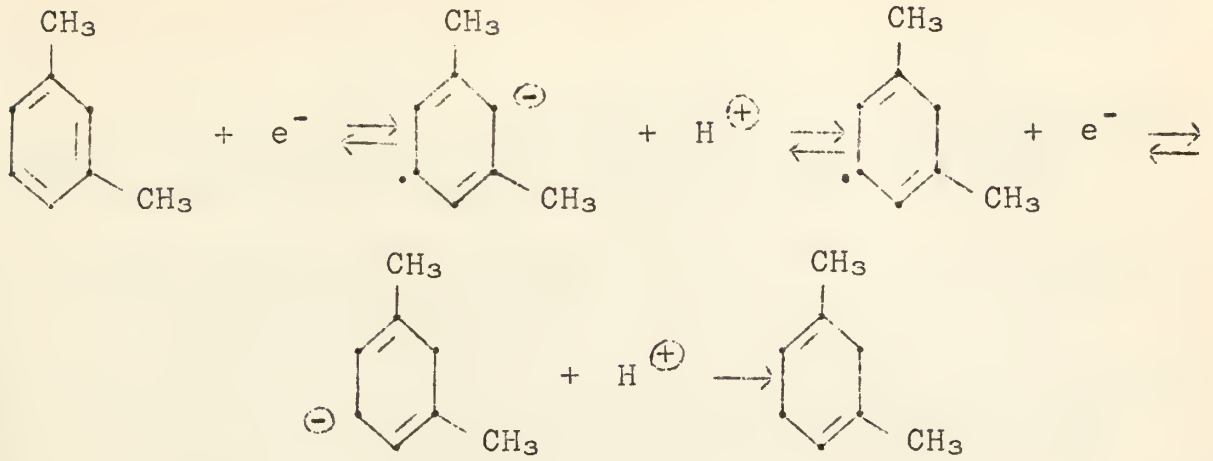
The type of substitution on the aromatic rings greatly influences the position of electron attack. Accordingly, the ring which is most negative will be the one that is attached to the oxygen after cleavage.

In 1944, Birch[6] showed that if available hydrogen were present in these reducing systems, different reducing properties were observed. Reaction of aromatic systems with sodium and alcohol in liquid ammonia caused reduction to take place at the aromatic nucleus to form a dihydroaromatic derivative.

Many aromatic systems have been reduced[6,7] successfully in this manner. A typical reaction is that of m-xylene.



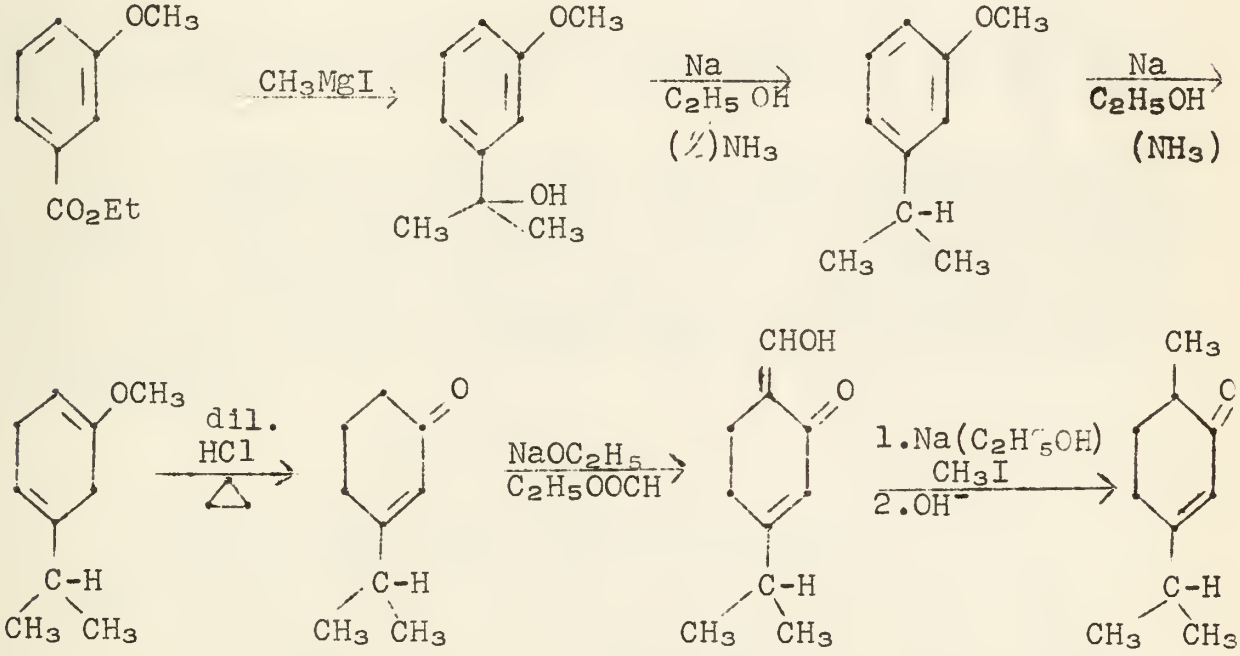
A probable mechanism for this reaction is:[8]



An alternative reaction path in some cases may involve the formation of the di-anion $Ar^{=}$ which can then add two protons from the alcohol to give the stable hydrogenated product.

Vinyl carbinol type compounds have been found[9] to be reduced to hydrocarbons by sodium and alcohol in liquid ammonia.

Application of these methods for synthetic purposes has recently become more extensive.[10,11,12] Another synthesis of carvone is:[10]



Although the Birch reaction has been used successfully with many aromatic compounds, in some cases the yields have been very low, as for example in the following conversion:

Recently[13,14] it was determined that if lithium was used instead of sodium and if the alcohol was added last much higher yields were realized in most instances.

The enhanced yields obtained with lithium appear to be due to the following factors:[13]

(1) The higher concentration of lithium due to its greater solubility.
(2) The slower rate of reaction of lithium with alcohols.
(3) The higher normal reduction potential of lithium.
(4) The greater tendency for lithium to react to form addition compounds.[15,16,17]

Further work on these reactions has shown that lithium in low molecular weight amines will selectively reduce aromatic hydrocarbons to monoolefins.

Naphthalene is converted mainly to 9,10-octalin.

The amine most commonly used in this reduction is ethylamine. Other amines which are equally satisfactory are methyl- and n-propylamines.

The mechanism for this reduction is postulated as being a rapid 1,4-addition of lithium. The organo-metallic compound so produced then reacts with the solvent to form a 1,4-dihydro product. In the basic medium this product rearranges to the more stable conjugated diene system. 1,4-Addition of lithium then reoccurs. Only very small quantities of the completely hydrogenated products are formed since 1,2-addition is slow in comparison.

BIBLIOGRAPHY

1. P. Lebeau and M. Picon, Comp. rend., 159, 70 (1914).
2. C. A. Kraus, Chem. Rev., 8, 251 (1931).
3. C. B. Wooster and J. F. Ryan, J. Am. Chem. Soc., 54, 2419 (1932).
4. P. A. Sartoretto and F. J. Sowa, ibid., 59, 603 (1937).
5. A. L. Kranzfelder, J. J. Verbanc and F. J. Sowa, ibid., 59, 1488 (1937).

6. A. J. Birch, J. Chem. Soc., 430 (1944).
7. A. J. Birch, A. R. Murray and H. Smith, ibid., 1945 (1951).
8. A. J. Birch, ibid., 1551 (1950).
9. A. J. Birch, ibid., 809 (1945).
10. A. J. Birch and S. M. Mukherji, ibid., 2531 (1949).
11. A. J. Birch, ibid., 367 (1950).
12. A. J. Birch, J. A. K. Quartey and H. Smith, ibid., 1768 (1952).
13. A. L. Wilds and N. A. Nelson, J. Am. Chem. Soc., 75, 5360 (1953).
14. A. L. Wilds and N. A. Nelson, ibid., 75, 5366 (1953).
15. R. A. Benkeser, R. E. Robinson, D. M. Sauve and O. H. Thomas, ibid., 77, 3230 (1955).
16. R. A. Benkeser, C. Arnold, Jr., R. F. Lambert and O. H. Thomas, Abstracts 128th Meeting Am. Chem. Soc., 70-O (1955).
17. R. A. Benkeser, G. Schroll and D. M. Sauve, Abstracts 127th Meeting Am. Chem. Soc., 21N (1955).

THEORETICAL ASPECTS OF NUCLEAR MAGNETIC RESONANCE

Reported by E. W. Cantrall October 21, 1955

In 1952, Felix Bloch and E. M. Purcell were awarded the Nobel Prize in Physics for their discovery of nuclear magnetic resonance, a phenomenon[1,2,3,4,5,6] which occurs when a substance containing magnetic nuclei is placed under the influence of two mutually perpendicular magnetic fields, one a stationary field and the other oscillating. The strength of the first and the frequency of the latter are matched in such a way that these microscopic magnets are caused to precess about their axes of rotation. The frequency at which precession occurs is termed the Larmor frequency, and the substance is said to be in a state of resonance.

Consideration of a simple case may serve to clarify what is meant by precession and resonance frequency and how these phenomena are brought about. In Figure 1 below, a series of arrows is used to represent microscopic protonic magnets, i.e., the protons found in some source of hydrogen atoms, such as water. Just as current passing through a loop of wire produces a magnetic field about the wire, the spin of the proton produces a magnetic moment, μ_p, in the direction of the axis of rotation. Let the head of the arrow be the north pole of the nuclear magnets and the top of the stationary magnet be its south pole. When the substance is put under the influence of this field of strength H_o, there is immediate space quantization which limits the alignment of these microscopic magnets to two orientations; i.e., parallel and anti-parallel to the direction of the stationary field. The number of orientations possible depends upon the spin of the nucleus and will, for the general case, be $(2I + 1)$, where I is the nuclear spin. When the oscillating field, H_1, (acting in the direction of the X-axis) is turned on, those magnets with their arrows pointed downward experience a torque, $(-\mu_p H_o \sin\theta)$. The energy required to completely turn an arrow which has its direction opposed to that of the stationary field is represented by

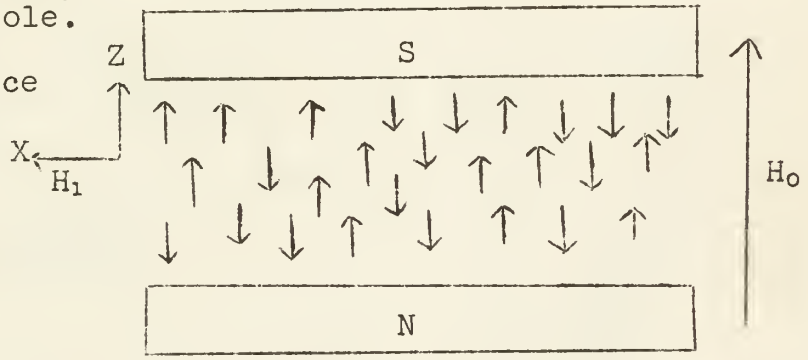


Figure 1.

$$W = -\int_0^{180^\circ} \mu_p H_o \sin\theta d\theta \qquad (1)$$

Bloch and Purcell have shown that the energy required to effec this transformation may also be expressed in terms of the fundamental energy equation

$$E = h\nu$$

where h is Planck's constant and ν is the frequency of the oscillating field when the substance is in a state of resonance.

Equating (1) and (2):

$$H_o = \frac{1}{2} \cdot \frac{h\nu}{\mu_p} \qquad \text{for the proton} \qquad (3)$$

$$H_o = I \cdot \frac{h\nu}{\mu} \qquad \text{for the general case} \qquad (4)$$

Associated with the precessing nucleus is an alternating magnetic flux, alternating in the present example across the XZ-plane. This magnetic flux may be detected by the voltage it induces in a coil of wire wrapped about the sample and at right angles to that of the alternating magnet.

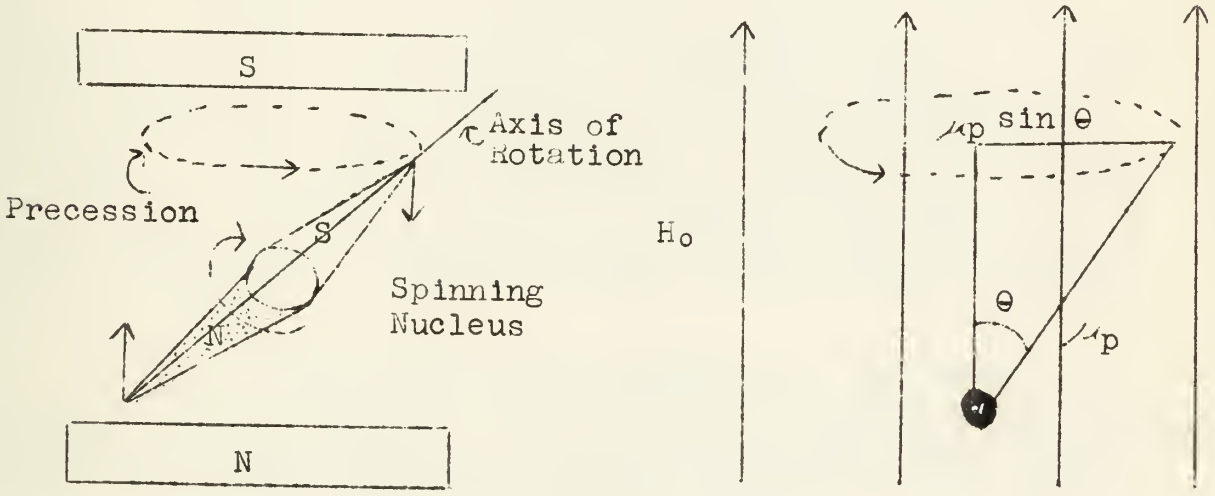


Figure 2.

Neither electrical fields, external or internal, nor motion of the nucleus itself produces any detectable effects on the nuclear magnetic moment. However, the principal cause of line broadening is dipole-dipole interaction exemplified in the case of ice in which one proton exerts on its nearest neighbor a field of several gauss, the oscillating component of which is in resonance with its neighbor's precession. Molecular motion in most liquids prohibits dipole-dipole interactions; consequently, most fluid substances give sharp and intense resonance lines.

That identical nuclei in the same applied field but in chemically different molecules do not precess at exactly the same frequency was first discovered by Knight[7]. The magnetic field at the atomic nucleus varies from the applied field as a result of diamagnetic shielding effects of the electron cloud about the nucleus. The atom's electron configuration differs slightly, depending upon what it is bonded to. The net result is a displacement of the resonance line termed "chemical shift". It is this phenomenon which has been most useful to organic chemists. If we assume[6,8] that $H = H_o + H_{Loc}$. where H = field at the nucleus, H_o = external applied field, and H_{Loc} = local shielding field; then by holding ν constant, the external field strength may be varied according to the shielding field, i.e., when the shielding field is large, a larger external field must be applied in order to penetrate it. Chemical shifts are measured in terms of

$$\delta = \frac{H_R - H_o}{H_R} \times 10^5$$

where H_R is the strength of the external field required to cause resonance in some reference sample, usually water.

A sample tube containing the nuclei to be studied is placed in the field of the permanent magnet[9,10,11,12]. There is a net alignment of the microscopic nuclear magnets in this field which is disturbed by the application of a second magnetic field, a weak radio-frequency field applied via the R-F transmitter. The precession of the nuclear magnets effected by the second field induces a small but detectable voltage in the receiver coil, which is picked up by the R-F receiver, is amplified, and then recorded on a graph. It is to be noted that the receiver coil is perpendicular to the transmitter coil to prevent signals from the driving field being picked up.

In the latest type of NMR equipment[11], the sample is rapidly spun between the poles of the stationary magnet to minimize field gradients. This treatment provides considerably better resolution than was formerly available. Also high resolution spectrometers now require only a 0.01 ml. sample.

Complete reviews of the literature concerning NMR and its applications are available[13,14] and include the literature through 1954.

BIBLIOGRAPHY

1. Darrow, K. K., Bell System Tech. J., 32, 74-99 (1953).
2. Purcell, E. M., Am. J. Phys., 22, 1-8 (1954).
3. Purcell, E. M., Science, 118, 431-36 (1953).
4. Bloch, F., ibid., 118, 425-31 (1953).
5. Bloch, F., Am. Scientist, 43, 48-62 (1955).
6. Obermayer, A. S., MIT Seminars, Fall 1953, pp. 179-86.

7. Knight, W. D., Phys. Rev., 76, 1259-60 (1949).
8. Gutowsky, H. S., McCall, D. W., McGarvey, B. R., and L. H. Meyer, J. Chem. Phys., 19, 1328 (1951).
9. Varian Associates, Palo Alto, Calif., publication no. 42.
10. Varian Associates, Palo Alto, Calif., publication no. 76.
11. Varian Associates, Palo Alto, Calif., publication no. 142.
12. Rogers, Emery, Industrial Laboratories, 6(9), September 1955.
13. Gutowsky, H. S., Ann. Rev. of Phys. Chem., 5, 333-56 (1954).
14. Shoolery, J. N., and H. E. Weaver, ibid., 6, 433-56 (1955).

NUCLEAR MAGNETIC RESONANCE: APPLICATIONS TO ORGANIC CHEMISTRY

Reported by Louis R. Haefele October 21, 1955

The usefulness of nuclear magnetic resonance to organic chemistry depends primarily upon the so-called "chemical shift", whereby the applied magnetic field is altered, due to a shielding effect of the electrons surrounding an atom. This causes a shift in the frequency of the resonance for the nucleus. The "chemical shift", then, is dependent upon the electron density about the atom and therefore upon the electronegativity of the group to which it is attached. Gutowsky[1] has compiled a chart of "chemical shifts" for the proton resonance of twenty-five common functional groups as determined by a study of over one hundred compounds.

N.M.R. is probably most useful for work involving hydrogen, which has excellent magnetic properties[2]. This is fortunate, since it is often difficult to apply such things as infrared and x-ray techniques in the case of hydrogen, due, in the former case to the complexity of many spectra, and in the latter to the difficulty of locating the hydrogen atom.

A number of applications of this method involve the quantitative determination of the number of non-equivalent hydrogens present in a molecule. This can be done easily and accurately by means of graphical integration to find the area under each of the proton peaks in the spectrum. For example, the spectrum of toluene consists of two distinct peaks[3], one corresponding to the resonance of the hydrogens attached directly to the aromatic nucleus and the other, to those of the methyl group. The areas under these peaks are found to be in a ratio of 5:3, corresponding to five aromatic hydrogens and three for the methyl group.

Arnold[4] has studied the N.M.R. spectra of the first five primary alcohols. Three peaks were obtained in each case (except methanol which had only two), corresponding to proton resonance frequencies for OH, CH_2, and R groups. The results are summarized in Table I which gives the ratio of the areas under the respective peaks, taking the hydroxyl area as unity in each case.

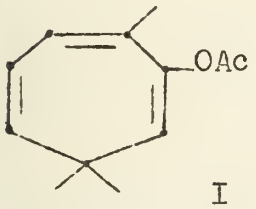
Table I

Alcohol	Calculated Ratio ($R/CH_2/OH$)	Observed Ratio ($R/CH_2/OH$)
CH_3OH	3/1	2.7/1
C_2H_5OH	3/2/1	3/2.1/1
C_3H_7OH	5/2/1	5/1.8/1
C_4H_9OH	7/2/1	7.1/1.9/1
$C_5H_{11}OH$	9/2/1	9.2/1.7/1

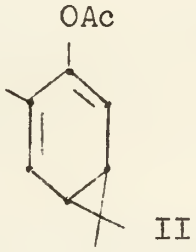
It is interesting to note that ethanol has been studied under higher resolution and with a carefully purified sample (5), and it is found that the hydroxyl peak is actually a triplet. This is attributed to spin-spin interactions of the proton with the hydrogens of the adjacent methylene group.

A more practical application of N.M.R. is found in the estimation of the composition of gasolines[3]. For an average premium gasoline, peaks can be distinguished with correspond to (a) protons attached directly to aromatic rings, (b) protons attached directly to doubly bonded carbon, (c) methyl and methylene groups attached to aromatic rings and (d) to double bonds and (e) normal, branched and cyclic alkanes of all types.

A recent example of the use of proton resonance spectra in organic structure proof involves its use in the elucidation of the structure of derivatives of eucarvone enol[6]. The problem was to determine whether the compounds had the cycloheptatriene structure (I) or the caradiene structure (II).



I



II

The N.M.R. spectrum of the enol acetate of eucarvone showed distinct peaks for the proton resonance for four ethylenic hydrogens, six gem-dimethyl hydrogens and for the CH_3-C= system, but none for the two tertiary bridge hydrogens of II. Thus it may be concluded that eucarvone enol acetate has the structure I.

Directly related to the quantitative estimation of the number of non-equivalent hydrogens in a molecule is a method whereby the ratio of keto to enol forms in a tautomeric mixture may be determined without disturbing the equilibrium.[7] For example, with acetylacetone, four peaks are obtained; two, of approximately equal area, corresponding to the CH and OH of the enol form, one for the CH_2 of the keto form, and the fourth for the methyl groups of both species. By comparing the area under the OH peak with one-half the area under the CH_2 peak (two H's) a good value for the proportions of keto and enol forms can be obtained.

Mixtures of cis-trans isomers can be analyzed in a similar fashion[3], since the environments of the protons are different in the two isomers, thus giving two peaks. From the area under the bands, the ratio of isomers can be calculated.

Such analyses are not limited to mixtures of isomers, but can be used for quantitative analysis of mixtures of almost any compounds. Thus with a mixture of benzaldehyde, ethanol and toluene[8], peaks can be distinguished for aldehyde, hydroxyl and methyl hydrogens. From the relative heights of the peaks it is possible to determine the composition of the mixture.

Still another use of N.M.R. which might be of great use to organic chemists is the determination of isotope content of a sample, although this is limited to use with isotopes which have a magnetic moment other than zero. In the case of a C^{12},

C^{13} mixture[5], the C^{13} spin of $^1/_2$ splits the proton resonance signal into a doublet which is superimposed on the peak for the $C^{12}H$ resonance. By comparing the amplitudes of the three peaks the relative proportions of the isomers can be determined

Analysis of H_2O, D_2O mixtures may also be carried out by means of N.M.R.[3] This is done simply by comparing H or D signals of an unknown sample with control samples of known deuterium content. The method will permit quantitative determination with an accuracy of ± 0.2%.

Nuclear magnetic resonance has recently been applied to a number of problems which have puzzled chemists for some time. For example, it has been postulated[9,10] that rotation about the C-N bond of amides is restricted, an important consideration in the structure of peptides, but conclusive proof of this fact has never been given. Phillips[11] recently reported a study of dimethylformamide and dimethylacetamide, where he obtained two proton resonance peaks for the methyl groups. This indicates that the two groups are not equivalent and therefore rotation about the C-N bond must be restricted.

Evidence has also been obtained by means of N.M.R. which supports the existence of a zwitter ion type configuration in crystalline glycine[12], and a planar structure for urea[13].

The use of N.M.R. is by no means limited to proton resonance spectra. A great deal of work has been done, for example, on fluorocarbons, and the method can conceivably be utilized in any case where one is dealing with an isotope of non-zero spin.

BIBLIOGRAPHY

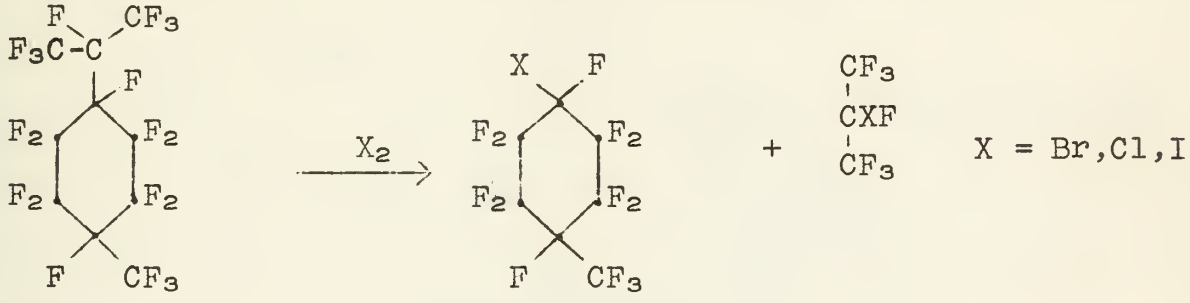
1. L. H. Meyer, A. Saika and H. S. Gutowsky, J. Am. Chem. Soc. 76, 4567 (1953).
2. H. S. Gutowsky, Ann. Rev. Phys. Chem., 5, 333 (1954).
3. Varian Associates, Inc., Palo Alto, Calif., Pub. 142.
4. J. T. Arnold, S. S. Dharmatti and M. E. Packard, J. Chem. Phys., 19, 507 (1951).
5. Varian Associates, Inc., Palo Alto, Calif., Pub. 76.
6. E. J. Corey, H. J. Burke and W. A. Remers, J. Am. Chem. Soc., 77, 4941 (1955).
7. H. S. Jarret, M. S. Sadler and J. M. Shoolery, J. Chem. Phys., 21, 2092 (1953).
8. E. Rogers, Industrial Laboratories, 6 (9) September (1955).
9. S. Mizushima, T. Shimanouchi, S. Nagakura, K. Kuratani, M. Tsuboi, H. Baba and O. Fujioka, J. Am. Chem. Soc., 72, 3490 (1950).
10. L. Pauling, The Nature of the Chemical Bond, p. 207, Cornell University Press (1948).
11. W. D. Phillips, J. Chem. Phys., 23, 1363 (1955).
12. T. M. Shaw, R. H. Elsken and K. J. Palmer, Phys. Rev., 85, 762A (1952).
13. E. R. Andrew and D. Hyndman, Proc. Phys. Soc. (London), A, 66, 1187 (1953).

ORGANIC FLUORINE COMPOUNDS

Reported by R. J. Crawford October 28, 1955

Since World War II great progress has been made in the chemistry of organic fluorine compounds. The initial stimulus along this line came during the war with the discovery of efficient electrolytic methods for producing fluorine[1], and the preparation of the perfluorocarbons[2]. The main object at that time was to produce particularly inert materials which could not be affected by uranium hexafluoride.

Perfluoroalkanes. Because of their remarkable physical properties these compounds have become important industrial commodities. Their main characteristic being the inertness of the C-F bond, by virtue of which they show extreme stability to chemical and thermal processes. Their surface tensions, viscosities, refractive indexes and boiling points are very low whereas their densities are high. Reactions of these compounds are few and occur only at high temperatures. Recent investigations[3] have illustrated their ability to partake in free radical reactions at high temperatures. It is assumed that the bond between the two tertiary carbons is cleaved homolytically and the radicals react with the halogens.



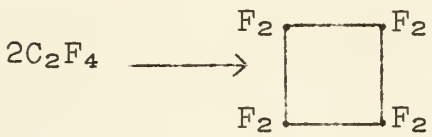
Support for this view was gained by heating perfluoro (1-methyl 4-isopropylcyclohexane) in the presence of toluene, whereupon dibenzyl and the analogous H substituted products were obtained.

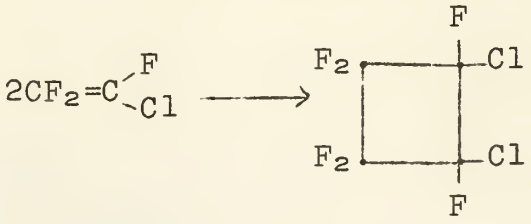
Alkenes. The reactions of fluorinated olefins follow the same general trend as do the hydrocarbon olefins, but their products are not always as easily predicted. Bearing in mind the strong positive inductive effect, and the hyperconjugative effect of the trifluoromethyl group one can predict the products of addition reactions[4].

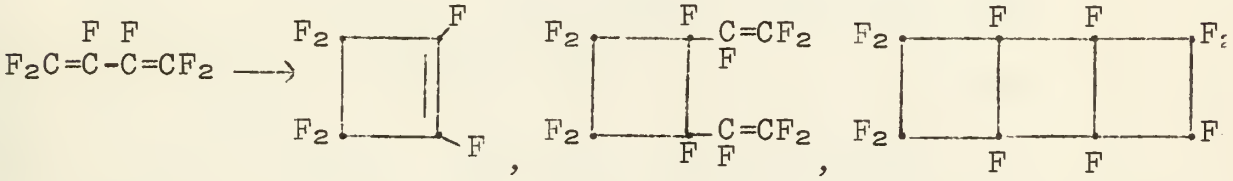
Nucleophilic addition occurs in the presence of alkaline catalysts and certainly in the case of highly fluorinated olefins, more readily than electrophilic addition. Amines, thiols, alcohols, phenols and Grignard reagents are added in the presence of basic catalysts[5].

The ability to form cyclic dimers appears to be unique to fluorinated olefins. Not only do they react with themselves but with other olefins to form cyclobutane derivatives. With

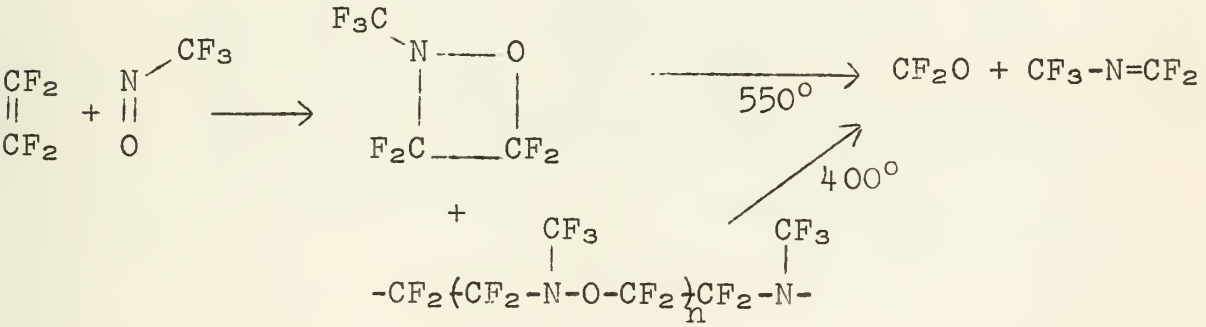
butadiene the formation of a cyclobutane occurs in preference to a Diels Alder reaction[6]. When heated to 150-180° hexafluorobutadiene is converted to hexafluorocyclobutene and a mixture of dimers and trimers[7].







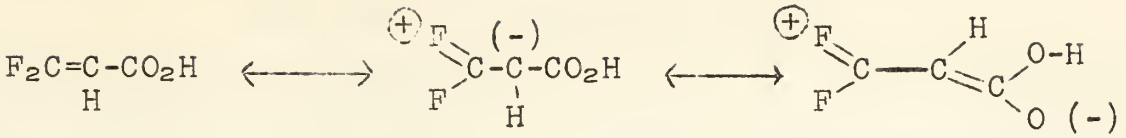
Tetrafluoroethylene has been found to react in a similar fashion with trifluoronitrosomethane to produce the substituted 1,2-oxazetidine and a polymer. The ratio of the products are controlled by the temperature of the reaction[8].



Various reagents have been used to telomerize tetrafluoroethylene and products of various chain length may be obtained depending upon the concentration of the chain transfer agent[9].

Alkynes. Allowing for the effect of the trifluoromethyl group on the direction of addition to the triple bond, the perfluoroalkynes which have been investigated in any detail are very similar to the corresponding hydrocarbons[10,11]. Thus if there is an acetylenic hydrogen in the molecule it can react with Grignard reagents, and the silver, cuprous and mercury acetylides may be prepared in the usual fashion; the acetylene may be regenerated with acid.

Acids. The various fluoro acids have been prepared and their strengths determined. Trifluoromethylsulphonic acid is of comparable strength to perchloric acid[12]. The perfluoro saturated acids are found to be much stronger than their fatty acid analogues, but the fluoroacrylic acids are not as strong as the corresponding chloro-acids. This may be explained by the increased importance of the resonance structures I and II[13].



I II

BIBLIOGRAPHY

1. H. R. Leech, Quat. Rev., 3, 22 (1949).
2. Slesser and Schram, "Preparation, Properties, and Technology of Fluorine and Organic Fluorocompounds" McGraw-Hill, New York, 1951.
3. G. B. Barlow, M. Stacey and J. C. Tatlow, J. Chem. Soc., 1749 (1955).
4. W. K. R. Musgrave, Quat. Rev., 8, 334 (1954).
5. P. Tarrant and D. A. Warner, J. Am. Chem. Soc., 76, 1624 (1954).
   W. R. James, W. H. Pearlson and J. H. Simons, ibid., 72, 1761 (1950).
6. M. W. Buxton and J. C. Tatlow, J. Chem. Soc., 1177 (1954).
7. R. N. Haszeldine in Annual Reports of the Chemical Society, Vol. LI, p. 289 (1954).
8. D. A. Barrand R. N. Haszeldine, J. Chem. Soc., 1881 (1955).
9. R. N. Haszeldine, ibid., 3761 (1953).
10. R. N. Haszeldine, ibid., 588 (1951).
11. A. L. Henne and M. Nager, J. Am. Chem. Soc., 74, 650 (1955).
12. H. J. Emelius, R. N. Haszeldine and Ram Chand Paul, J. Chem. Soc., 563 (1955).
13. A. L. Henne and C. J. Fox, J. Am. Chem. Soc., 76, 479 (1954).

ORGANIC REACTIONS EFFECTED BY IONIZING RADIATION
PART ONE: NON AQUEOUS SYSTEMS

Reported by R. A. Scherrer October 28, 1955

Real progress toward illucidation of the chemical reactions that have been going on for thousands of years due to cosmic radiation has only been made in the last ten years. During early investigations, products were so many and complex it was difficult to grasp the fundamentals. These reactions are not as haphazard as was once thought, however. Recent investigations have been fruitful from the standpoint of possible commercial applications[1,2] as well as that of increasing our understanding of mechanisms and excited states. With a reasonable certainty of inexpensive radiation in the future more investigators are looking into its sometimes unique action on organic compounds.

In the category of ionizing radiation are α, β, γ rays, X-rays and neutrons. Except for neutrons, the primary interaction is with the target electrons, the photons or particles knocking them to a higher level or from their orbit with enough energy that they in turn cause further ionization. A one Mev electron has the equivalent energy of about 50,000 bonds. Neutrons interact with the nuclei [(n, γ), (n, α), (n, 2n), etc.] giving particles which interact as above. In general it can be said that the products obtained using different radiations will be the same, varying in relative amounts, but not type[3].

These interactions can result in the following:

$$M \rightsquigarrow M^{+} + e^{-} \qquad \text{ionization}$$
$$M \rightsquigarrow M^{*} \qquad \text{excited state}$$
$$\text{then} \quad e^{-} + M \longrightarrow M^{-}$$
$$\text{or} \quad e^{-} + M^{+} \longrightarrow M^{*}$$

(ratio not known

The process is not completely understood. Spiers, in "The Primary Act"[4] lists 32 further interactions leading to positive ions, negative ions, changes of one to the other, loss of electrons from negative ions and recombinations that might occur.

An interesting application of γ rays is in the chlorination of benzene and toluene[5,6].

$$C_6H_6 + 3\,Cl_2 \xrightarrow[CCl_4]{\gamma(CO^{60})} \text{1,2,3,4,5,6-hexachlorocyclohexane (mixture of isomers)} \qquad (1)$$

This reaction is rapid at R.T. and gives the same product as photochlorination (same % gamma isomer). Toluene, however, does not.

$$C_6H_6 \cdot CH_3 \quad 3\,Cl_2 \xrightarrow[\text{toluene}]{\gamma(CO^{60})} \text{1-methyl-1,2,3,4,5,6-hexachlorocyclohexane} \qquad (2)$$

Since this latter reaction has a chain length of about 10^3, the authors suggest that this means the propagation goes by a mechanism different from any known at present. Other observations were a) neither benzyl-, benzal-, nor benzochlorides underwent the above reaction, b) $\geq$ 1% benzyl chloride caused reaction 1 above "to virtually stop", and c) benzene reacted faster than chlorobenzene which reacted faster than toluene. It is possible to postulate a mechanism based on the work of Burton and Patrick concerning the protection by benzene of cyclohexane toward dehydrogenation[7,8], the transfer of energy from an alkyl side chain to the benzene ring[9] and the stability of benzyl chloride hexachloride.

Studies[10] on the beta particle (tritium), radiolysis of acetylene and deuteroacetylene to form benzene and cuprene (a polymer) indicate that the products result from initially different excited states of acetylene, since benzene formation is independent of acetylene pressure. Ingold's[11] picture of the first excited state of acetylene fits into this picture nicely.

Radiation can make an ordinarily soft sheet of plastic stronger than steel. This is the effect of cross linking already formed polymers. The mechanism of this action[13,14] is first, rupture of the H-C bond, combination of H· with a hydrogen of another chain, and linking of the carbon radicals formed. When there is approximately one crosslink per molecule, the mass suddenly becomes infusable and insoluble in most organic solvents. A possible commercial application is gamma ray vulcanization of rubber[15]. Not all polymers crosslink. A competing, and in some cases the only action is splitting of the C-C bonds. Even this degradation is useful in special cases[1].

Radiation can be used to polymerize olefins. Advantages are: there is no catalyst contamination; the reaction can be run at room temperature, thus lessening decomposition of heat sensitive molecules and lowering branching; polymers can be made that have never been obtained before (polyperfluoropropylene, polyperfluorobutadiene, polyperfluoroacrylonitrile)[2].

Polymerizations can even be run in the solid state[16]. Pure crystals of sublimed acrylamide (m.p. 88°) have been polymerized to a M.W. $\geq$ 50,000 by gamma rays at 35°.

A feeling for the action of ionizing radiation can possibly best be gained by looking at its effects on pure compounds. Let us consider the reaction of methyl alcohol[17]. This reaction has possibilities as a commercial method for preparing ethylene glycol. The mechanism of this reaction has recently been studied. The products and their corresponding G values (100ev yield) are given in Table I. The mechanism postulated is given at the left.

Table I

	Product	$G(CO^{60})\gamma$	G 28Hev He^{++} ions
$CH_3OH \longrightarrow CH_2OH + H$ (1)	H_2	4.0	3.46
$CH_2OH \longrightarrow H_2CO + H$ (2)	CO	0.16	0.23
$H + CH_3OH \rightarrow CH_2OH + H_2$ (3)	CH_4	0.24	0.36
$2CH_2OH \longrightarrow CH_2OHCH_2OH$ (4)	CH_2O	1.3	1.67
$2H \longrightarrow H_2$ (5)	$HOCH_2CH_2OH$	3.0	1.74
$H + CH_2OH \longrightarrow CH_3OH$ (6)			

The fact that He^{++} ions, which produce a path of higher ion (radical) density, give a lower yield of glycol to aldehyde is taken as an indication that reactions 5 and 6 occur to a greater extent. Further information that $G_{ald.}$ is the same at 0°C, but that G_{glycol} is lower at that temperature indicates that formation of the latter takes place as a secondary reactic outside of the ionized track, where bulk temperature is important.

McDonell and Newton[18] have made one of the most complete radiation decomposition studies to date in work on the alpha bombardment of ten normal, iso, and tertiary aliphatic alcohols. The products are consistent with principal bond rupture at the carbinol carbon.

In all, radiation studies have been done on about 100 pure organic compounds. The results of nearly all of these have been compiled by Tolbert and Lemmon[19].

BIBLIOGRAPHY

1. S. S. Jones, Can. Chem. Processing 39, Vol. 4, p. 36 (1955).
2. Editors, Chem. Week Jan. 29, 1955, p. 48.
3. G. Friedlander and J. Kennedy, Introduction to Radiochemistry (1949) John Wiley and Sons, Inc., New York.
4. F. W. Spiers, Disc. Faraday Soc. 12, 13 (1952).
5. D. Harmer, L. Anderson and J. Martin, Chem. Eng. Progress Sym. No. 11, 50, 253 (1954).
6. B. G. Bray, Geneva Conference Aug. 22, 1955, paper No. 168. Nucleonics 13 (9) 92 (1955).
7. M. Burton and W. Patrick, J. Phys. Chem. 58, 421 (1954).
8. R. R. Hentz, J. Phys. Chem., 59, 380 (1955).
9. R. R. Hentz and M. Burton, J. Am. Chem. Soc., 73, 532 (1951)
10. L. Dorfman and F. Shipko, J. Am. Chem. Soc.,77, 4723 (1955).
11. C. K. Ingold and G. W. King, J. Chem. Soc., 2702 (1953).
12. Editors, Modern Plastics 32, (7) 83 (1955).
13. E. Henley, Modern Plastics 32, (7) 88 (1955).
14. A. Charlesby, Radiation Res. 2, 96 (1955).
15. C. Bopp and O. Sisman Nucleonics 13 (7) 28 (1955).
16. R. Mesrobian et. al., J. Chem. Phys. 22, 565 (1954).
17. W. R. McDonell and S. Gordon, J. Chem. Phys. 23, 208 (1955).
18. W. McDonell and A. Newton, J. Am. Chem. Soc., 76, 4651 (1954)
19. B. Tolbert and R. Lemmon, Radiation Res. 3, 52 (1955).

ORGANIC REACTIONS EFFECTED BY IONIZING RADIATIONS
PART TWO: AQUEOUS SYSTEMS

Reported by W. DeJarlais November 4, 1955

Reactions of organic compounds in aqueous solution with x, α, β and γ rays and neutrons are primarily those of indirect action, i.e. the radiation is absorbed by the water molecules, producing species which then interact with any solute present. The assumption is made that the solute's concentration be small enough that direct activation by the radiation is negligible. The nature of the effect on an organic compound is dependent on the nature of the radiation, its intensity, the presence of oxygen in the solution as well as the nature of the organic solute. The exact mechanism of these interactions is obscure.

According to the general theory advanced by Weiss[1], the net effect is the production of hydroxyl radicals and hydrogen atoms, by way of charged intermediates. It is supposed that the interaction of the radiation with water involves the two processes of excitation and ionization:

$$H_2O \longrightarrow H_2O^*$$

$$H_2O \longrightarrow H_2O^+ + e$$

then,
$$H_2O^+ \longrightarrow H^+ + \cdot OH$$

The ejected electron may have sufficient energy to cause further ionization, depending upon the energy of the radiation. Such an electron quickly loses energy by collisions with water molecules and when it has energy of the order kT (the Boltzman constant times the absolute temperature) the reaction[2]:

$$H_2O + e \longrightarrow {}^-OH + H\cdot$$

can occur. This last step usually takes place at some distance from the site of the original ionization and hence, radical recombination:

$$H\cdot + \cdot OH \longrightarrow HOH$$

is not as effective as in the case of the dissociation of the activated water molecules, where the radicals have little chance to diffuse away from each other. To the net processes proposed by Weiss:

$$H_2O \longrightarrow \cdot H + \cdot OH$$

$$2H_2O \longrightarrow H_2 + H_2O_2$$

it has recently been shown that a third must be added[3]:

$$2H_2O \longrightarrow 2H\cdot + H_2O_2$$

Since H· and HO· may not be produced in equivalent amounts.

Direct evidence in support of this mechanism is obtained in the polymerization of aqueous acrylonitrile by γ-rays or x-rays[4]. The O-H absorption band is observed in the polymer, and when D_2O is used as a solvent the C-D stretching band in the infrared is seen.

Stein and Weiss[5] found that when a saturated aqueous solution of benzene was subjected to mixed neutron and γ-radiation, the products were phenol, catechol, hydroquinone, biphenyl and an unidentified aliphatic aldehyde or a mixture of aliphatic dialdehydes. The presence of dissolved oxygen has the effect of increasing oxidation reactions. Its action is:

$$H\cdot + O_2 \longrightarrow HO_2\cdot$$

In the absence of air more biphenyl and some terphenyl were formed[6]. Air caused the yield of phenol to increase by a factor of five. It is of note that no resorcinol was found.

When solutions of phenol were treated with x-rays in the presence of dissolved oxygen the products were: catechol, hydroquinone, o-benzoquinone and some p-benzoquinone[7]. Autoxidation was shown not to be the cause of the quinone formation. Quinone formation does not take place from catechol or hydroquinone as: 1. addition of either catechol or hydroquinone did not increase the quinone yield, 2. quinone formation is linearly dependent upon dose and doesn't show the characteristic induction period of a secondary reaction, 3. in neutral solutions where catechol and hydroquinone are more easily oxidized, quinone formation does not take place. Again no resorcinol was found. Comparison with the action of Fenton's reagent[8], a known free hydroxyl radical producing agent, showed no qualitative difference in the results as far as could be determined.

Investigation of the action of x-rays on sodium benzoate in aqueous solutions in the presence of dissolved air showed that all three mono-hydroxy benzoic acids were produced in the ratio of 5:2:10 for ortho, meta and para, respectively[9]. Some decarboxylation occurred with the formation of biphenyl. Decarboxylation has also been observed in the case of high energy β-rays acting upon p-aminobenzoic acid and niacin[10,11].

If the substitution were haphazard, the expected ortho: meta: para ratio would be 2:2:1, in the absence of steric effects. It has been shown on theoretical grounds that all mono-substituted benzenes should have the same orientation effect in free radical substitutions[12].

Further work has shown that when saturated aqueous solutions of nitrobenzene are irradiated with x-rays, all three mono-hydroxyl nitrobenzenes are formed, the para in about twice the amount of either the ortho or meta[13]. The formation of nitric acid was observed. When saturated aqueous solutions of chlorobenzene were irradiated with x-rays, the three mono-hydroxy chlorobenzenes were obtained[14]. The para isomer was the chief product. Treatment of chlorobenzene in saturated

aqueous solution with Fenton's reagent gave the same results, so far as could be determined. Biphenyl was formed in each case but no chlorobiphenyls. It is remarkable that the formation of biphenyl is favored by the presence of oxygen as the reductive dechlorination of chlorobenzene is known to occur readily[15].

Keller and Weiss[16] investigated the effects of 200 kv. x-rays on cholesterol and two of its esters, sodium cholesteryl succinate and cholesteryl acetate. Some of these irradiations were run in 90% acetic acid. This was shown to yield the same results as with water except for the production of esterified alcohol groups in some cases. The chief effects of the radiations are hydroxylation of the 5-6 double bond, and, in the case of large doses, oxidation of the 7 carbon atom to a keto group. Again Fenton's reagent was found to give agreement with the x-ray results[17]. The results were later confirmed using aqueous methanol solutions instead of acetic acid-water[18]. In runs using methanol-water the intermediate oxidation product, 7-hydroxycholesterol, was also isolated.

With cholic acid Keller and Weiss observed the conversion of a 3-hydroxy group to a keto group[19]. More recently cortisone and desoxycorticosterone have been investigated by Weiss and co-workers?[0] X-radiation of these compounds were carried out both in the presence of air and in its absense. In a vacuum, dehydroxylation and reduction of a double bond occur. Weiss and co-workers also claim to have evidence that the following occur:

1. Complete reduction of the Δ^4-3-keto group to give 3β-hydroxyl derivatives.

2. Reduction of the 3-keto group before reduction of the double bond.

3. Addition of one •OH and one •H to the double bond.

4. Elimination of a carbon atom from ring A to give A-nor-3-keto derivatives. It was shown that hydrogen and hydrogen peroxide in the concentration produced in the radiolysis were without action. Therefore, the effects are due to the presence of •OH and •H alone. With oxygen present the results were considerably different, as might be expected. However, except for the small amount of adrenocorticosterone and some of the suspected 17α,21-dihydroxy-A-norpregnane-3,11,20-trione, the products could not be identified. It has now been shown that ring contraction does take place. It is not certain what becomes of the lost carbon atom. The yield of carbon dioxide was far too small to account for it. No carbon monoxide, formic acid or formaldehyde was detected. At present studies are under way using C^{14} in the 4 position to see if the missing carbon is possibly present as an angular methyl group on carbon 5.

Studies have also been carried out in aqueous solutions using indole, lactic acid, amino acids, amines and dyes as solutes?[1-25]

BIBLIOGRAPHY

1. J. Weiss, Nature 153, 148 (1944).
2. M. Burton, Brit. J. Radiol. 24, 416 (1951).
3. A. O. Allen, Radiation Res. 1, 85 (1954).
4. F. J. Dainton, Brit. J. Radiol. 24, 428 (1951).
5. G. Stein, J. Weiss, J. Chem. Soc., 3249 (1949).
6. G. Stein, J. Weiss, ibid., 3254 (1949).
7. G. Stein, J. Weiss, ibid., 3265 (1951).
8. F. Harber, J. Weiss, Proc. Roy. Soc. A. 146, 332 (1934).
9. H. Loebl, G. Stein, J. Weiss, J. Chem. Soc., 405 (1951).
10. M. Corson, S. A. Goldblith, S. E. Proctor, J. R. Hogness, W. H. Longham, Arch. Biochem.Biophys. 33, 263 (1951).
11. S. A. Goldblith, B. E. Proctor, J. R. Hogness, W. H. Longham, J. Biol. Chem. 179, 1163 (1949).
12. G. W. Wheland, J. A. C. S. 64, 90 (1942).
13. S. Loebl, G. Stein, J. Weiss, J. Chem. Soc., 2704 (1950).
14. G. R. A. Johnson, G. Scholes, J. Weiss, ibid., 3275 (1951).
15. C. Kelber, Ber. 50, 309 (1907).
16. M. Keller, J. Weiss, J. Chem. Soc. 2709 (1950).
17. G. K. Clemo, M. Keller, J. Weiss, ibid. 3470 (1950).
18. B. Coleby, M. Keller, J. Weiss, ibid., 1250 (1954).
19. M. Keller, J. Weiss, ibid., 25 (1951).
20. R. Allenson, B. Coleby, J. Weiss, Nature 175, 720 (1955).
21. C. B. Alsopp, Disc. Faraday Soc. 229 (1952).
22. G. R. A. Johnson, G. Scholes, J. Weiss, J. Chem. Soc., 3091 (1953).
23. G. R. A. Johnson, G. Scholes, J. Weiss, Science 114, 412 (1951).
24. G. G. Jayson, G. Scholes, J. Weiss, J. Chem. Soc., 2594 (1955).
25. Day and Stein, Nucleonics 8, II 34 (1950) for example.

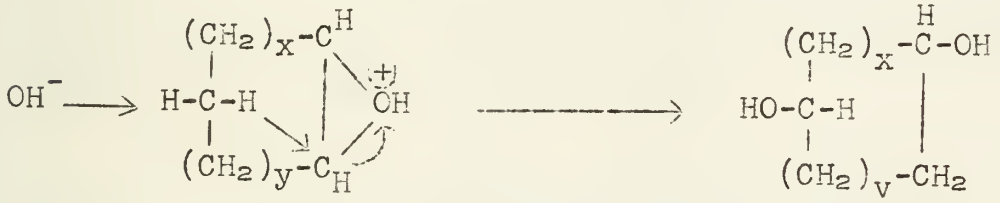
TRANSANNULAR REACTIONS AND INTERACTIONS

Reported by Kenneth Conrow November 4, 1955

The non-classical view that functions on opposite sides of ring compounds of the right size (8 to 11 members, inclusive) can interact has been conclusively established in a number of cases. This ability is ascribed to the proximity of the groups which is induced by the pucker of the ring system.

Cope[1], Prelog[2,3,4] and coworkers have shown that cycloölefins of the 8,9,10 and 11 membered carbocyclic series give unexpected products when oxidized with performic acid, giving 1,4, 1,5, 1,6, and unidentified diols respectively. In the case of the 9,10 and 11 membered rings none of the normal 1,2-glycol can be detected; in the 7 and 12 membered rings, only the 1,2-glycol is isolated. The reaction is stereospecific in the 8 and 10 membered rings; the cis-cyclooctene, cis-cyclodecene and trans-cyclodecene each give only one of the possible stereoisomeric diols. In contrast cis and trans-cyclononene both give a mixture of the stereoisomeric 1,5-cyclononanediols. The configuration of the diols has not been established, but a consideration of the mechanism postulated by Cope and Prelog which involves a double Walden inversion leads, for example, to the likelihood that the cis-cyclodecene gives cis-1,6-cyclodecanediol.[5]

The production of these non-classical products is explained on the basis of a transannular hydride ion shift under influence of an attacking basic group to open the protonated form of the epoxide ring at first formed by the action of performic acid on the double bond. Some support for this sequence is gained from the hydrolysis of cyclooctene-cis-oxide with formic acid to give exactly the same mixture of classical and transannular products as was obtained by direct action of performic acid on the olefin.[1]



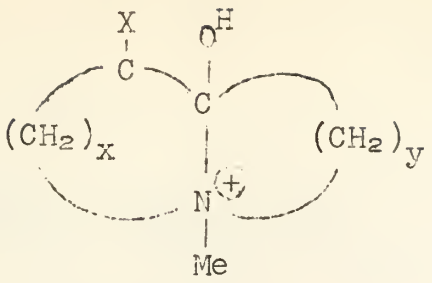
Prelog[4] used 1,2-C^{14}-cyclodecylamine to get quantitative data on the relative amounts of classical and transannular reaction upon treatment with nitrous acid. The main product, cyclodecene, was oxidized without further rearrangement to sebacic acid which was subjected to successive Schmidt degradations; the CO_2 evolved in each degradative step was collected and measured for radioactivity. The minor product, cyclodecanol, was oxidized to the ketone, formylated and oxidized to sebacic acid which was then degraded as in the case of cyclodecene. A system of equations was then set up relating the found radioactivity of each pair of carbon atoms to that to be expected in the possible classical, 1,2, 1,5, and 1,6-hydride shift reaction courses. A solution of the system

shows that in the elimination reaction 62% of the product results from classical elimination, 24% from a 1,2-hydride shift, 6% from a 1,5-hydride shift and 8% from a 1,6-hydride shift - a total of 14% by transannular reaction. In the substitution product, 46% of the cyclodecanol was produced without a hydride ion shift, 33% with a 1,2-shift and 21% by a transannular shift. These results are roughly comparable to the yields (5-30%) of transannular products from the performic oxidation of the cyclic olefins.

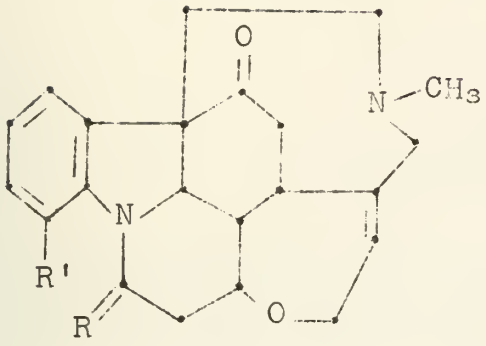
Other examples of transannular reactions include: Heating 1,6-ditosylcyclodecanediol with diethylaniline results in a mixture of 1,9 and 9,10-octalins.[6] Similar treatment of trans-tosylcyclodecene-6-ol gives a mixture of cis-1,2-octalin and 1,9-octalin.[7] In a similar reaction, cyclodecanone is converted to a mixture of 1-keto-9,10-octalin and trans-decalone by the action of two moles of N-bromosuccinimide followed by heating with dimethylaniline. Treated in the same manner, cyclononanone gives 1-keto-8,9-hydrindene.[8] Rearrangement of trans-cyclodecene to the cis isomer (83% yield, 2-naphthalene sulfonic acid as catalyst) gives also 7% of a mixture of the isomeric decalins.[9]

An example of transannular interaction, as opposed to reaction, in the carbocyclic series is provided by a comparison of (4.4) paracyclophane with (6.6) paracyclophane.[10,11] When (4.4) paracyclophane is acetylated a monoacetyl derivative is produced, even in the presence of two moles of acetyl chloride. The presence of the acetyl group in the first ring deactivates the second ring toward acetylation by a mechanism which can only be transannular. Similar treatment of (6.6) paracyclophane gives a diacetyl derivative. Hydrogenation with three moles of hydrogen over Pt gives principally the half reduced compound from (4.4) paracyclophane, but gives a random mixture from (6.6) paracyclophane. The explanation is that the interaction is such that the first ring is more easily reduced than the second which becomes an isolated benzene ring after the reduction of the first. In the case of the (6.6) paracyclophane both rings are effectively isolated and hence are reduced independently. The consequences of π electron interaction in this type of system are also evident in a study of the u.v. spectra of a series of cyclophanes.[12]

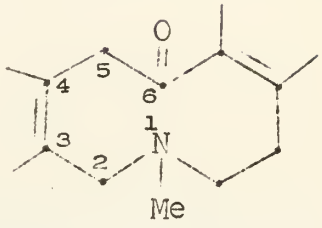
The alkaloids N-methyl pseudostrychnidine (III, R = 2H, R' = H) and N-methyl pseudostrychnine (III, R = O, R' = H) and probably vomicine (III, R = O, R' = OH) exhibit a transannular tertiary nitrogen-carbonyl interaction.[13,14,15] What is apparently the first published idea of transannular interaction[16] was in connection with the protopine family of alkaloids which contain the large ring system IV. Members of this family form transannular salts of type II[17,18] and exhibit carbonyl absorbtions in the infrared at lowered frequency i.e. 1661-1658 cm.$^{-1}$.[19] Cryptocavine, originally thought to possess a 5 rather than 6 keto group, was investigated with respect to its ability to form transannular salts and shown to be identical with cryptopine.[18]



II



III



IV

BIBLIOGRAPHY

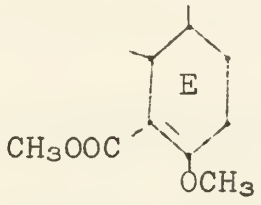
1. A. C. Cope, S. W. Fenton and C. F. Spencer, J.A.C.S., 74, 5885 (1952).
2. V. Prelog, K. Schenker and W. Küng, Helv. Chim. Acta, 36, 471 (1953).
3. V. Prelog and K. Schenker, Helv. Chim. Acta, 35, 2048 (1952).
4. V. Prelog, H. J. Urech, A. A. Bothner-By and J. Würsch, Helv. Chim. Acta, 38, 1095 (1955).
5. K. R. Henery-Logan, MIT Seminars, 1952-1953, p. 188.
6. A. C. Cope and George Holzman, J.A.C.S., 72, 3062 (1950).
7. A. C. Cope, R. J. Cotter and G. G. Roller, J.A.C.S., 77, 3594 (1955).
8. K. Schenker and V. Prelog, Helv. Chim. Acta, 36, 896 (1953).
9. A. C. Cope, D. C. McLean and N. A. Nelson, J.A.C.S., 77, 1628 (1955).
10. D. J. Cram and J. Abell, J.A.C.S., 77, 1179 (1955).
11. D. J. Cram and R. W. Kierstead, J.A.C.S., 77, 1186 (1955).
12. D. J. Cram, N. L. Allinger and H. Steinberg, J.A.C.S., 76, 6132 (1954).
13. F. A. L. Anet, A. S. Bailey and Sir Robert Robinson, Chem. and Ind., 944 (1953).
14. R. Huisgen, H. Wieland and H. Eder, Ann., 561, 193 (1949).
15. O. Hafliger and V. Prelog, Helv. Chim. Acta, 32, 1851 (1949).
16. W. O. Kermack and R. Robinson, J. Chem. Soc., 121, 435f (1922).
17. F. A. L. Anet and Leo Marion, Can. J. Chem., 32, 452 (1954).
18. A. F. Thomas, Leo Marion and R. H. F. Manske, Can J. Chem. 33, 570 (1955).
19. L. Marion, D. A. Ramsay and R. N. Jones, J.A.C.S., 73, 305-8 (1951).

STEREOCHEMISTRY OF RESERPINE AND DESERPIDINE

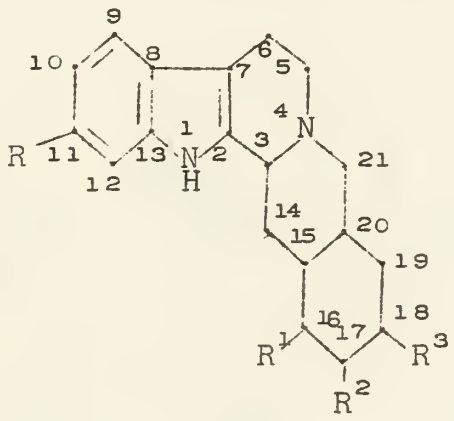
Reported by Ralph J. Leary November 11, 1955

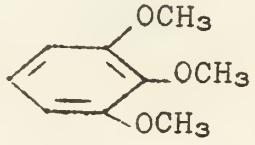
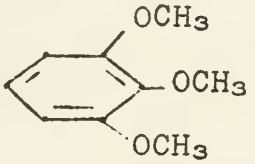
Reactions of reserpine[1] I

1. I + alcoholic NaOH → Reserpic acid II
2. II + CH_2N_2 → Methyl reserpate III
3. III + p-toluenesulfonyl chloride → methyl reserpate-18-tosylate IV
4. IV + $LiAlH_4$ → Reserpinol V
5. I + $LiAlH_4$ → Reserpindiol VI
6. IV + Collidine → methyl anhydroreserpate + Product isomeric with IV[5]

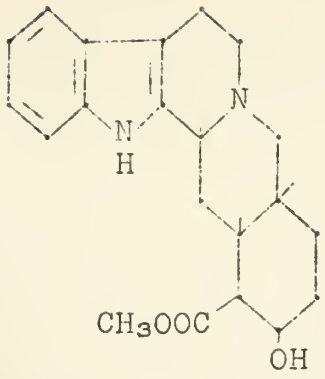


Deserpidine[2] VII reacts in a manner similar to reserpine except for the detosylation of methyl deserpidate tosylate with collidine.



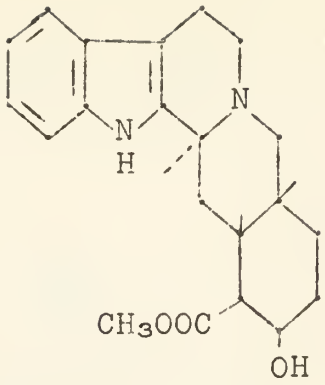
I	$R=OCH_3$	$R^1=COOCH_3$	$R^2=OCH_3$	$R^3=O-C(=O)-$ 
II	$R=OCH_3$	$R^1=COOH$	$R^2=OCH_3$	$R^3=OH$
III	$R=OCH_3$	$R^1=COOCH_3$	$R^2=OCH_3$	$R^3=OH$
IV	$R=OCH_3$	$R^1=COOCH_3$	$R^2=OCH_3$	$R^3=-O_2SC_7H_7$
V	$R=OCH_3$	$R^1=CH_2OH$	$R^2=OCH_3$	$R^3=H$
VI	$R=OCH_3$	$R^1=CH_2OH$	$R^2=OCH_3$	$R^3=OH$
VII	$R=H$	$R^1=COOCH_3$	$R^2=OCH_3$	$R^3=O-C(=O)-$ 

During the course of conversions reserpine and deserpidine are converted to α-yohimbine VIII and 3-epialloyohimbine IX.



Alloyohimbane Configuration[3]

VIII

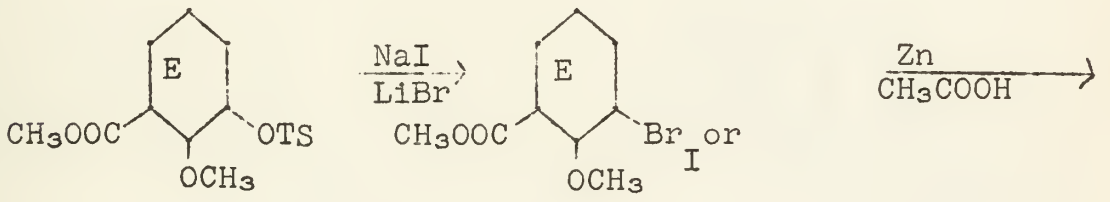


Epialloyohimbane Configuration[3]

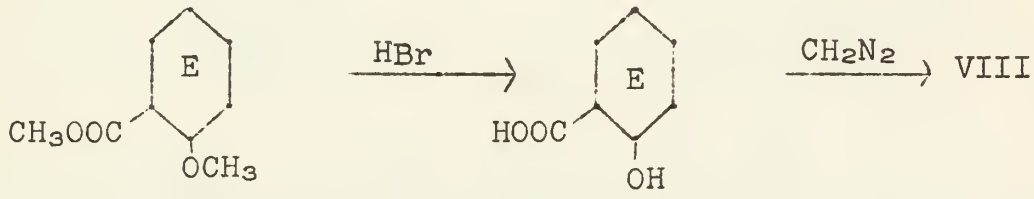
IX

VIII and IX are not absolute configurations
VIII defines the hydrogen at C-3 cis to the hydrogens at C-15 and 20
IX defines the hydrogen at C-3 trans to the hydrogens at C-15 and 20

Methyl deserpidate tosylate is converted to α-yohimbine VIII by the following reactions[4]:



X

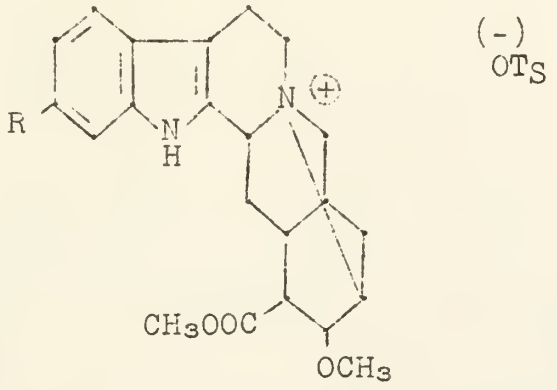


XI

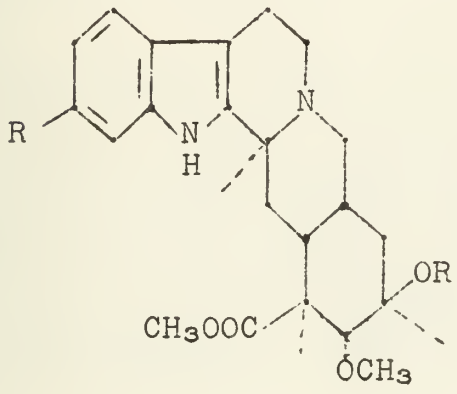
It would seem logical on the basis of the reactions above to assign the alloyohimbane configuration to the basic ring system of deserpidine. However, there is evidence which shows that reserpine, deserpidine and their derivatives undergo acid or base catalyzed epimerization at the C-3 center. It can also be shown that the C-3 center is the only center epimerized. It therefore seems probable that reserpine and deserpidine are derivatives of 3-epi-α-yohimbine.

Since reserpic acid II readily lactonizes the substituents at C-16 and 18 are postulated to be cis to each other.[4-5]

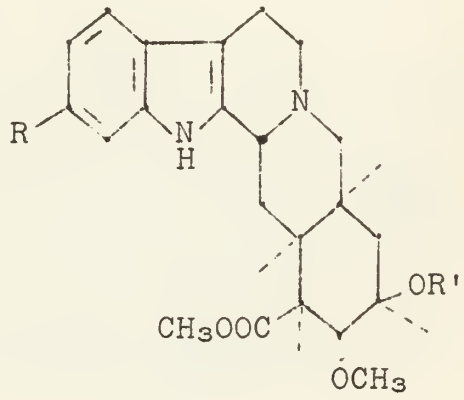
Evidence for the cis relationship of the hydrogens at C-15 and 20 was obtained by the collidine detosylation of methyl reserpate-18-tosylate IV[5]. Not only was methyl anhydroreserpate formed but also a product that was isomeric with the starting tosylate. This compound was shown to be a quaternary salt and its structure was formulated as:



The formation of the N^4-C-18 bond requires a cis D/E ring juncture. The cis D/E ring juncture of reserpine has also been proved by synthesis[6]. Selection of configuration B over A was based upon the following observations.

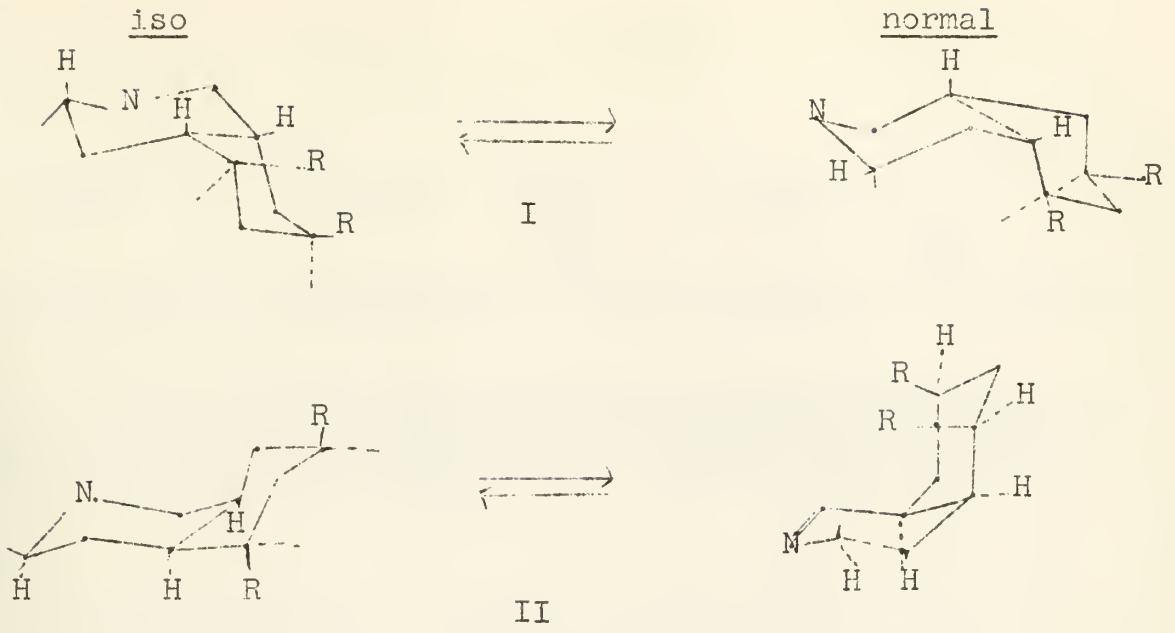


A



B

It was assumed previously that the driving force for the epimerization reaction at C-3[7,8] of the alkaloids resided in the greater stability of alloyohimbane over the 3-epialloyohimbane skeleton. However, further investigation revealed that allo- and 3-epialloyohimbane, without asymmetric substitution at C-16, 17 and 18, under conditions of isomerization are of approximately equal stability. The reason for complete epimerization of the alkaloids and their derivatives must therefore lie in the steric relationship of the substitution in ring E. On the basis of A, the iso compound (conformation I), with 1,3-diaxial interaction not possessed by the normal compound, would be the less stable of the isomer pair. However, B (conformation II) gives a clear explanation for the greater stability of the iso compound.

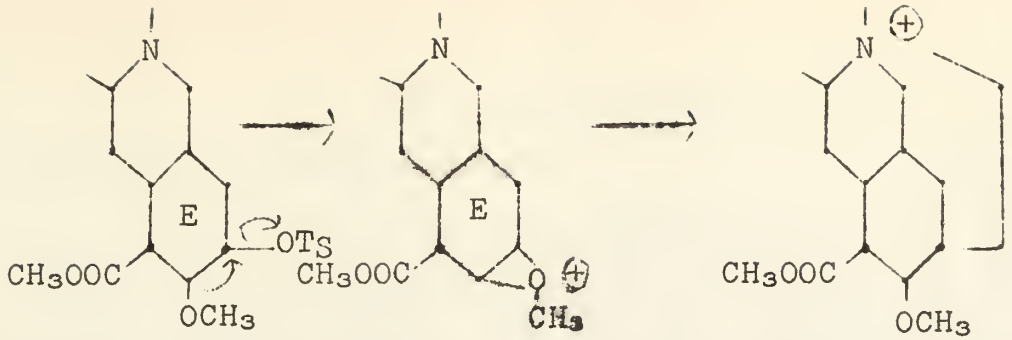


Further, 3-isoreserpic acid does not form a lactone as is obtained from reserpic acid. On the basis of I, 3-isoreserpic acid should readily lactonize whereas the conformation II for the iso compound would explain the difficulty encountered in lactone formation.

The absolute configuration for yohimbine indicates that the hydrogen at C-3 is in the α-orientation. The contribution of such an axial H is shown by the difference in molecular rotation between a series of 3 yohimbane derivatives and their corresponding tetradehydro compounds (in which the asymmetry at C-3 is destroyed). The values vary from -586 to -602°. The difference between a series of 3 alloyohimbane derivatives and their corresponding tetradehydro derivatives are likewise highly negative. Therefore, the hydrogen at C-3 in alloyohimbane is α and 3-epialloyohimbane possesses absolute configuration at C-3, 15, 20 indicated in B.[8,9,10,11]

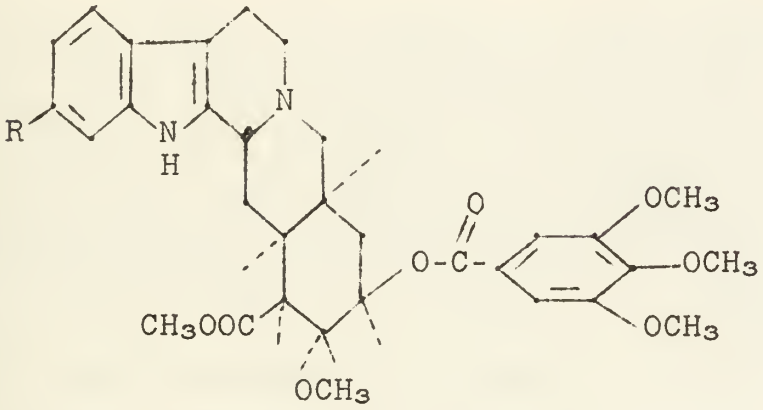
By application of Hudson's Lactone Rule the groups at C-16 and C-18 are oriented in the β-position.[5-8-10-11]

Finally, the stereochemical course of the detosylation of methyl reserpate tosylate to methyl anhydroreserpate and the concurrent internal quaternization of methyl reserpate tosylate can be most readily explained by neighboring group participation of a C-17 methoxyl placed <u>trans</u> to the groups at C-16 and C-18.[7-8-11-12]



The internal quaternization can be considered to proceed by double inversion.

Conversion of deserpidinol to rauwolscinyl alcohol also places the 17-OCH_3 trans to the C-16 and 18 substituents. The stereochemical structure for reserpine and deserpidine can be written as follows:



Reserpine R=OCH_3
Deserpidine R=H

BIBLIOGRAPHY

1. University of Illinois Organic Seminars May 20, 1955.
2. E. Schlittler, et.al., Exper. 11, 64 (1935).
3. E. Schlittler, et.al., J.A.C.S., 77, 3547 (1955).
4. E. Schlittler, et.al., J.A.C.S., 77, 1071 (1955).
5. O. Wintersteiner, et.al., J.A.C.S., 77, 2028 (1955).
6. E. E. Van Tamelen, et.al., J.A.C.S., 77, 3930 (1955).
7. E. Wenkert and L. H. Liu, Exper., 11, 302 (1955).
8. E. Schlittler, et.al., Exper. 11, 303 (1955).
9. C. F. Huebner and E. Wenkert, J.A.C.S., 77, 4180 (1955).
10. O. Wintersteiner, J.A.C.S., 77, 4687 (1955).
11. E. Schlittler, et.al., J.A.C.S., 77, 4335 (1955).
12. E. E. Van Tamelen and P. D. Hance, J.A.C.S., 77, 4692 (1955).

THE IVANOFF REAGENT

Reported by Norman Shachat November 18, 1955

Ivanoff (1) found that phenylacetic acid salts behaved anomalously toward Grignard reagents. This same effect was noticed earlier by Grignard (2) in an attempt to prepare diethylbenzylcarbinol from the salt, $C_6H_5CH_2CO_2MgX$, and ethylmagnesium bromide. Ethylene was evolved, and after hydrolysis, phenylacetic acid was obtained in accordance with the following sequence:

$$C_6H_5CH_2CO_2MgCl + C_2H_5MgBr \longrightarrow C_6H_5\underset{\displaystyle MgBr}{\underset{|}{C}}HCO_2MgCl + \overline{C_2H_6}$$

$$C_6H_5\underset{\displaystyle MgBr}{\underset{|}{C}}HCO_2MgCl \xrightarrow{H_2O} C_6H_5CH_2CO_2H + Mg(OH)Br + Mg(OH)Cl$$

Ivanoff proved the existence of the complex, now called the Ivanoff reagent, by obtaining phenylmalonic acid by carbonation He further showed that aliphatic Grignard reagents, with the exception of methylmagnesium iodide, and a few aryl Grignard reagents react similarly to give phenylmalonic acid in yields of 40-60%. Most aryl Grignard reagents gave substituted β-hydroxybutyric acids(3). For example, 2,3,4-triphenyl-3-hydroxybutyric acid was obtained in 61% yield:

I $$C_6H_5CH_2CO_2MgCl + C_6H_5MgBr \longrightarrow C_6H_5\underset{\displaystyle MgBr}{\underset{|}{C}}HCO_2MgCl + C_6H_6$$

II $$C_6H_5CH_2CO_2MgCl + C_6H_5MgBr \longrightarrow C_6H_5CH_2\overset{\displaystyle O}{\overset{\|}{C}}C_6H_5$$

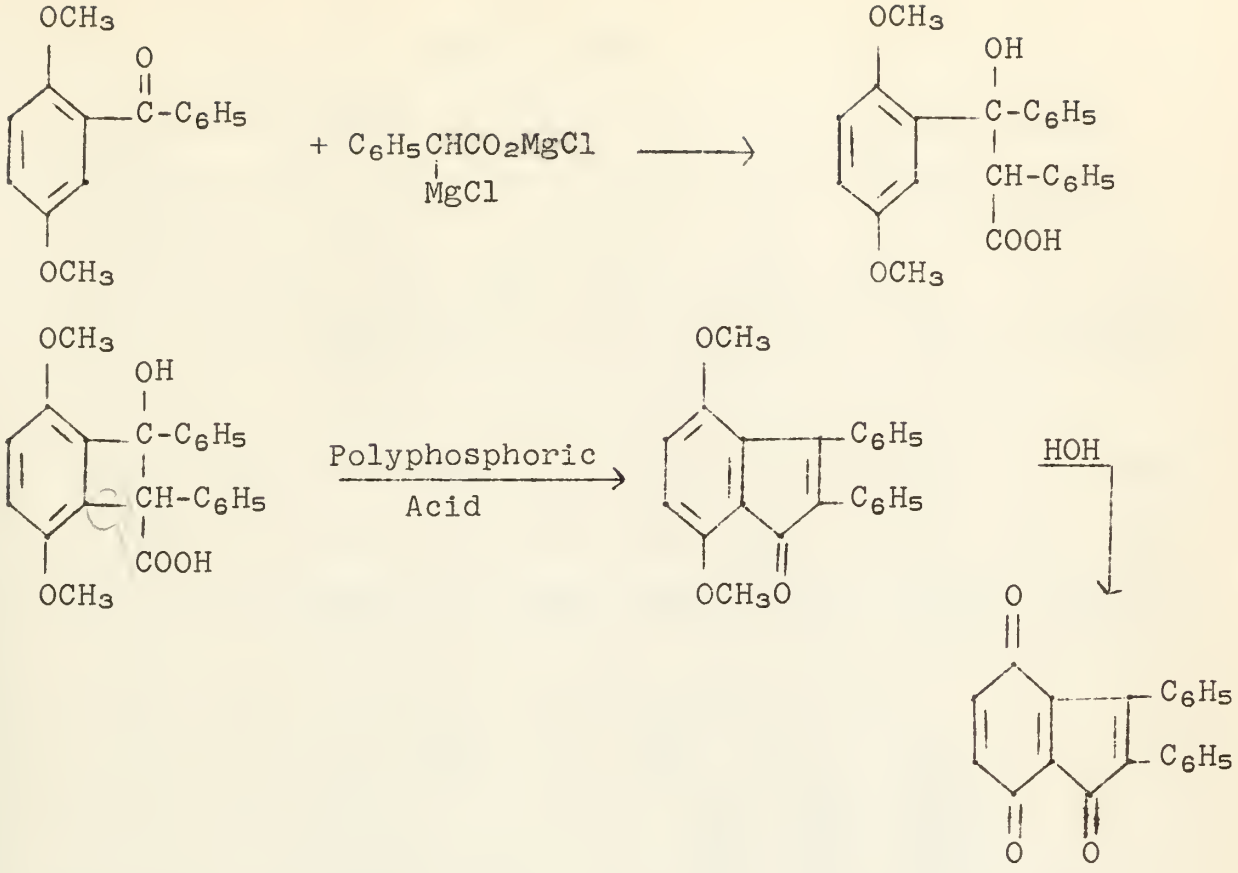
III $$C_6H_5\underset{\displaystyle MgBr}{\underset{|}{C}}HCO_2MgCl + C_6H_5CH_2\overset{\displaystyle O}{\overset{\|}{C}}C_6H_5 \longrightarrow C_6H_5CH_2\text{-}\underset{\displaystyle C_6H_5}{\underset{|}{\overset{\displaystyle OH}{\overset{|}{C}}}}\text{---}\underset{\displaystyle H}{\underset{|}{\overset{\displaystyle C_6H_5}{\overset{|}{C}}}}\text{-}CO_2H$$

The difference in the reactivity of alkyl reagents as compared with most aryl reagents was attributed to the difference in the rate of reaction I as compared to reaction II (4,5).

Ortho halogen substituents in the phenyl ring of the salt, $C_6H_5\overline{CH_2CO_2}MgX$, because of the inductive effect, activate the methylene hydrogens, so that even aryl Grignard reagents give good yields of Ivanoff reagent (1,4,6).

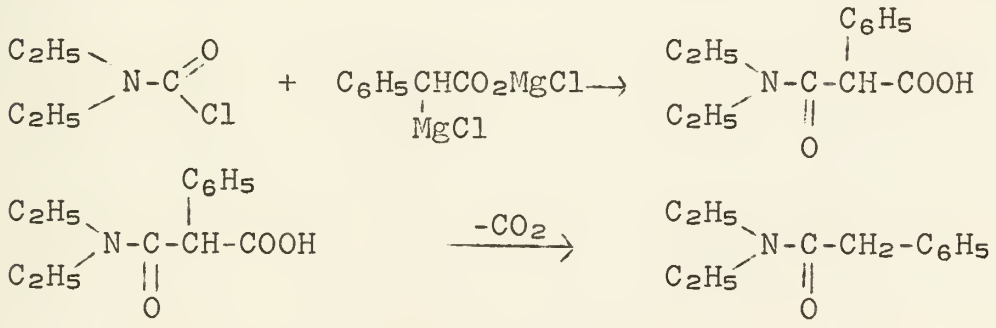
The sodium salt of phenylacetic acid was found to react with Grignard reagents in a somewhat similar manner to the magnesium chloride salt (4,7).

As might be anticipated, the Ivanoff reagent behaves as a typical Grignard reagent, thereby making available a useful synthetic tool. With ketones (7,16,18), substituted β-hydroxypropionic acids can be obtained in high yields. For example, Koelsch and Prill (15) made use of this reaction in the following synthesis:



Substituted β-hydroxyaliphatic acids are formed similarly from aldehydes in high yields (8). Acyl halides react to give very pure ketones in 50-75% yields, and substituted hydroxyglutaric acids in 10-15% yields (9). More recently attempts to prepare diketones by reaction with diacyl halides proved much less successful (13,14).

A recent interesting synthetic application is the reaction of the Ivanoff reagent with isocyanates, carbamyl chlorides, and isothiocyanates to yield substituted phenylacetamides and phenylthioacetamides (17). For example, diethylphenylacetamide can be prepared in approximately 71% yield as follows:



$C_6H_5CH_2CN$ (10), $C_6H_5CH{=}CHCH_2CO_2H$ (11), $CH_3CH{=}CHCH_2CO_2H$ (11), and 2-furylacetic acid (12) were shown to react with some Grignard reagents in an analagous manner to the salt, $C_6H_5CH_2CO_2MgX$.

BIBLIOGRAPHY

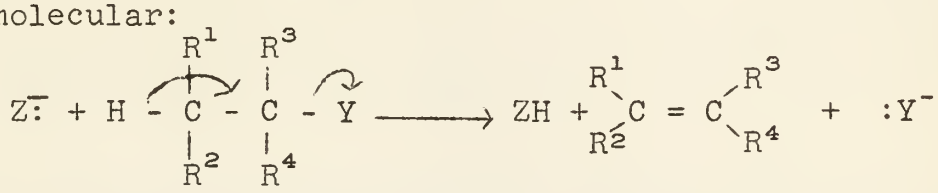
1. Ivanoff and Spassoff, Bull. Soc. Chim. [4], 49, 19-23 (1931).
2. Grignard, Bull. Soc. Chim., 31, 751-757 (1904).
3. Ivanoff and Spassoff, Bull. Soc. Chim. [4], 49, 371-380 (1931).
4. Ivanoff, Bull. Soc. Chim. [5], 4, 682 (1937).
5. Ivanoff and Spassoff, Bull. Soc. Chim. [4], 51, 619 (1932).
6. Ivanoff and Pchenitchny, Bull. Soc. Chim. [5], 1, 223-233 (1934).
7. Ivanoff and Spassoff, Bull. Soc. Chim. [4], 49, 377-379 (1931).
8. Ivanoff and Nicoloff, Bull. Soc. Chim. [4], 51, 1325-1331 (1932).
9. Ivanoff and Nicoloff, Bull. Soc. Chim. [4], 51, 1331-1337 (1932).
10. Ivanoff and Paounoff, Compt. Rend., 197, 923-925 (1933).
11. Ivanoff and Pchenitchny, Bull. Soc. Chim. [5], 1, 233-235 (1934).
12. Ivanoff and Shopoff, C. A., 49, 8190a (1955).
13. Stefanova, C. A., 42, 4156 (1948).
14. Ivanoff and Marekoff, C. A., 48, 10591d (1954).
15. Koelsch and Prill, J. A. C. S., 67, 1296 (1945).
16. Blicke and Zinnes, J. A. C. S., 77, 5168 (1955).
17. Blicke and Zinnes, J. A. C. S., 77, 4849 (1955).
18. Ivanoff, Mihova and Christova, Bull. Soc. Chim. 4, 51, 1321-1325 (1932).
19. Blicke, Zinnes, J. A. C. S., 77, 5399 (1955).

STERIC EFFECTS IN UNIMOLECULAR OLEFIN-FORMING ELIMINATION REACTIONS

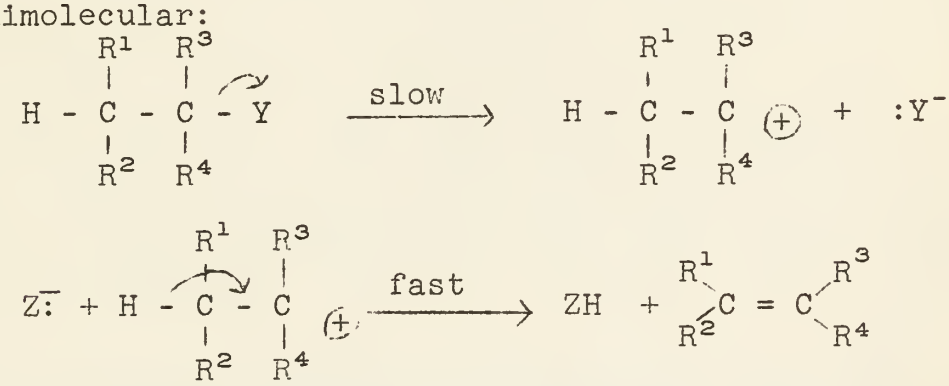
Reported by Joe A. Adamcik November 18, 1955

In 1927 Hanhart and Ingold[1] recognized the bimolecular mechanism in certain olefin-forming elimination reactions and in 1935 Hughes[2] recognized the unimolecular mechanism in other examples of the same reaction.

Bimolecular:



Unimolecular:



(Charges shown on Y and Z are relative, not absolute.)

Since the bimolecular olefin-forming elimination reactions of quaternary ammonium ions were fundamentally similar, it was puzzling that the contradictory orientation rules of Hofmann[3] and Saytzeff[4] should exist. The Hofmann rule, which originally referred to elimination reactions in quaternary ammonium hydroxides, requires, in its general form, the preferential formation of the least alkylated ethylene. The Saytzeff rule, developed to apply to the elimination reactions of alkyl halides, requires that the formation of the most alkylated olefin should be favored.

Hanhart and Ingold[1] proposed an explanation for Hofmann rule orientation. In 1941[5] and in more complete form in 1948[6] Hughes, Ingold and their coworkers proposed an explanation for the operation of these two rules within their respective spheres. According to their proposal, Hofmann rule elimination was the result of the dominance of the inductive effect. The inductive effect would be strongest if -Y were positively charged, explaining Hofmann rule orientation in bimolecular decompositions of 'onium ions. The Saytzeff rule was considered to be the result of the dominance of the electromeric effect, i.e., stabilization of the incipient double bond of the transition state by hyperconjugation. It was proposed that the electromeric effect was dominant in bimolecular eliminations involving alkyl halides, and all unimolecular eliminations.

Unimolecular eliminations almost invariably proceed with concurrent substitution. As has been pointed out[6], the proportion of olefin formed is often more simply related to structure than the separate rate of the elimination process. The proportion of olefin formed[7] is identical with the ratio $k_E/k_E + k_S$ where k_E is the rate of the elimination step and k_S is the rate of the substitution step.

Hughes, Ingold and coworkers[6] presented considerable experimental evidence, both olefin yield and orientational data, which was consistent with their interpretation. However, in the case of unimolecular elimination reactions of tertiary alkyl halides and sulfonium ions, only two alkyl groups, t-butyl and t-amyl, were considered.

Previously, Brown and coworkers[8,9] had introduced the concept of B strain and had proposed, among other things, that B strain was important in determing the direction of dehydration of alcohols. In subsequent papers they[7,10,11,12,13] have developed evidence for the participation of steric strain in determining the rate and direction of unimolecular elimination reactions. They have presented considerable evidence that B strain is of importance in determining the rate of ionization of tertiary halides and alcohols since the formation of the planar carbonium ions would involve release of strain. This factor does not, of course, affect olefin yield or orientation.

It is important to distinguish the separate steric effects envisaged by Brown and coworkers[7,13] which can affect olefin yield and the direction of elimination. They are (1) steric assistance of proton expulsion (2) steric hindrance to substitution and (3) steric destabilization of the transition state leading to the olefin. Effect (1) would increase k_E while effect (2) would decrease k_S. Since it has not been possible to determine k_E or k_S individually, but only the ratio $k_E/k_E + k_S$ the separate contributions of effects (1) and (2) have not been observed. However, Brown and coworkers have obtained considerable evidence which they interpret as showing that the olefin proportion does in fact rise with increasing steric requirements in the manner expected.

Effect (3) would be expected to affect the orientation of the entering double bond. Brown and Berneis[11] showed that dimethylneopentylcarbinyl chloride, when decomposed in an aqueous medium, produced the 1-olefin as the major olefinic product thereby exhibiting elimination according to the Hofmann rule. This fact was interpreted as being due to the interference of the cis-methyl and t-butyl groups.

The proposals of Brown and coworkers have been criticized by Hughes, Ingold and Shiner[14]. Brown and Fletcher[7] considered the olefin yields from the series $Et_xMe_{3-x}CCl$, which showed an initial increase with increasing x but remained nearly constant for the last two members, to provide evidence for a steric effect. Hughes, Ingold and Shiner pointed out that Brown and Fletcher neglected an important statistical factor and were able to reproduce Brown and Fletcher's olefin

yields on the basis of certain assumptions based on the electromeric effect. Brown and coworkers[13] have shown that the procedure of Hughes, Ingold and Shiner is not satisfactory for two other series of compounds and therefore the agreement in the first series is probably fortuitous. As Brown and Fletcher's original explanation is not adequate the explanation of this series is rather obscure. Brown and coworkers[13] state that there may be steric hindrance to the expulsion of a proton.

The high olefin yields obtained from the solvolysis of dimethyl- and diethyl-t-butyl carbinyl chlorides were also considered by Brown and Fletcher[7] to be evidence for the participation of steric effects. Hughes, Ingold and Shiner[14] considered that the possibility of Wagner-Meerwein rearrangement made these cases unsuitable for comparison with the others. Brown and coworkers[13] have shown, however, that the related halides dimethyl-t-amylcarbinyl chloride and methyl-ethyl-t-butylcarbinyl chloride undergo unimolecular elimination without rearrangement, although they also lead to high olefin yields.

Finally, Hughes, Ingold and Shiner[14] stated that elimination according to the Hofmann rule in the case of dimethylneopentylcarbinyl chloride[11,13] could be due to hyperconjugation of the t-butyl-to-carbon bond. However, their objection to Brown and coworkers'[11,13] original interpretation is based upon the impossibility of explaining the results in terms of effects (1) and (2) rather than in terms of effect (3) which would explain them. Furthermore, Brown and coworkers[13] show that the regular increase in the ratio of 1- to 2- olefin which would be expected in the series $RCH_2CBr(CH_3)_2$ as R is varied through methyl, ethyl, isopropyl, and t-butyl if this explanation is valid is not observed; rather there is a sharp increase when R is t-butyl as would be expected on the basis of the steric strain hypothesis.

BIBLIOGRAPHY

1. W. Hanhart and C. K. Ingold, J. Chem. Soc., 997 (1927).
2. E. D. Hughes, J. Am. Chem. Soc., 57, 708 (1935).
3. A. W. Hofmann, Ann. 78, 253 (1851); 79, 11 (1851).
4. A. Saytzeff, Ann. 179, 296 (1875).
5. E. D. Hughes and C. K. Ingold, Trans. Faraday Soc. 37, 657 (1941).
6. M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Woolf, J. Chem. Soc., 2093 (1948) and preceding papers (ibid., 2038-2093). C. K. Ingold "Structure and Mechanism in Organic Chemistry", Cornell University Press, 1953, pp. 419-472 also contains a discussion of this proposal.
7. H. C. Brown and R. S. Fletcher, J. Am. Chem. Soc., 72, 1223 (1950).
8. H. C. Brown, H. Bartholomay, Jr. and M. D. Taylor, J. Am. Chem. Soc., 66, 435 (1944).

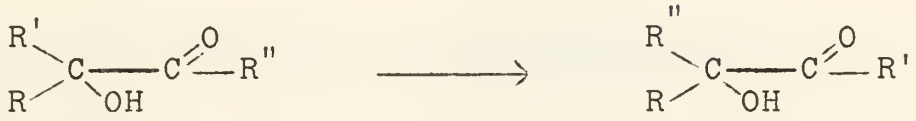
9. H. C. Brown, Science 103, 385 (1946).
10. H. C. Brown and R. S. Fletcher, J. Am. Chem. Soc., 71, 1845 (1949).
11. H. C. Brown and H. L. Berneis, J. Am. Chem. Soc., 75, 10 (1953).
12. H. C. Brown and R. B. Kornblum, J. Am. Chem. Soc., 76, 4510 (1954).
13. H. C. Brown and I. Moritani, J. Am. Chem. Soc., 77, 3623 (1955) and preceding papers in this series (ibid., pp. 3607-3622).
14. E. D. Hughes, C. K. Ingold and V. J. Shiner, Jr., J. Chem. Soc., 3827 (1953).

A NEW ROUTE TO TERTIARY α-KETO ALCOHOLS

Reported by H. S. Killam December 2, 1955

Tertiary α-keto alcohols have been the object of numerous investigations not only in the synthetic field but also in the study of reaction mechanisms.

The acid catalyzed isomerization of compounds similar to (I) has been studied by Favorsky.[1]

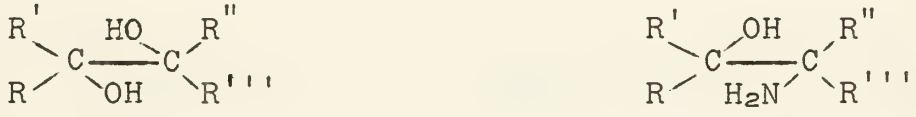


I

R=H; R'=Me, Et; R"=Pr, t-Bu, ∅

R=Me; R'=Me; R"=iPr

Interest has also been shown in the possibility of the conversion of this type of compound into the asymmetric bitertiary glycols (II) and amino alcohols (III).[2,3,4]

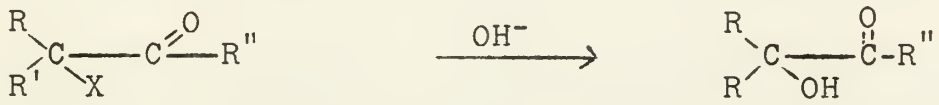


II III

Recently,[5] cycloketols have been prepared with a view to subsequent conversion into α,α'-dihydroxy ketones. This sequence appears not only in the cortisone series but also in other compounds which exhibit biological activity.

Preparation:

1. Probably the oldest and most frequently used method of preparation of tertiary α-ketols is the alkaline hydrolysis of the corresponding α-haloketone.

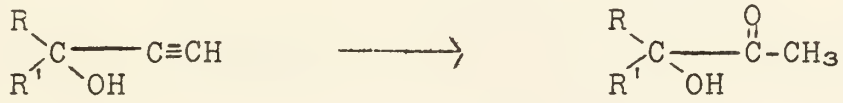


Undesired characteristics of this reaction are the following:

(1) The preparation of the desired α-haloketone is complicated by isomer formation.[6]

(2) Preparation of the haloketone may also be accompanied by formation of the α,α'-dihaloketone.
(3) The hydrolysis of the haloketone may be followed by isomerization of the product.[7]
(4) Hydrolysis may lead to the formation of the carboxylic acid.[8]

2. Satisfactory results have been obtained by the hydration of the α-acetylenic alcohol to the corresponding α-ketol.[10]

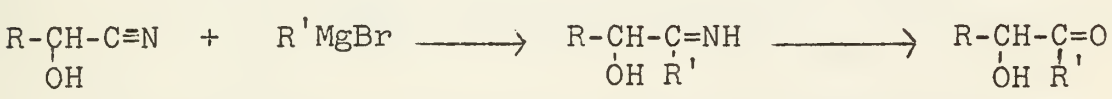


In the cyclic series this method affords good yields of the cyclopentane, -hexane and -heptane derivatives.[5]

Although the reaction conditions are ideal for isomerization, abnormal results have been observed in only one case.[11,12] However, attempts to prepare α-ketols by hydration of substituted acetylenic alcohols has led to the formation of the corresponding β-ketol instead of the desired α-ketol.[13]

3. A comparatively new method of α-ketol preparation[14] consists of treating the α-hydroxy acid with methyllithium. In this manner the cyclohexyl and cyclopentyl ketols were prepared in good yields.

4. One of the simplest methods of preparing I should be the treatment of the cyanohydrin of the ketone with a Grignard reagent. This reaction would lead to the α-imino-alcohol and thence by hydrolysis to the α-ketol in a manner analogous to the Blaise reaction.

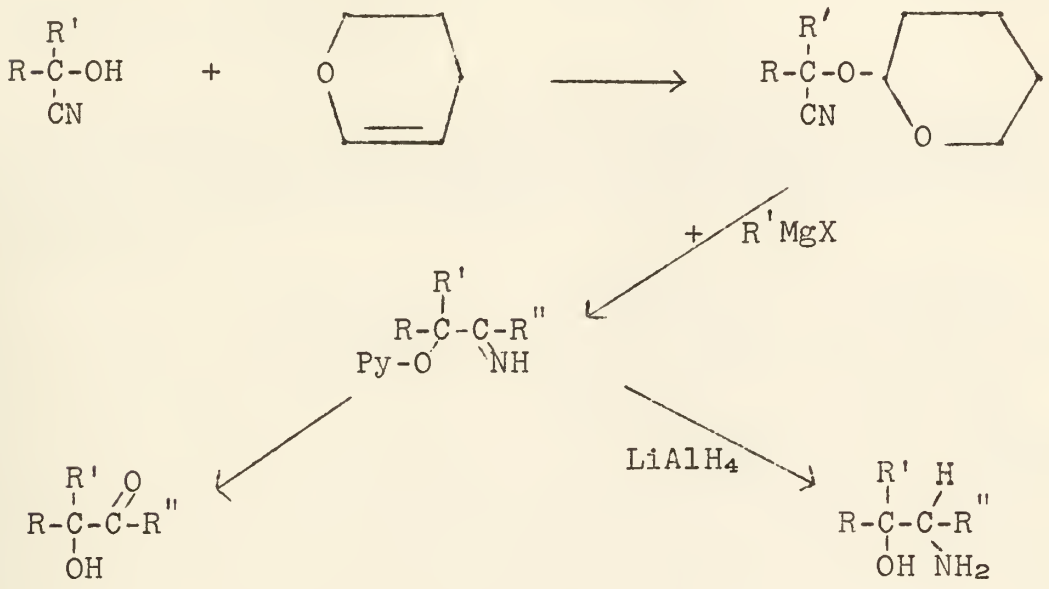


Investigations[9] indicated that this reaction did not proceed as smoothly or as directly as would be predicted. Only in special cases was it found to be of preparative value.

Elphimoff-Felkin,[17] on exploring the possibilities of modifying this procedure, found that its shortcomings were due to the decomposition of the cyanohydrin at the temperature necessary for reaction to occur. Further work showed that if the carbinol were first protected by reaction with 2,3-dihydropyran the subsequent treatment with the Grignard reagent did not cause decomposition of the starting material. Acetals of this type had been shown not only to be easily decomposed in acid but also to be unreactive toward the Grignard reagent.[16] During the course of this study it was

found that reduction of the imino intermediate with lithium aluminium hydride produced the corresponding tertiary α-amino alcohol in good yields.

The reaction of alcohols with 2,3-dihydropyran had been reported earlier by Paul.[15]



BIBLIOGRAPHY

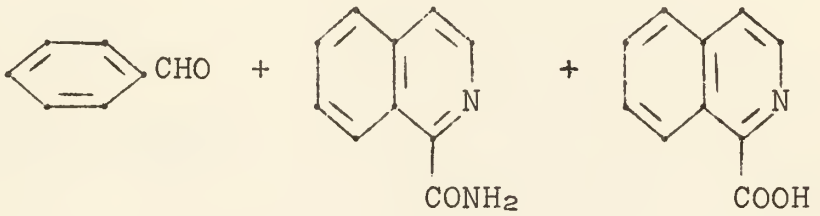
1. A. E. Favorsky, Bull. soc. chim., 39, 216 (1926).
2. W. J. Hickinbottom, A. Hyatt and M. Sparke, J. Chem. Soc., 2533 (1954).
3. I. Elphimoff-Felkin and B. Tchoubar, Compt. rend., 231, 1314 (1950).
4. I. Elphimoff-Felkin and B. Tchoubar, ibid., 236, 387 (1953).
5. J. Billimoria and N. Maclagan, J. Chem. Soc., 3257 (1954).
6. A. Smith, W. Wilson and R. Woodger, Chem. and Ind., 309 (1954).
7. A. Oumnoff, Bull. soc. chim., 43, 563 (1928).
8. B. Tchoubar and O. Sackur, Compt. rend., 208, 1020 (1939).
9. D. Gauthier, ibid., 152, 1259 (1911).
10. W. J. Hickinbottom, A. Hyatt and M. Sparke, J. Chem. Soc., 2529 (1954).
11. H. E. Stavley, J. Am. Chem. Soc., 61, 79 (1939).
12. M. W. Goldberg, R. Aeschbacher and E. Hardegger, Helv. Chim. Acta, 26, 680 (1943).
13. A. W. Johnson, The Acetylenic Alcohols, E. Arnold and Co., London, pp. 102-105, 355-356.
14. J. D. Billimoria and N. F. Maclagan, J. Chem. Soc., 3067 (1951).
15. R. Paul, Bull. soc. chim. France, 1, 971 (1934).
16. W. E. Parham and E. L. Anderson, J. Am. Chem. Soc., 70, 4987 (1948).
17. I. Elphimoff-Felkin, Bull. soc. chim. France, 748 (1955).

ACID HYDROLYSIS OF REISSERT COMPOUNDS

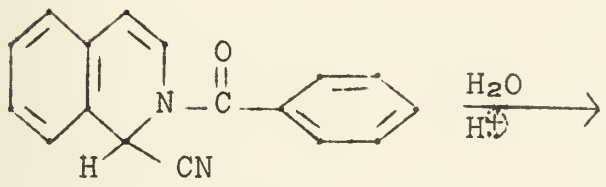
Reported by J. S. Dix December 2, 1955

Reissert compounds are valuable as reagents for the preparation of aldehydes[1,2,3], and in the synthesis of substituted isoquinolines and quinolines[4]. The formation of an aldehyde is achieved by the acid hydrolysis of its corresponding Reissert compound.

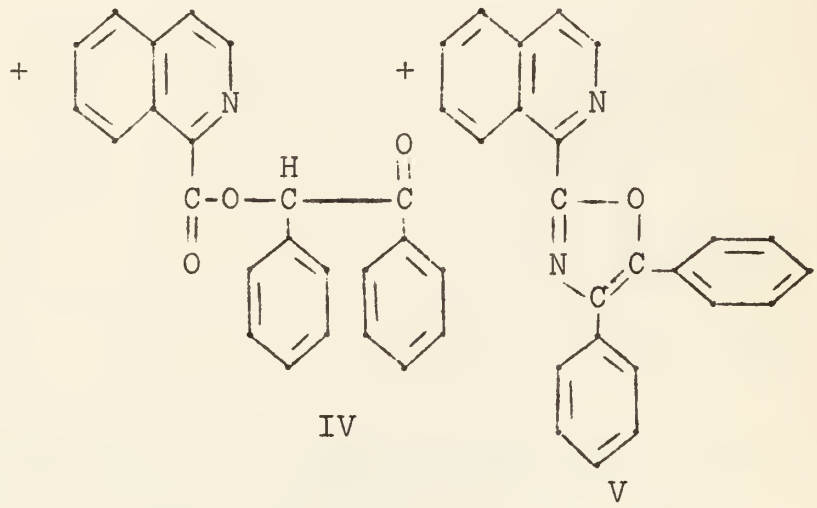
A typical Reissert compound, 1-cyano-2-benzoyl-1,2-dihydroisoquinoline (I) yields upon acid hydrolysis a variety of products besides benzaldehyde: (II), (III), (IV)[1], and (V)[5]. Analogous products are formed by the quinoline Reissert compound.



II III



I



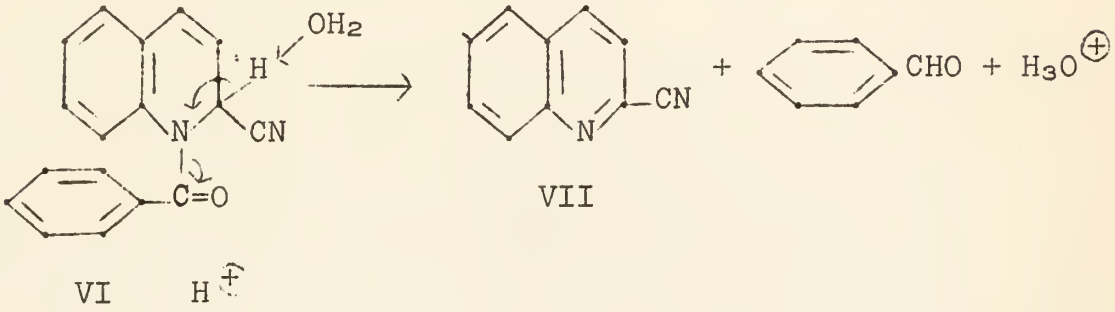
IV V

In addition to being able to account for these products, any proposed mechanism must be consistent with the investigation of Swain and Sheppard[6], who found a small isotope effect in the hydrolysis of (VI) with H_2SO_4-t.

Mechanisms which deal only with the primary products of hydrolysis - i.e., benzaldehyde and quinaldonitrile (VII) or its derivatives - have been proposed for VI by Swain

(Mechanism A)[6], and also by Colonna (Mechanism B)[7], who suggests an analogy with the reaction of quinoline N-oxide, benzoyl chloride, and potassium cyanide.

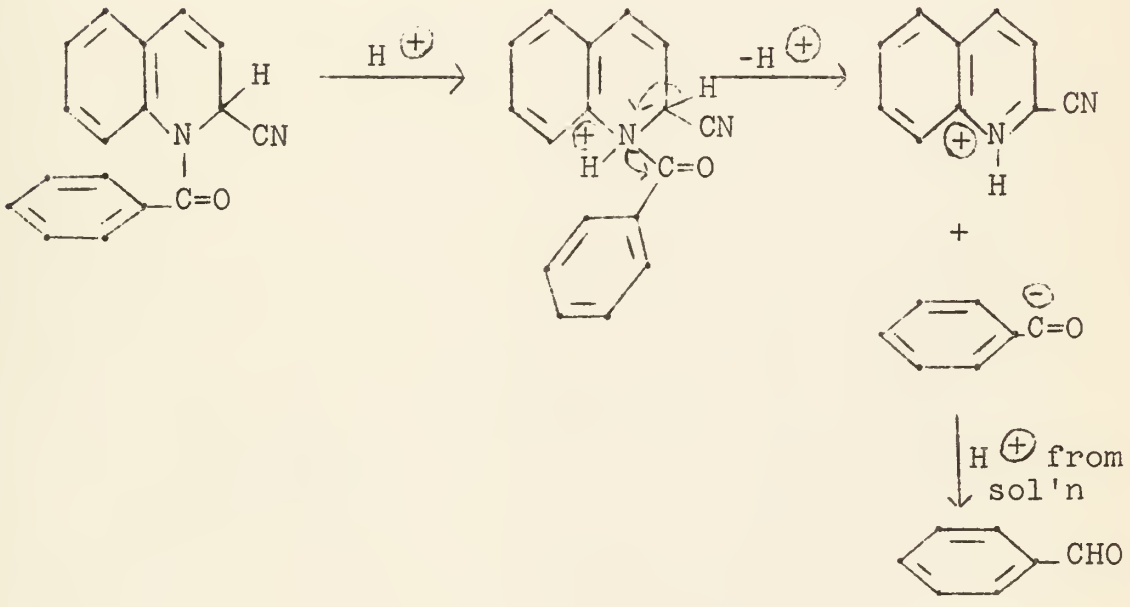
Mech. A



VI H⊕ VII

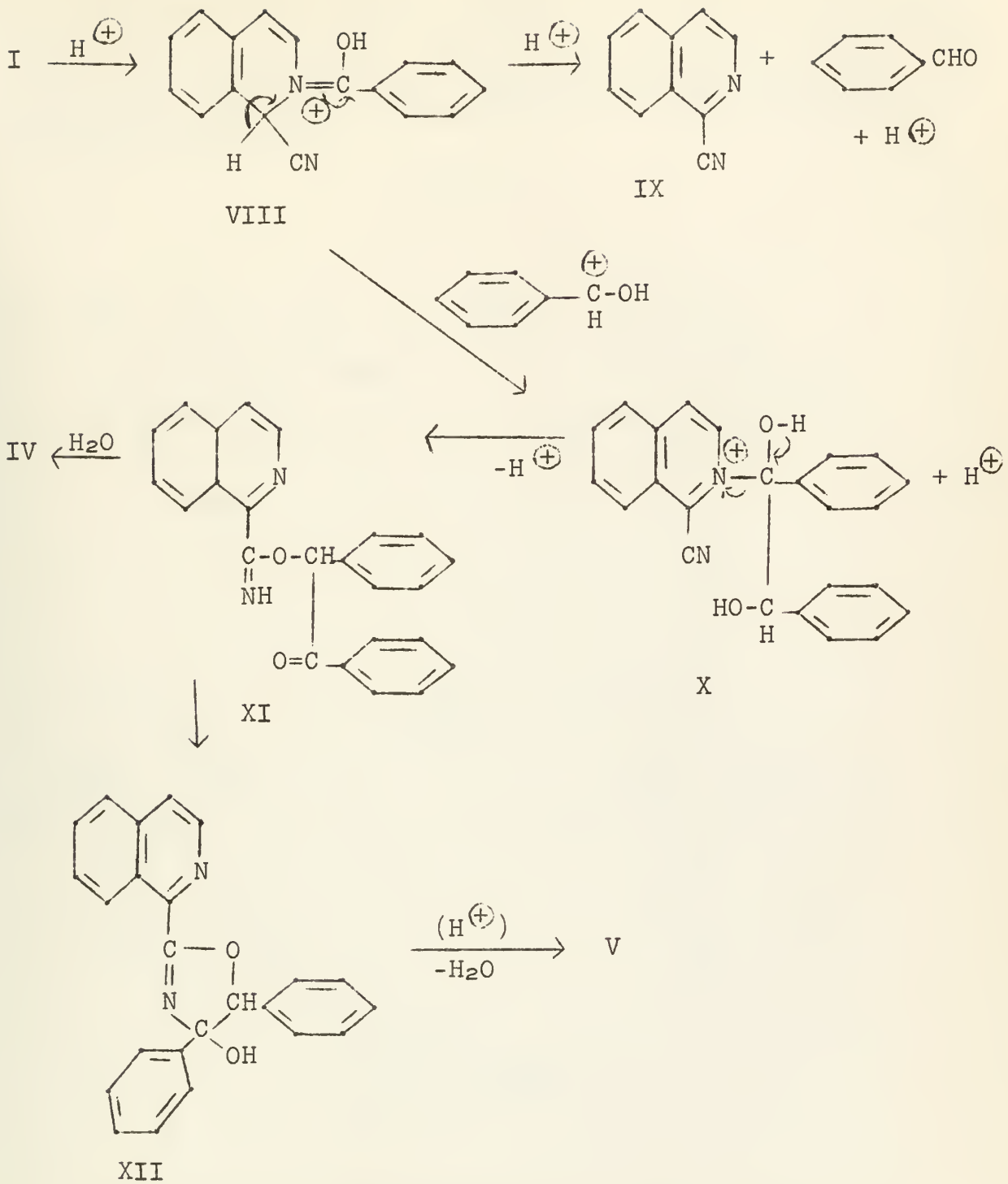
(as activated complex)

Mech. B



McEwen and his co-workers[5,8] originally proposed a mechanism much like mechanism A, but which would account for the other products by postulating competition between the conjugate acid of the benzaldehyde formed and a proton for acceptance of an electron pair of the original carbonyl carbon:

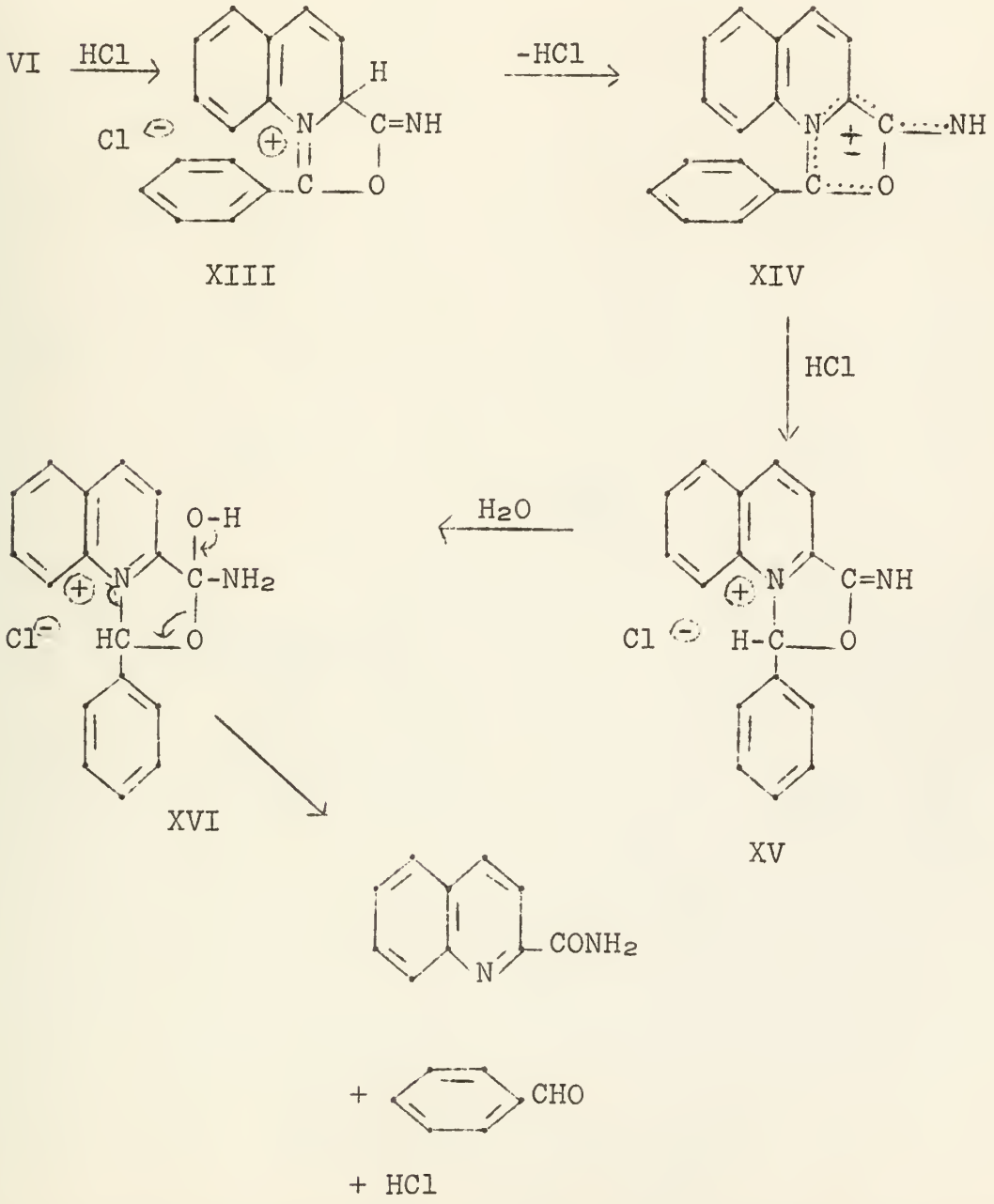
Mech. C



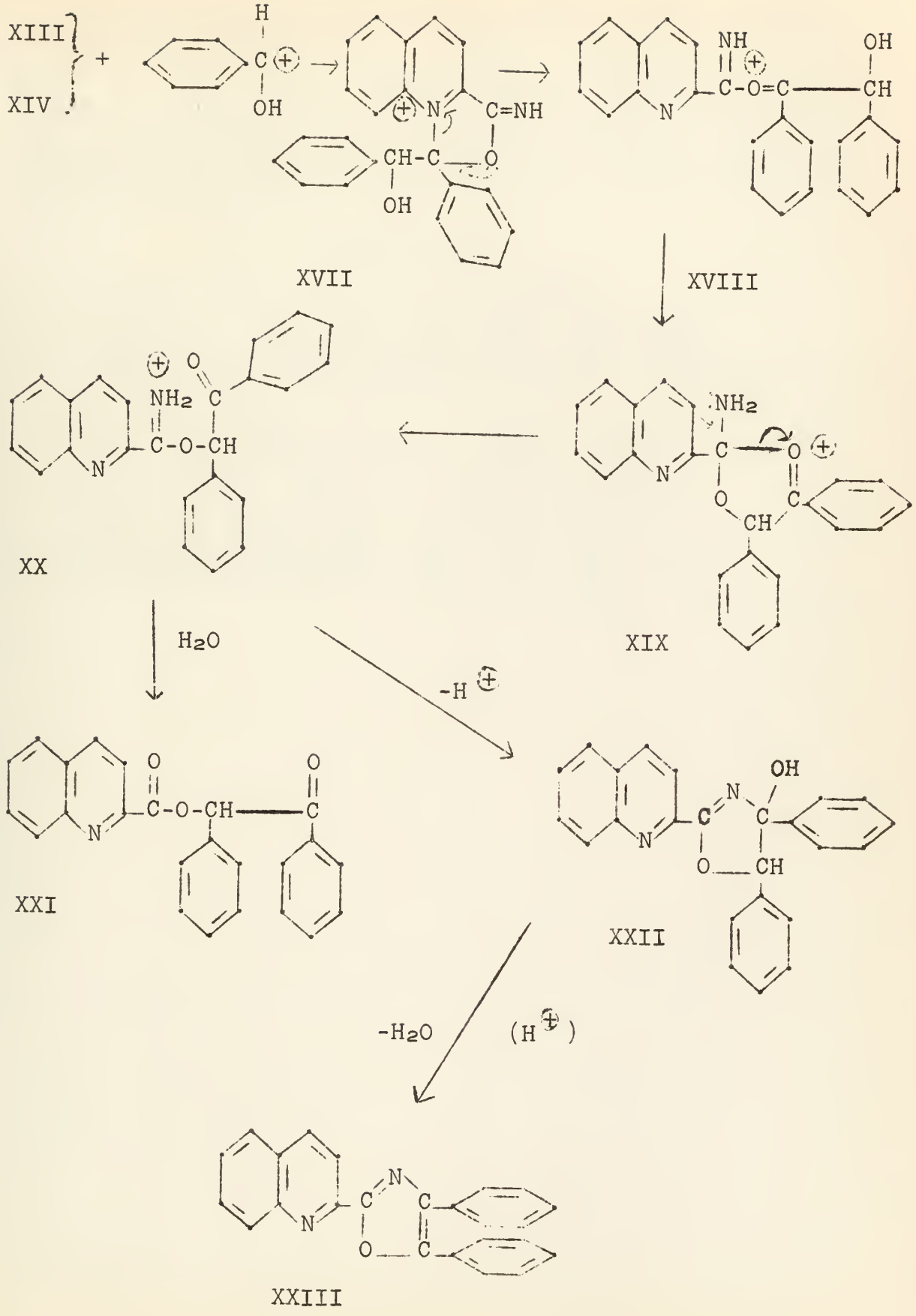
The mechanisms considered thus far have assumed the nitrile which is formed (as IX) is hydrolyzed to its amide or acid and therefore cannot be isolated from the reaction mixture. However, McEwen and Cobb[9] in further studies have obtained results which lead them to believe that quinaldonitrile (or isoquinaldonitrile) cannot be an intermediate in the reaction. Hydrolysis of VI in concentrated hydrochloric acid was allowed to go to partial completion. Unreacted VI, quinaldamide, quinaldic acid, benzoin quinaldate, and benzaldehyde were recovered, but no VII. An amount of VII equal to that of the

benzaldehyde isolated, and therefore equal to the minimum amount of VI hydrolyzed, was hydrolyzed under the same conditions. In two trials, 14% and 39% of VII were recovered. When approximately equimolar amounts of VI and VII were used, 11% of VII was recovered. In accordance with their belief that these results show that no nitrile can be formed during hydrolysis, McEwen and Cobb formulate the mechanism below for acid hydrolysis of VI (hydrolysis of I would proceed by an analogous mechanism).

Mech. D



The other products can be accounted for by assuming addition of the conjugate acid of the benzaldehyde to either XIV or XIII


XIII
XIV
+
XVII
XVIII
XIX
XX
XXI
XXII
XXIII
H_2O
$-H^{\oplus}$
$-H_2O$
$(H^{\oplus})$

Unstable compounds have been formed by the reaction of a benzoyl Reissert compound with anhydrous hydrogen chloride in an inert solvent[5,9,10,11]. Such a compound isolated by McEwen and Cobb yielded benzaldehyde by hydrolysis in acidic, basic, or neutral media. The compound contained chlorine, but elemental analysis did not agree with XIII or XV. The authors considered it to be a mixture, evidently too unstable to purify, but regarded its behavior as strong evidence in favor of mechanism D.

BIBLIOGRAPHY

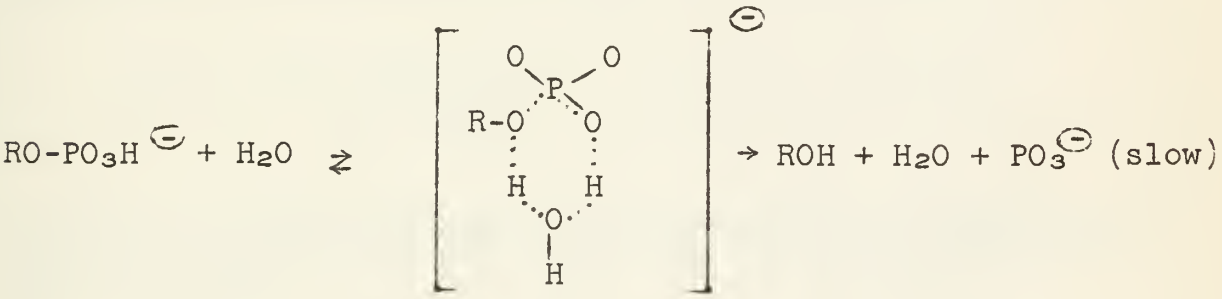
1. Reissert, Ber. 38, 1603, 3426 (1905).
2. Woodward, J. Am. Chem. Soc., 62, 1626 (1940).
3. Grosheintz and Fischer, ibid., 63, 2021 (1941).
4. Samuels, Org. Chem. Seminar, U. of Ill., 1953-1954, I, 18.
5. McEwen, Kindall, Hazlett and Glazier, J. Am. Chem. Soc., 73, 4591 (1951).
6. Swain and Sheppard, Abst. of Papers of 127th Meeting A.C.S., March 29 to April 7, 1955, p. 40N.
7. Colonna, Gazz. chim. ital., 82, 503 (1952).
8. McEwen and Hazlett, J. Am. Chem. Soc., 71, 1949 (1949).
9. McEwen and Cobb, ibid., 77, 5042 (1955).
10. Kaufmann and Dändliker, Ber., 46, 2924 (1914).
11. Haworth and Perkin, J. Chem. Soc., 127, 1434 (1925).

MECHANISMS FOR THE HYDROLYSIS OF ORGANIC PHOSPHATES

Reported by John F. Zack, Jr. December 9, 1955

Monoaliphatic Phosphates: Early kinetic studies[1,2] showed that the rate of hydrolysis of simple monoaliphatic phosphates is related to the pH of the reaction medium. The rate of hydrolysis of methyl phosphate is slow in alkaline solution, rises to a maximum around pH 4, falls to a minimum at pH 1-2 and then rises again in strong acid. The kinetics of the hydrolysis are first-order[3]. The maximum rate occurs at the pH where the monoionic form is present in the greatest concentration. With the aid of the dissociation constants of monomethyl phosphate, and on the assumption that the monoionic form is the reacting species, it is possible to construct a theoretical curve of first order rate coefficients against pH which closely fits the observed rate curve in the pH range 1.5-9. Tracer studies using O^{18} have shown that a fission of the phosphorus-oxygen bond is involved. The same observations have been made for a great variety of monoalkyl phosphates[3,7].

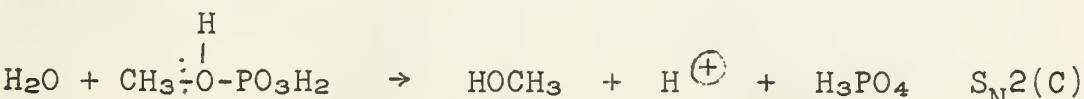
Several mechanisms for the hydrolysis have been postulated to fit these data. The most probable mechanism involves a cyclic transition state[4,5]:



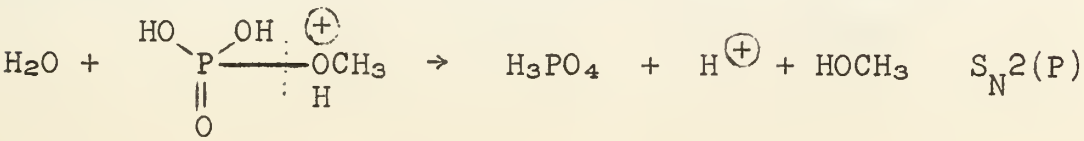
$$H_2O + PO_3^- \rightarrow H_2PO_4^- \quad \text{(fast)}$$

The dianionic form of the phosphate is stable to attack by OH^- because of electrostatic repulsion.

In strong acid the rate of hydrolysis of monomethyl phosphate is second order[3]. The rate determining step involves attack by solvent. Isotope studies show that both C-O and P-O bonds are broken. Therefore two reactions are taking place simultaneously:



$S_N2(C)$



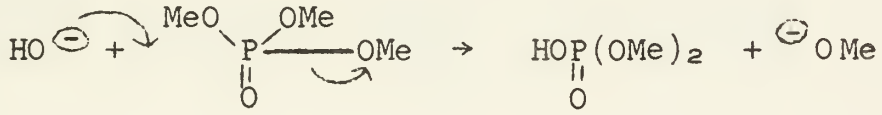
$S_N2(P)$

Monoaromatic Phosphates: Monoaromatic phosphate esters behave in the same manner as monoaliphatic phosphates in the pH range 1-9[3]. However, the aromatic esters are more reative. Greater stabilization of the transition state may explain this fact.

In contrast to aliphatic phosphates, no acid-catalyzed reactions were found in strong acid solutions[3]. Instead, a limiting rate of hydrolysis is approached. Isotope studies show that only the P-O bond is broken. The actual molecularity cannot be unequivocally assigned. The absence of acid catalyzed reactions with aryl phosphates results, no doubt, from the decreased basicity of the oxygen atom linking the phenyl group to the phosphorus atom.

Diesters of Phosphoric Acid: The rate of hydrolysis of dibenzyl phosphate in strong acid is very rapid[5]. This may be due to the ease with which the benzyl group forms a carbonium ion and enters into displacement reactions. Dimethyl phosphate is hydrolyzed in acid or neutral solutions but is stable in alkali[3]. On the other hand, diphenyl phosphate is hydrolyzed in basic solution[6]. The initial rate is proportional to the concentration of NaOH, although the rate with $Ba(OH)_2$ is much faster.

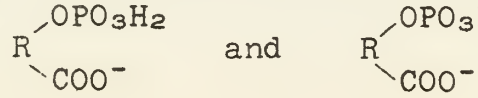
Triesters of Phosphoric Acid: The hydrolysis of trimethyl phosphate in the presence of NaOH is second order[3]. A P-O bond is broken and only one methyl group is displaced:



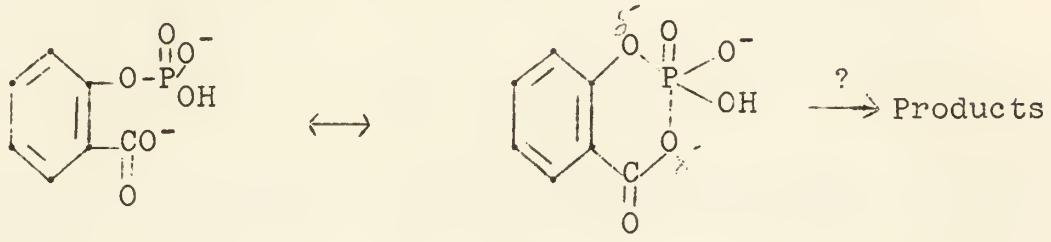
In acid, trimethyl phosphate is hydrolyzed in a bimolecular reaction which is not acid catalyzed. In this case, a C-O bond is broken:

A bimolecular reaction which forms methyl iodide takes place in the presence of iodide ion[3].

Neighboring Carboxyl: In aromatic phosphates, when a carboxyl group is present in an ortho-position the rate constant for the hydrolysis is about 10^5 times greater than for unsubstituted phosphates[8-10]. The maximum rate occurs at about pH 5.3. Evaluation of dissociation constants and partial rate constants indicate that the following are the principal reactive species:



Chanley et al. propose the following mechanism to explain the carboxylate participation:



Lanthanum hydroxide has been found to be a very effective catalyst in the hydrolysis of monophosphates[4]. The rate is increased considerably by a substituent in the β-position of the ester. A cyclic intermediate has been postulated in this case also.

Bibliography

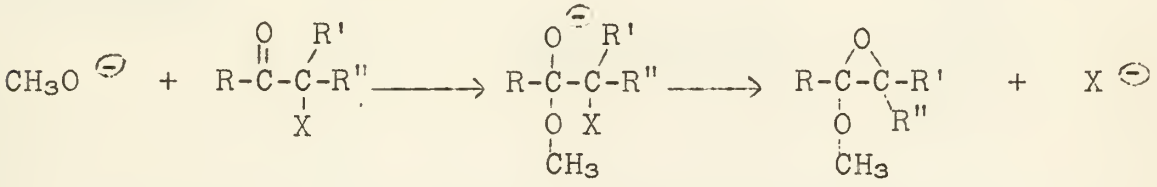
1. Bailly, Bull. soc. chem. (5), 9, 314 (1942).
2. Desjobert, ibid., 14, 809 (1947).
3. Barnard et al., Chem. and Ind., 760 (1955).
4. Butcher and Westheimer, J. Am. Chem. Soc., 77, 2420 (1955).
5. Kumamoto and Westheimer, ibid., 77, 2515 (1955).
6. Helleiner and Butler, Canad. J. Chem., 33, 705 (1955).
7. Swoboda and Crook, Biochem. J. 59, XXIV (1955).
8. Chanley, Gindler and Sobotka, J. Am. Chem. Soc., 74, 4387 (1952).
9. Chanley and Gindler, ibid., 75, 4035 (1953).
10. Chanley and Feageson, ibid., 77, 4002 (1955).

EPOXYETHERS

Reported by Willis E. Cupery December 9, 1955

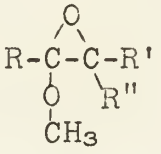
Epoxyethers have long been suggested intermediates in the reaction of α-haloketones with base to form α-hydroxy-ketals, acids, and esters.[1,2,3,4] It is only since 1949,[5] that general synthetic methods have been available and detailed studies of this type of compound made.

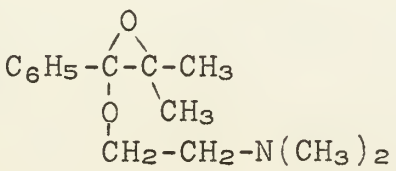
A general method for the preparation of epoxyethers involves attack by alcoholate ion at the carbonyl carbon of an α-haloketone or aldehyde:



A few epoxyethers can be prepared from vinyl ethers and a peracid, but precautions against further reaction of the epoxide with the acids present must be taken.[18,13]

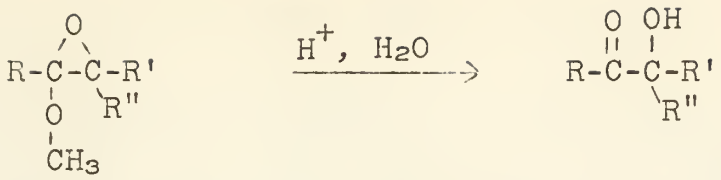
The cyclic epoxyether, 1,2-epoxy-3,4,6-triacetyl glucose has been prepared by treating 3,4,6-triacetylglucosylchloride with ammonia.[15]



	R	R'	R"	Yield	Reference
I	C_6H_5	CH_3	H	66%	5,6
II	C_6H_5			83%	7
III	C_6H_5	C_6H_5	H	33%	8
IV	H	C_2H_5	H	14%	9
V	H	C_5H_{11}	H	48%	9
VI	p-C_6H_5-C_6H_4	CH_3	CH_3	84%	10
VII	p-C_6H_5-C_6H_4	CH_3	C_2H_5	83%	11
VIII	C_6H_5	C_6H_5	C_6H_5	80%	12
IX	C_6H_5	CH_3	CH_3	70%	13
X				80%	14

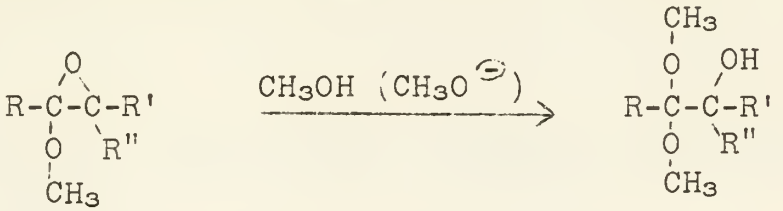
The following reactions of epoxyethers have been studied and appear to be general.

Hydrolysis



This reaction goes in good yield and has been used to characterize epoxyethers. With V, the α-hydroxyheptaldehyde dimer was obtained.[9] The aminoepoxyether, X, reacted very much more slowly, as would be expected from the positive charge the molecule would assume in acidic media.[14]

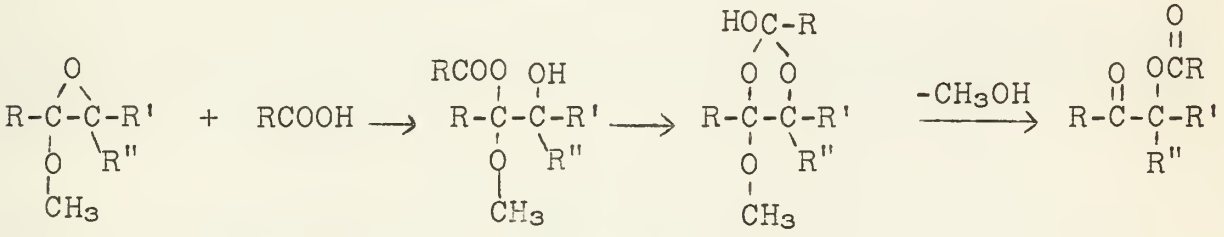
Alcoholysis



Ward[1] and Kohler[2] both proposed an epoxyether as an intermediate in the formation of α-hydroxyketals from certain haloketones with alcoholate ion. This has been supported by the demonstration that this reaction is general for epoxyethers. VIII required dilute acid to undergo this reaction.[12] The reaction was greatly hindered by the amino group in X.[14]

Ring Opening With Organic Acids[10]

Epoxyethers undergo ring opening reactions with organic acids to produce α-ketoesters. This is pictured as an attack at the more positive of the epoxide carbons by the anion of the acid, followed, in turn, by internal ester interchange and the irreversible loss of methanol.



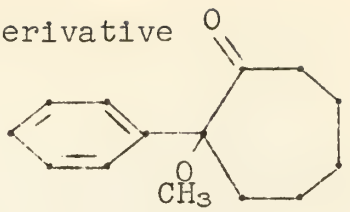
A

This reaction has been most studied for VI with 3,5-dinitrobenzoic acid. Intermediates assigned structure A have been isolated in two cases.[9,10]

Rearrangements with Lewis Acids[11]

The rearrangement of epoxides with Lewis acids has long been recognized as a form of pinacol rearrangement, and subject to the same general considerations. In this case, the opening of the epoxide ring corresponds to carbonium ion formation in an ordinary pinacol rearrangement. In every case, the α-methoxyketone is the only product isolated. The relative ease of migration of groups was found to be: H>alkyl>phenyl, and

$H > C_2H_5 > CH_3$. An interesting tropolone derivative was formed from II in 72% yield.



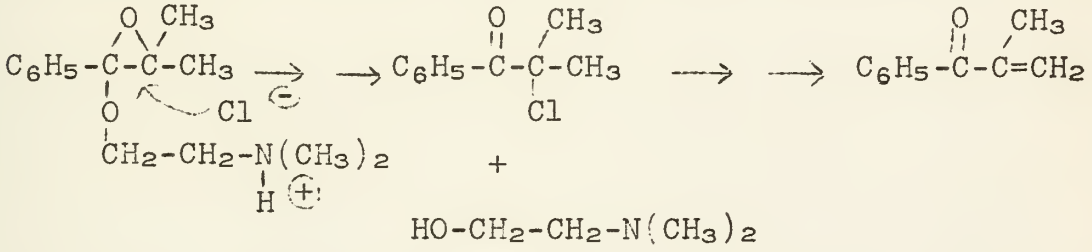
Reactions with Grignard Reagents[16]

The reactions of epoxides with Grignard reagents are well known and have been extensively reviewed.[17] Epoxyethers undergo Grignard attack more easily than other epoxides, but they share the complication caused by Lewis acid ring opening before Grignard attack. With phenylmagnesium bromide, I gave a 42% yield of the product formed by normal attack at the more positive epoxide carbon, and a 24% yield of the product formed by attack at the carbonyl carbon following rearrangement.

A hindered Grignard reagent, such as t-butylmagnesium chloride gives only "rearrangement product", while diphenylmagnesium, which does not catalyze rearrangement, gives only the normal product.

A Special Reaction of an Amino Epoxyether[14]

The hydrochloride of the aminoepoxyether, X, when heated to 150° gives a good yield of α-methylacrylophenone, and α-chloroisobutyrophenone can be isolated as an intermediate. This indicates an attack by a nucleophilic agent at the less positive of the epoxide carbons, after the following scheme:



If attack at the other carbon atom took place, a chlorohydrin would result, which would doubtless be dehydrohalogenated to give the starting epoxide and thus be fruitless from the point of view of reaction.

BIBLIOGRAPHY

1. A. M. Ward, J. C. S., 1929, 1541.
2. E. P. Kohler and C. R. Addinall, J. A. C. S., 52, 3729 (1930).
3. A. E. Favorski, J. Russ. Phys. Chem. Soc., 26, 559 (1894).
4. W. D. McPhee and E. Klingsberg, J. A. C. S., 66, 1132 (1944).
5. T. I. Temnikova and E. N. Kropacheva, J. Gen. Chem., U.S.S.R., 19, 1917 (1949).
6. C. L. Stevens, W. Malik and R. Pratt, J. A. C. S., 72, 4758 (1950).
7. C. L. Stevens and E. Farkas, J. A. C. S., 74, 618 (1952).
8. C. L. Stevens, M. L. Weiner and R. C. Freeman, J. A. C. S. 75, 3977 (1953).
9. C. L. Stevens, E. Farkas and B. Gillis, J. A. C. S., 76, 2695 (1954).
10. C. L. Stevens and S. J. Dykstra, J. A. C. S., 75, 5975 (1953).

11. C. L. Stevens and S. J. Dykstra, J. A. C. S., 76, 4402 (1954).
12. C. L. Stevens and J. J. DeYoung, J. A. C. S., 76, 718 (1954).
13. C. L. Stevens and J. Tazuma, J. A. C. S., 76, 715 (1954).
14. C. L. Stevens and B. V. Ettling, J. A. C. S., 77, 5412 (1955).
15. a) P. Brigl, Z. Physiol. Chem. 122, 245 (1922).
b) W. J. Hickenbottom, J. C. S., 1928, 3140.
16. C. L. Stevens, M. L. Weiner and C. T. Lenk, J. A. C. S., 76, 2698 (1954).
17. N. C. Gaylord and E. I. Becker, Chem. Revs. 49, 413 (1951).
18. for example: B. Belleau and T. F. Gallagher, J. A. C. S., 74, 2816 (1952).

REDUCTIONS WITH FORMIC ACID

Reported by C. W. Schimelpfenig December 9, 1955

Formic acid has been observed to serve as a reducing agent in biological systems, in inorganic oxidation-reduction systems, and with organic compounds over catalysts specific for the dehydrogenation of formic acid. However, attention should be given to the recent advances in the use of formic acid and formate ion (1) in determining the mechanism of the Leuckart reaction and in extending the reaction to new classes of compounds, (2) in the reduction of enamines and heterocyclic analogs, and (3) in reactions involving carbonium ions.

The detailed mechanism of the Leuckart reaction has been the subject of a previous seminar[1], the first step of which is:

$$RR'CO + HCONH_2 \longrightarrow RR'C(O^{\ominus})-NH_2CHO^{\oplus} \longrightarrow RR'C(OH)-NHCHO$$

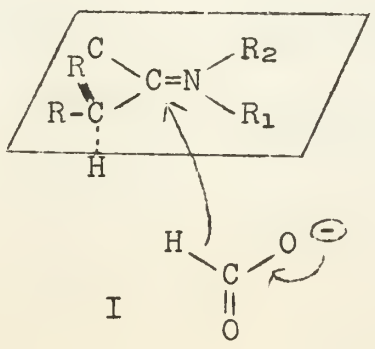
The introduction of $MgCl_2$ as a catalyst, which results in slightly higher yields than usually obtained with refluxing formamide (95% from benzophenone compared with 87%), necessitates the consideration of an alternate first step:

$$RR'CO + H^{\oplus} \longrightarrow RR'C(OH)^{\oplus} \xrightarrow{HCONH_2} RR'C(OH)-NH_2CHO^{\oplus} \longrightarrow RR'C(OH)-NHCHO + H^{\oplus}$$

The stereochemistry of the reaction has been studied[3] by comparing the relative amounts of the isomeric amine products from fixed-ring ketones

Ketone	Products	Reference
2-methylcyclohexanone	40% trans amine 60% cis amine	3
camphor	70% isobornylamine 30% bornylamine	4,5
ℓ-menthone	72% neomenthylamine 28% menthylamine	6

These data have been interpreted as the result of an intermediate stage such as I in which the formate ion approaches from the least hindered side of the plane



I

Early applications of the Leuckart reaction to aliphatic ketones, aromatic aldehydes and ketones, formaldehyde, heterocyclic aldehydes and ketones, and quinones have been summarized.[7]

If the carbonyl group is located in an optimum position, the reaction may be used for the production of heterocyclic compounds. Examples are the formation of 5-(2-carboxyethyl)-2-pyrrolidone from γ-ketopimelic acid[8], 5-methyl-2-pyrrolidone from levulinic acid[9], and 3-phenylphthalimidine from o-benzoylbenzoic acid[10].

Previous failure of the Leuckart reaction to give the normal product with benzoin has been overcome by first methylating benzoin and then hydrolyzing the amino methyl ethers produced[11].

The first successful application of the Leuckart reaction to α,β-unsaturated ketones was the reduction of benzalacetone to 2-amino-4-phenylbutane[12].

An interesting field of reductions, that of aliphatic enamines and heterocyclic analogs, was opened with the report of Mayo[13] that N,N-dimethylpiperidinium formate was produced (59%) from pyridine, formic acid, and methanol or formaldehyde. A large number of enamines of aliphatic aldehydes have been reduced[14] to the corresponding saturated amines. Lukeš and coworkers[9,15-20] have made an extensive investigation into the reduction of heterocyclic bases by means of formic acid and formic acid-potassium formate mixtures. Some of their results are tabulated below.

Heterocyclic N-Base	Product	Reference
1,1-dimethyl-2-methylene-pyrrolidinium hydroxide	1,2-dimethyl-pyrrolidine	15
1,1-dimethyl-Δ^2-pyrrolinium formate	1-methylpyrrolidine	16
β-picoline	3-methyl-Δ^3-piperidine	17
1-methyl-5-ethyl-Δ^4-2-pyrrolone	1-methyl-5-ethyl-2-pyrrolidone	9
1,2,6-trimethylpyridinium formate	Corresponding tetrahydro- and hexahydro-bases	18
1,2-dimethylpyridinium formate	Corresponding tetrahydro- and hexahydro-bases	19
methyl betaine of picolinic acid	N-methylpiperidine and N-methyl-Δ^3-piperidine	20
methyl betaine of nicotinic acid	N-methylpiperidine and N-methyl-Δ^3-piperidine	20
methyl betaine of isonicotinic acid	N-methylpiperidine-4-carboxylic acid	20

These reductions may be considered as 1,2- and 1,4-reductions followed by a double bond shift in the acidic medium.

It has been reported[21] that triphenylmethyl formate, having the characteristic red color, is stable at 20°. However, at 49° carbon dioxide is evolved and a 74% yield of triphenylmethane is obtained in ten minutes. It is of interest that the corresponding silicon compounds[22] do not react in this manner.

BIBLIOGRAPHY

1. R. S. Colgrove, Univ. of Illinois Organic Seminar, Dec. 7, 1951.
2. V. J. Webers and W. F. Bruce, J. Am. Chem. Soc., 70, 1422 (1948).
3. D. S. Noyce and F. W. Bachelor, J. Am. Chem. Soc., 74, 4577 (1952).
4. R. Leuckart and E. Bach, Ber. 20, 104 (1897).
5. O. Wallach and J. Griepenkerl, Ann., 269, 347 (1892).
6. J. Read and G. J. Robertson, J. Chem. Soc., 1926, 2209.
7. M. L. Moore in Organic Reactions, Vol. V, 301 (John Wiley and Sons, 1949).
8. R. Lukeš and F. Šorm, Coll. Czech. Chem. Commun., 12, 278 (1947).
9. R. Lukeš and M. Večeřa, Coll. Czech. Chem. Commun. 18, 243 (1953).
10. G. Caronna, et.al., Gazz. chim. ital. 83, 308 (1953).
11. R. Quelet and E. Frainnet, Compt. rend. 236, 492 (1953).
12. O. R. Irwin, Thesis, Univ. of Missouri, 1950; Microfilm Abstracts 10, no. 3, 27.
13. F. R. Mayo, J. Org. Chem. 1, 496 (1936).
14. P. L. deBenneville and J. H. Macartney, J. Am. Chem. Soc., 72, 3073 (1950).
15. R. Lukeš, Coll. Czech. Chem. Commun. 10, 66 (1938).
16. R. Lukeš and J. Přeučil, Coll. Czech. Chem. Commun. 10, 384 (1938).
17. R. Lukeš and J. Pliml, Coll. Czech. Chem. Commun. 15, 463 (1950).
18. R. Lukeš and J. Jizba, Coll. Czech. Chem. Commun. 19, 930 (1954).
19. R. Lukeš and J. Jizba, Coll. Czech. Chem. Commun. 19, 941 (1954).
20. R. Lukeš, et.al., Coll. Czech. Chem. Commun. 19, 949 (1954).
21. S. T. Bowden and T. F. Watkins, J. Chem. Soc., 1940, 1333.
22. H. Gilman and K. Oita, J. Am. Chem. Soc., 77, 3386 (1955).

QUATERENES

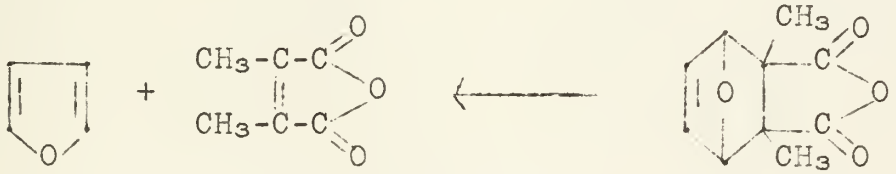
Reported by G. W. Griffin December 16, 1955

The similar formulations for furan and pyrrole might lead one to expect these heterocycles to display some parallelisms in chemical properties. Many examples that support this supposition appear in the literature, although these heterocycles usually differ in reactivity.

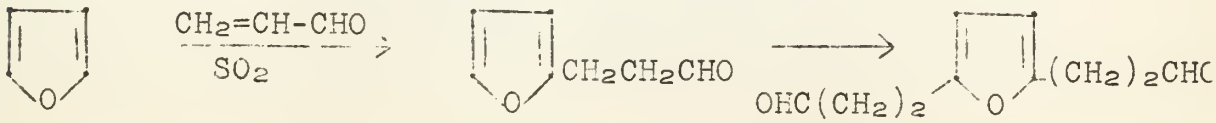
The attack of electrophilic agents on derivatives of both furan and pyrrole occurs preferentially at the α position.[1,2] Pyrrole, however, also undergoes β substitution readily. With furan itself direct β substitution has not been conclusively demonstrated.

In 1,4-addition reactions furan is extremely reactive. Diels-Alder additions with furan are so general that this reaction has been proposed as a means of preparing derivatives for identification.[3] Ordinary dienophiles such as maleic anhydride do not add to pyrrole but form α-substituted products.[4]

In the presence of weak dienophiles even furan fails to react. An illustration of this fact is seen in the attempted preparation of a cantharidin precursor from furan and dimethylmaleic anhydride.[5,6]



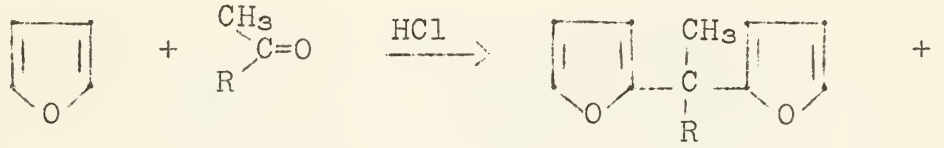
No adduct can be isolated from this reaction when it is carried out under a variety of conditions since the equilibrium is in favor of the dissociation products. Similarly furan does not form adducts with such dienophiles as vinyl phenyl ketone[7], β-nitrostyrene[8,9], acrolein, and crotonaldehyde.[2] However, in the presence of a variety of acid catalysts an addition type of reaction occurs with formation of non-cyclic derivative similar to those encountered with pyrrole.[10,11]



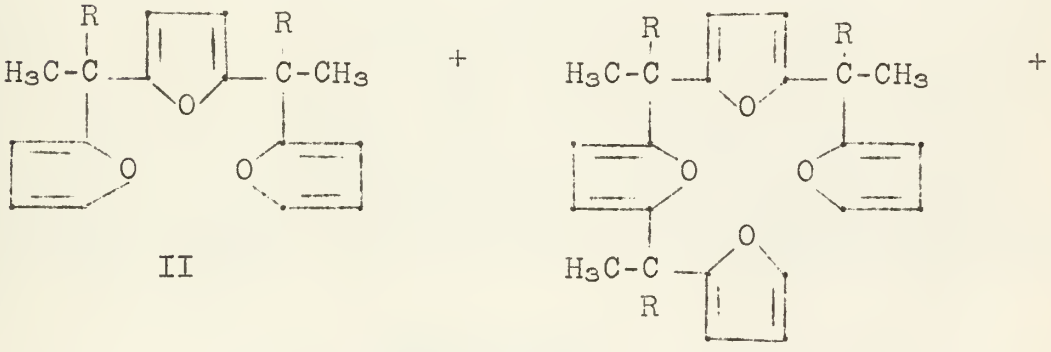
Furan, like pyrrole, will undergo additions to carbonyl groups. Thus furan reacts with chloral to form 1-furyl-2,2,2-trichloroethanol.[12]

In a similar manner treatment of furfuryl alcohol with formaldehyde gives a polymeric 2,5-furandimethanol.[3]

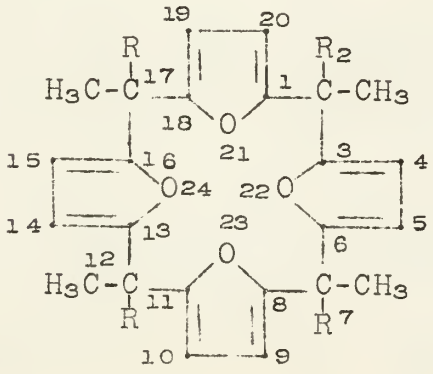
In view of these similarities it is not surprising that furan has recently been shown to react with several methyl ketones in a manner reminiscent of pyrrole.[13] Substances called cyclic anhydrotetramers (IV) which are analogous to porphyrinogens[14-19], are isolated in addition to several intermediate polycondensation products (I,II and III).



I



II III

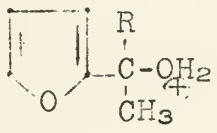


IV

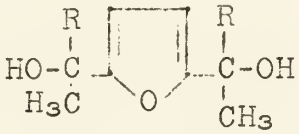
The ratio of the products may be varied by the ratio of reagents employed. The difurylalkane (I) is converted to the cyclic anhydrotetramer (IV) by treatment with a ketone and hydrochloric acid. This reaction has been used to establish the cyclic nature of (IV), since the same pair of products (cis and trans isomers) is obtained from an unsymmetrical difurylalkane and a symmetrical ketone or from a symmetrical difurylalkane and an unsymmetrical ketone. The cis and trans isomers can be distinguished by dipole moment measurements.

A cyclic anhydrotetramer cannot be prepared from 2,5-bis-(dimethylfurfuryl)—furan (II, R=CH_3) and a ketone. Instead a polymer and an anhydrohexamer appear to be formed. Unsymmetrica anhydrotetramers are obtained, however, when III (R=CH_3) is treated with either aldehydes or ketones.

These reactions are assumed to proceed by way of protonated tertiary alcohols such as (V).



V



VI

It is improbable that the conjugate acid of (VI) is an intermediate because 2,5-diisopropylolfuran (VI, R=CH_3) is converted to resins on treatment with HCl and furan. Since it is anticipated that cyclic anhydrotetramers will be prepared containing ring systems other than pyrrole and furan, it has been suggested by Ackman, Brown and Wright that the name "quaterene" be used to describe a closed system of four methylene-bridged 1,4-disubstituted cyclopentadienes. Thus IV (R=CH_3) becomes 2,2,7,7,12,12,17,17-octamethyl-21,22,23,24-tetroxaquaterene.

BIBLIOGRAPHY

1. Gilman and Wright, Chem. Revs., 11, 323 (1932).
2. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, New York, 1950, Vol. I, p. 143.
3. Wright and Gilman, Ind. Eng. Chem., 40, 1517 (1948).
4. Diels and Alder, Ann., 490, 267 (1931).
5. Bruchhausen and Bersch, Arch. Pharm., 266, 697 (1928).
6. Diels and Olson, J. prackt. Chem., 156, 285 (1940).
7. Allen, Bell, Bell and Van Allan, J. Am. Chem. Soc., 62, 656 (1940).
8. Allen, Bell and Gates, J. Org. Chem., 8, 373 (1943).
9. Allen and Bell, J. Am. Chem. Soc., 61, 521 (1939).
10. Sherlin, Berlin, Serebrennikova and Rabinovich, J. Gen. Chem. (U.S.S.R.), 8, 7 (1938).
11. Alder and Schmidt, Ber., 76, 183 (1943).
12. Willard and Hamilton, J. Am. Chem. Soc., 73, 4805 (1951).
13. Ackman, Brown and Wright, J. Org. Chem., 20, 1147 (1955).

14. Dennstedt and Zimmerman, Ber., 20, 2449 (1887).
15. Tschelincev and Tronov, J. Russ. Phys. Chem. Soc., 48, 1197 (1916); C. A., 11, 1418 (1917); cf. C. A., 11, 452 (1917).
16. Rothemund, J. Am. Chem. Soc., 61, 2912 (1939).
17. Aronoff and Calvin, J. Org. Chem., 8, 205 (1943).
18. Calvin, Ball and Aronoff, J. Am. Chem. Soc., 65, 2259 (1943).
19. Ball, Dorough and Calvin, J. Am. Chem. Soc., 68, 2278 (1946).

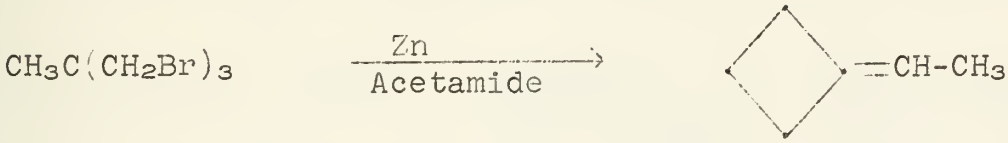
NEW CYCLOBUTANE DERIVATIVES: PREPARATION AND REACTIONS

Reported by J. H. Rassweiler December 16, 1955

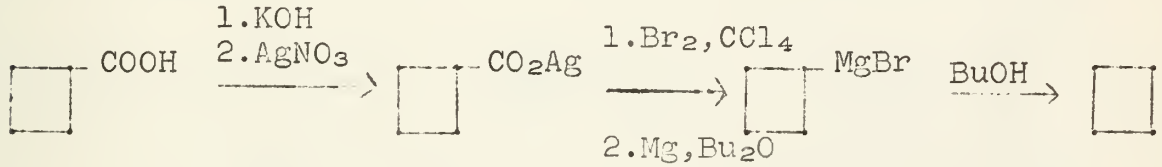
Cyclobutanes present two problems in their preparation and reactions. One is the low yields afforded by most general preparations and the other is the inability of the cyclobutane derivatives thus formed to undergo further transformations.

Willstätter's preparation[1] of cyclobutane and its improvements through the Curtius acid azide method; the attack of light on cyclopentanone to produce cyclobutane and carbon monoxide[2]; and the Wurtz reduction of tetramethylene bromide all give unusually low yields and, generally, difficulties in the separation of the products.

Other methods are more effective but not yet completely acceptable. Perkins malonic ester synthesis[3] is limited, generally, to acid derivatives. The reaction of diazomethane and ketene gives good yields but cannot be widely applied. The preparation of monosubstituted rings with 1,1,1-tri(bromomethyl)-alkanes[4] has proved very effective.



A large range of monoderivatives can be prepared from these compounds[5,6]. Cyclobutane was isolated in an overall yield of 40% by Cason and Way[7] from cyclobutane carboxylic acid;

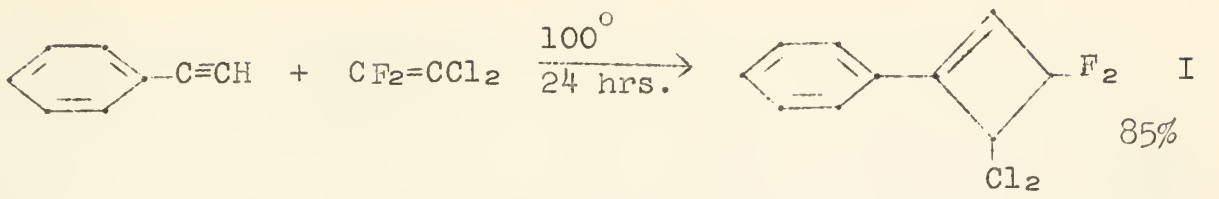


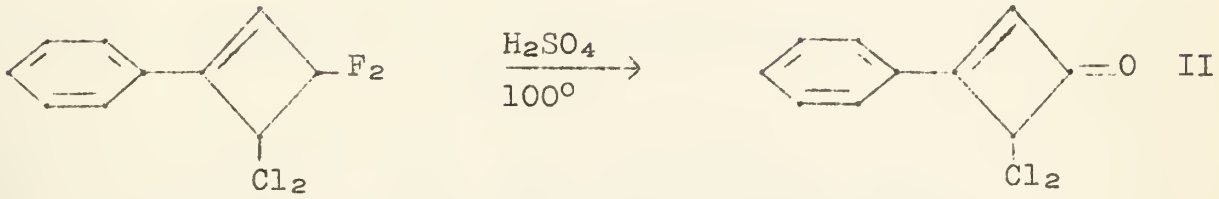
but the scarcity of the starting material limits this reaction.

The addition of alkyl substituted ethylenes to ethylenes or acetylenes would be an ideal method for the preparation of cyclobutane derivatives. Except for a few cases, this has proved unsuccessful. Dimerization of ketenes[8] has long been recognized but is not a useful preparative method. The thermal and light catalysed dimerization of unsaturated compounds has proved successful in a few cases such as: acrylonitrile,[9] cinnamic acid and its derivatives[10,11]. The addition of ethylenes to diphenyl ketene[12] goes easily but has a limited scope. Recently, the thermal dimerization of fluorinated ethylenes[13,14] and the addition of fluoroethylenes to numerous unsaturated compounds has afforded a good preparative approach to many fluorinated cyclobutanes, but further transformation was hindered by the inertness of the resultant fluoro compounds.

Roberts and co-workers[15] undertook to use the activation of fluorine in cycloaddition and to develop a method of removing

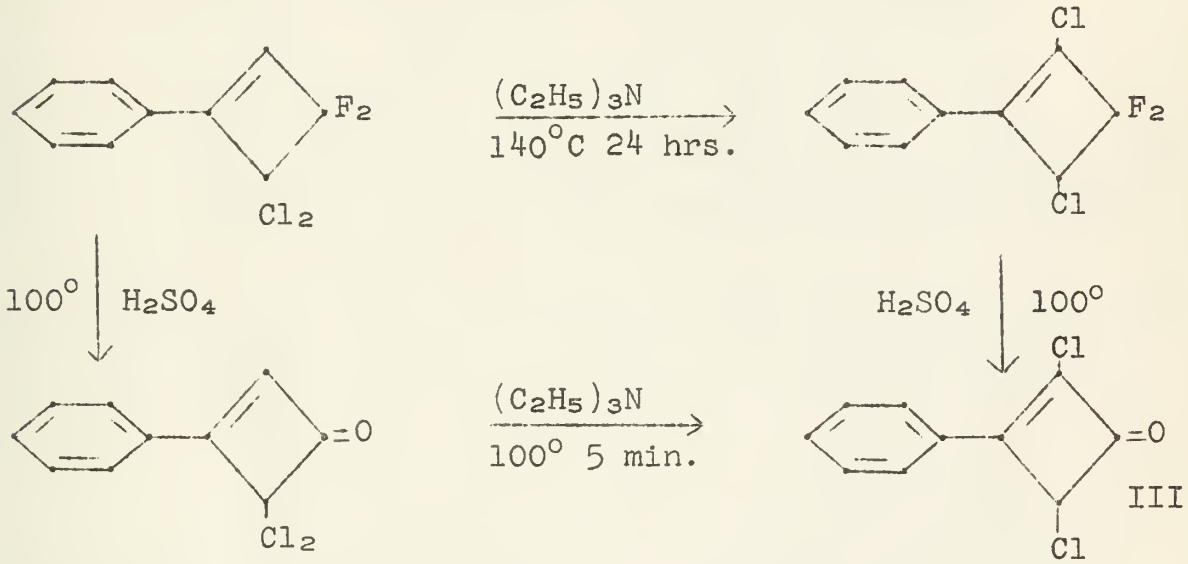
fluorine to give reactive cyclic products[16]. Their in-





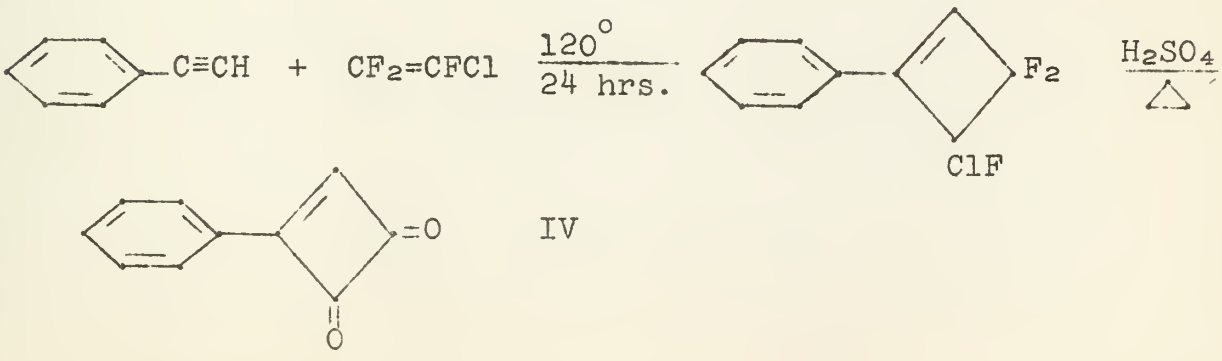
vestigations proved I to be of considerable interest, especially in view of the ease with which the fluorine could then be removed.

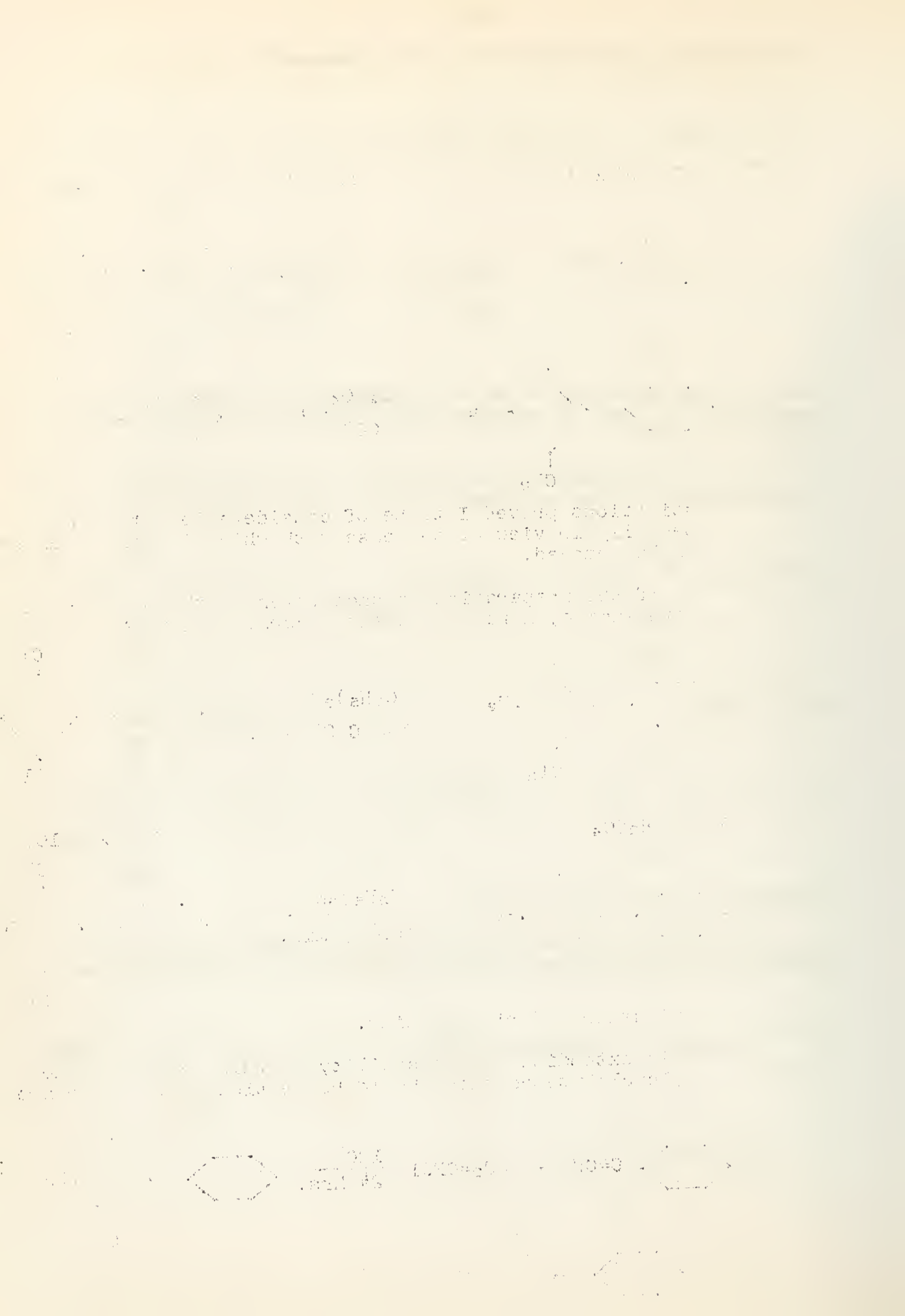
If the preparation is undertaken in the presence of triethylamine, a rearrangement occurs. III undergoes



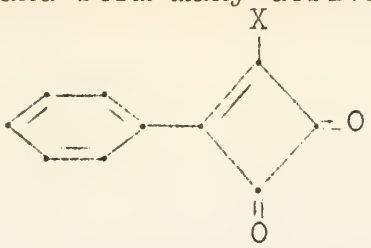
racemization and ring opening.

In extending the versatility of this reaction, the phenylcyclobutenediones should be mentioned[17]. These are re-





active compounds and form many derivatives of the type where



X = Cl,Br,I,OCH_3,NH_2,OH. These are all stable and react in a manner analogous to benzo or naphthoquinones.

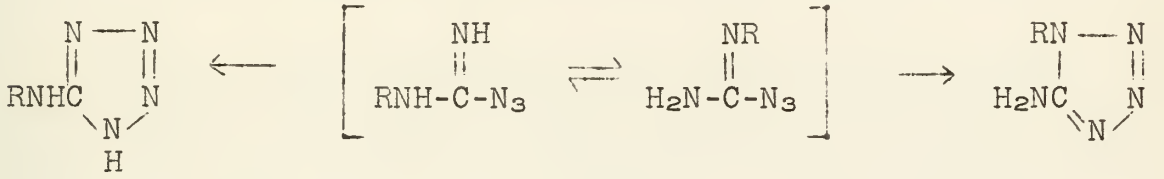
REFERENCES

1. R. Willstätter, Ber., 38, 1992 (1905).
2. S. W. Benson, J. Am. Chem. Soc., 64, 80 (1942).
3. J. Cason, J. Org. Chem., 14, 1036 (1949).
4. J. M. Derfer, J. Am. Chem. Soc., 67, 1863 (1945).
5. E. M. Hancock and A. C. Cope, Org. Syn., 26, 38.
6. L. B. Morton, J. Am. Chem. Soc., 55, 4571 (1933).
7. J. Cason and R. L. Way, J. Org. Chem., 14, 31 (1949).
8. W. E. Hanford and J. C. Sauer, Org. Reactions, 3 127.
9. E. C. Coyner, J. Am. Chem. Soc., 71, 324 (1949).
10. K. Alder and E. Ruder, Ber., 74B, 905, 920 (1941).
11. Ahmed Mustafa, Chem. Rev., 51, 1 (1952).
12. H. Staudinger and E. Suter, Ber., 53, 1092 (1920).
13. A. L. Henne and R. P. Ruh, J. Am. Chem. Soc., 69, 279 (1947
14. M. Prober and W. Miller, J. Am. Chem. Soc., 71, 598 (1949).
15. J. D. Roberts, 14th National Organic Chemistry Symposium of the American Chemical Society, Abstracts June 1955 pp. 21.
16. J. D. Roberts and G. B. Kline, J. Am. Chem. Soc., 75, 4765 (1953).
17. J. D. Roberts and E. J. Smutny, J. Am. Chem. Soc., 77, 3420 (1955).

ISOMERIZATION OF 5-AMINOTETRAZOLES

Reported by M. E. Peterson January 6, 1956

Since Thiele first reported the preparation of 5-aminotetrazole,[1] many methods have been devised for synthesis of it and its derivatives. Preparation of the 1-alkyl- and 1-aryl-5-aminotetrazoles has been accomplished through syntheses starting with monosubstituted thioureas, cyanamides, nitriles and aminoguanidines.[2] Proposed mechanisms for each of these methods suggest the formation of a substituted guanyl azide as an intermediate. Theoretically, with the guanyl azide as an intermediate, ring closure could occur in two directions, thus forming substituted-5-aminotetrazoles.

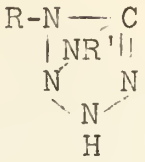


Stollé and Heintz[3] did report the formation of a small amount of 5-anilinotetrazole along with 1-phenyl-5-aminotetrazole when phenyl thiourea was treated with sodium azide and lead oxide. Other early workers were able to isolate only the 1-substituted-5-aminotetrazoles and no consideration seems to have been given to isolation of the other isomer. Then, in 1951, Lieber, Henry and co-workers made use of an aminoguanidine with a highly electronegative substituent to cause cyclization to proceed in the other direction.[4] Further proof that cyclization could proceed in both directions was provided when 5-methylamino-(11%), 5-cyclohexylamino-(2%) and 5-benzylamino-tetrazole(2.6%) were recovered from the mother liquors after the corresponding 1-alkyl isomers had been removed.[5]

While investigating the properties of some 5-alkylaminotetrazoles Garbrecht and Herbst observed that 5-methylaminotetrazole possessed a double melting point.[6] 1-Phenyl-5-aminotetrazole and 1-(4-nitrophenyl)-5-aminotetrazole also exhibited the same property. Henry and co-workers[5] identified the higher melting material from 5-methylaminotetrazole as 1-methyl-5-aminotetrazole. Subsequently, the other higher melting compounds were identified as the isomeric 5-arylamino compounds. Several other examples of this thermal isomerization were later reported.

The observed rearrangement of the 5-aminotetrazoles could be explained by postulating a guanyl azide intermediate. However, Garbrecht and Herbst thought it unlikely that this intermediate could explain both the low temperature cyclization and the thermal rearrangement. If the azide were involved in the rearrangement, it seemed unlikely that the 1-aryl-5-amino compound would be formed at all. In order to explain the rearrangement they proposed a nitrogen bridge structure I.[7]

This intermediate would explain both the isomerization of



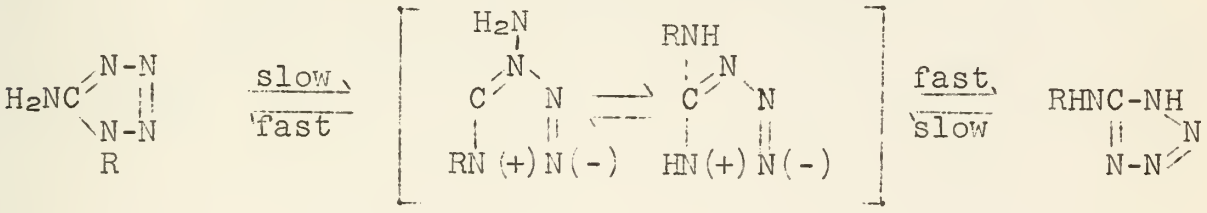
a, R=Aryl; R'=H
b, R=H; R'=Alkyl

I

1-aryl- to 5-arylaminotetrazoles (a), and 5-alkylamino- to 1-alkyl-5-aminotetrazoles (b). Both R-carrying nitrogens are equivalent in the ring. When R is aryl, rupture of the RN-N bond would yield the 5-arylamino compound; when R' is alkyl, rupture of the RN-N bond would give the 1-alkyl-5-amino-tetrazole.

Finnegan, Henry and Lieber also observed the thermal rearrangement of the 5-alkylaminotetrazoles to the 1-alkyl-5-amino isomer.[5] Recovery of both isomers of the methyl benzyl substituted derivative and formation of the two isomers in roughly the same ratio on cyclization of 1-benzyl-2-methyl-3-azido guanidine suggested that the reaction might reach an equilibrium. Further investigation confirmed the idea of an equilibrium.[8]

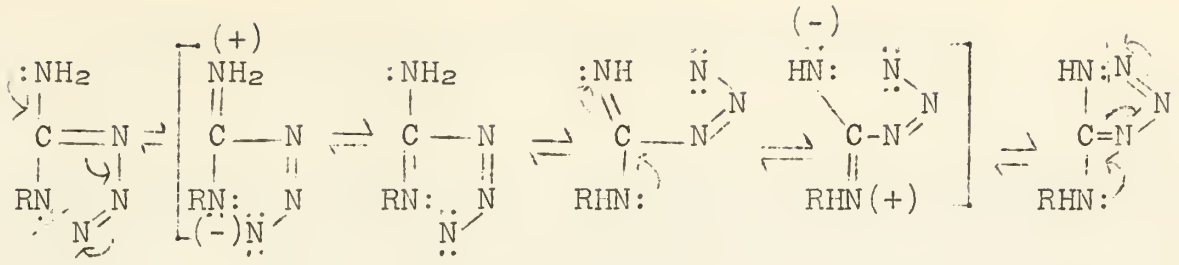
These workers propose that the isomerization does involve an activated guanyl azide intermediate. A ring structure such as that proposed by Garbrecht and Herbst did not seem feasible because such an intermediate would not explain the influence of substituents on the position or relative rate of equilibrium. So they first proposed the following mechanism[8]



A

which adequately accounts for the attainment of equilibrium and for the product ratio obtained. However, on the basis of this mechanism, the rate of forward reaction should be decreased by electronegative groups in the 1-position. Kinetic rate studies showed the reverse to be true.

A mechanism (B) has since been proposed that satisfies the known properties of the substituted 5-aminotetrazoles and, in addition, accounts for observed rate changes with change in the electronegativity of substituents.[9] This mechanism is dependent on the shift of a pair of electrons from the 5-amino group into the tetrazole ring which would facilitate heterolysis of the N-N bond. Either electronegative substitution on the 1-position or electropositive substitution on the 5-position would enhance the shift of the electron pair into the ring.



B

Data compiled from the kinetic studies is in accord with the above mechanism. The tetrazole ring is in itself electronegative and withdraws electrons from the amino group. The isomerization has been found to be first order. Calculation of the entropies of activation and frequency factors indicate that the isomerizations are not complicated by stearic factors or the necessity for oriented energetic collisions.[9]

BIBLIOGRAPHY

1. Thiele, Ann., 270, 1 (1892).
2. F. B. Benson, Chem. Revs., 41, No. 1 (1947).
3. Stollé and Heintz, J. prakt. Chem., 147, 286 (1937).
4. E. Lieber, E. Sherman, R. A. Henry and J. Cohen, J. Am. Chem. Soc., 73, 2327 (1951).
5. W. G. Finnegan, R. A. Henry and E. Lieber, J. Org. Chem., 18, 779 (1953).
6. W. L. Garbrecht and R. M. Herbst, J. Org. Chem., 18, 1022 (1953).
7. W. L. Garbrecht and R. M. Herbst, ibid., 18, 1269 (1953).
8. R. A. Henry, W. G. Finnegan and E. Lieber, J. Am. Chem. Soc., 76, 88 (1954).
9. R. A. Henry, W. G. Finnegan and E. Lieber, ibid., 77, 2264 (1955).

STRUCTURE DETERMINATION BY RAMAN SPECTROSCOPY

Reported by W. A. Remers January 6, 1956

INTRODUCTION: Raman discovered[1] in 1928 that when monochromatic light is scattered by molecules, other frequencies are present in the spectrum of the scattered light. The differences between the frequencies of the exciting light and the scattered light could be correlated with the vibrational and rotational frequencies of the bonds and functional groups of the molecules. Within a few years, many other investigators entered the field and extended Raman's findings. During the 1930's the Raman spectra of thousands of compounds were measured and classified. These data have been compiled in several comprehensive volumes.[2,3,4,5,6]

Most organic chemists have made no use of this wealth of data because of the cumbersome techniques involved in obtaining Raman spectrograms of their own compounds. Recently, however, recording Raman spectrophotometers which are efficient, easy to operate, and relatively inexpensive have been developed for use in the research laboratory. They should be effective in the future in promoting a more widespread use of Raman spectra, giving the organic chemist valuable aid in his research.

THEORY:[2,3,7] To produce the Raman effect, molecules are irradiated with monochromatic light. When these quanta of energy collide or interact with a molecule, part of the energy they represent may be distributed throughout the molecule in all of its vibrational and rotational degrees of freedom. Light is emitted from the molecule at frequencies lower than that of the incident light, unless the absorbing molecule is already in a higher energy level than normal. The differences in frequencies of the exciting light and the emitted light may correspond directly to the frequencies of vibration and rotation of atoms within the molecule.

The Raman effect is similar to infrared absorption in that the force constants of the bonds determine the frequencies of the absorbed or scattered light. The frequency of the Raman displacement for a particular bond or group is equal in magnitude to the frequency of the infrared absorption of that bond or group. Infrared absorption occurs only when there is a change in the electric moment of a molecule, the Raman effect occurs only when there is a change in polarizability; hence, vibrations which are unsymmetrical with respect to the symmetry axes of a molecule appear strongest in absorption, the symmetrical vibrations being strongest in the Raman effect.

Light emitted in the Raman scattering varies from frequency to frequency in its intensity and in its polarization characteristics. Determining whether the light at each frequency is polarized or depolarized is of the greatest importance in establishing the symmetry class of a molecule.

APPLICATIONS: Many bonds and functional groups can be identified by their characteristic Raman displacements.[2,3,4,5,6] A few of these are listed below:

Bond or Group	Raman Displacement, $\Delta\nu$ (cm.$^{-1}$)
C - H (stretch)	2850-3500 depending on nature
C - D (stretch)	2080-2260 of compound
-C ≡ CH	2120 for C≡C stretch, 3340 for C-H
-C ≡ C- (stretch)	2235
C = O (stretch)	1710 (unconjugated ketone)
C = C	
cis-2-pentene	1248-1266, 1375, 1658
trans-2-pentene	1298-1313, 1378, 1674

Raman spectroscopy is especially useful in detecting these groups in highly symmetrical molecules. Diphenyl acetylene shows no acetylenic band in the infrared, but shows a very strong Raman displacement of 2211 cm.$^{-1}$.[7] Similarly, tetrachloroethylene shows no ethylenic band in the infrared, but does in the Raman.[8] In long chain hydrocarbons containing a single acetylenic bond, the intensity of infrared absorption is strongest when the bond is terminal, weakest when it is in the center of the molecule. The intensity of its Raman scattering is opposite to this.[9]

Since Raman spectrophotometers are effective in the infrared region of 400-100 cm.$^{-1}$, which is not reached by infrared absorption instruments, they should be very useful in detecting carbon-halogen bonds. The determination of the configurations of polyhalogenated aromatic and aliphatic compounds and of axial and equatorial bromine in cyclohexane systems should be especially valuable.

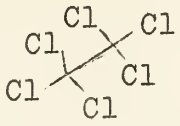
In addition to the detection of specific functional groups for smaller molecules, or for molecules possessing a high degree of symmetry a more definite and complete determination of structure can usually be made. Structures are assumed and the selection rules, which determine the number and characteristics of the infrared and Raman bands, are predicted for these structures by use of group theory. Observed Raman and infrared bands are assigned to fundamental modes of vibration of the molecule, or to their overtone or combination frequencies. Agreement between the predicted and observed bands is strong evidence that a particular assumed structure is correct. For the complete determination of a structure, the following data are essential:

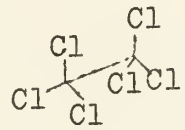
1. Complete Raman and infrared spectra throughout the region 100-4000 cm.$^{-1}$.
2. A reliable determination of which of the bands are fundamentals.
3. Reliable, quantitative values of the depolarization factors, in order to determine the number of polarized and unpolarized frequencies of light.

Certain generalizations have been made[10] from the selection rules:

1. Totally symmetrical vibrations are always polarized in the Raman, other vibrations are depolarized.
2. The greater the symmetry of the molecule, the greater the number of forbidden fundamentals, combinations, and overtones.
3. If a center of symmetry is present, no frequency appears in both the Raman and infrared spectra.
4. The greater the symmetry, the greater the tendency toward a small number of fundamental vibrations of a particular type.

As an example of complete structure determination,[11] consider the three possible structures for hexachloroethane.

1. staggered structure  (D_{3d} symmetry type)

2. eclipsed structure  (D_{3h} symmetry type)

3. free rotation structure (D_{3h}' symmetry type

Selection rules predict three polarized lines for each structure. Six depolarized lines are predicted for D_{3h} and D_{3h}', three for D_{3d}. The observed spectrum has only three polarized and three depolarized lines; therefore, structure D_{3d} must be the correct one. D_{3d} has a center of symmetry, which is consistent with the fact that no coincident Raman and infrared bands are observed.

BIBLIOGRAPHY

1. C. V. Raman and K. S. Krishnan, Nature, 121, 501 (1928); C. V. Raman, ibid., p. 619; C. V. Raman, Indian J. Phys., 2, 387 (1928).
2. K. W. F. Kohlrausch, Ramanspektren, Edwards Bros., Ann Arbor, Mich., (1945).
3. J. H. Hibben, The Raman Effect and its Chemical Applications, A.C.S. Monograph Series, Reinhold Publishing Co., New York, 1939.
4. G. Herzberg, Infrared and Raman Spectra of Polyatomic Molecules, 1st. ed., D. van Nostrand Co., New York, 1945.
5. F. D. Rossini, American Petroleum Institute Catalog of Raman Spectral Data, Department of Chemistry, Carnegie Inst. of Tech., Pittsburg, Pa.
6. M. Magat, Numerical Data on the Raman Effect and Raman Effect, vols. XI and XII of Annual Tables of Constants and Numerical Data, McGraw-Hill Book Co., New York, 1936, 1937.
7. A. Dadieu and K. W. F. Kohlrausch, Monatsh. Chem., 60, 221 (1932).

8. Herzberg,loc. cit., p. 329.
9. Hibben, loc. cit., p. 200-208.
10. F. F. Cleveland, Raman Spectra, ch. 6 in Determination of Organic Structures by Physical Methods, Edited by E. A. Braude and F. C. Nachod, Academic Press, Inc., New York, 1955.
11. R. A. Carney and F. F. Cleveland, Phys. Rev., 75, 333 (1949); R. A. Carney, A. G. Meister and F. F. Cleveland, Phys. Rev., 77, 740 (1950).

ANODIC SYNTHESIS OF LONG CHAIN UNSATURATED FATTY ACIDS

Reported by Thet San January 6, 1956

The long chain unsaturated fatty acids, in recent years, have attracted much attention because of reports that a number of them are growth promoting factors for various micro-organisms. In his recent papers, Linstead has accomplished the anodic synthesis of a number of naturally occuring long chain unsaturated fatty acids, and their stereoisomers. These were obtained in high purity and with known configurations.

The electrolysis of a mixture of a monocarboxylic acid, RCOOH, and a half ester of a dicarboxylic acid $R'OOC(CH_2)_nCOOH$ is known to give rise to three main products: RR, $R(CH_2)_nCOOR'$ and $RO_2C[CH_2]_{2n}CO_2R'$ as a result of symmetrical and crossed coupling of the Kolbe type[1]. By a proper choice of the mono-carboxylic acid and the dicarboxylic acid, these three products can be made to have widely different molecular weights, hence they can easily be separated by distillation. This has therefore been developed into a general method for the synthesi of long chain fatty acids[2]. Many naturally occuring branched chain fatty acids have been synthesised by this method. This method however has a few limitations. Most α-alkyl substituted carboxylic acids give extremely low yield of coupled products on electrolysis. Also, when the α-position is substituted by phenyl, hydroxyl, halogen, etc., the Kolbe reaction is largely suppressed. The Kolbe reaction is totally suppressed when the acid used is α,β or β, γ unsaturated acid.[1]

Normal anodic coupling of olefinic acids has been reported in cases where the double bond is separated from the carboxyl group by at least two carbon atoms[1]. Linstead[3] observed that the configuration and position of the double bonds were preserved during the electrolysis. Anodic synthesis is therefore found to be generally applicable to the synthesis of unsaturate acids. It has an advantage over many other methods, in that it is stereospecific.

Other general methods for the synthesis of olefinic acids are:- (1) method used by Noller and Bannerot[4] (2) a method in which a symmetrical acyloin is employed as an intermediate[5] (3) Ahmad and Strong[6] developed a method based on the semi-hydrogenation of the corresponding acetylenic acid. (4) method developed by Bowman[7] in which a methoxy ketone is an intermediate.

Electrolysis of oleic and elaidic acids in the presence of excess methyl hydrogen adipate gave in each case three products, by symmetrical and unsymmetrical coupling of the two components[3]. The three products were separated by distillation and subsequent hydrolysis of the unsymmetrical products gave erucic and brassidic acids respectively (30%).

$$CH_3[CH_2]_7CH{:}CH[CH_2]_7COOH + HO_2C[CH_2]_4CO_2Me \xrightarrow{-2e} MeO_2C[CH_2]_8CO_2Me +$$

cis-oleic acid + $[CH_3[CH_2]_7CH{:}CH[CH_2]_7-]_2$ +
trans-elaidic acid

$$CH_3[CH_2]_7CH{=}CH[CH_2]_{11}CO_2Me \rightarrow CH_3[CH_2]_7CH{=}CH[CH_2]_{11}CO_2H$$

cis-erucic, trans-brassidic

This synthesis therefore confirms that erucic acid is a cis acid and that brassidic acid is trans. Bowman[7] synthesised these two acids according to the following scheme:

$$CH_3OCHRCOCl + (CH_2PhO_2C)_2CNa(CH_2)_{10}CO_2CH_2Ph \rightarrow$$

$$(CH_2PhO_2C)_2\text{-}\underset{\displaystyle CH_3OCHRC=O}{\overset{|}{C}}\text{-}(CH_2)_{10}\text{-}CO_2CH_2Ph$$

$$\text{(a) } \xrightarrow{H_2Pd\text{-}C} CH_3OCHR\text{-}CO\text{-}CH_2(CH_2)_{10}CO_2H \rightarrow \underset{\displaystyle \text{Al isopropoxide}}{CH_3OCHR\text{-}CHOH(CH_2)_{11}CO_2H}$$

$$\text{(b) } -CO_2$$

$$\xrightarrow{HBr} RCHBr\cdot CHBr(CH_2)_{11}CO_2H \xrightarrow{Zn} RCH{=}CH\text{-}(CH_2)_{11}CO_2H$$

mixture of erucic and brassidic

$R=CH_3[CH_2]_7$

Electrolysis of threo and erythro dihydroxystearic acids I, with methyl hydrogen adipate, followed by distillation and hydrolysis gave threo- and erythro- dihydroxybehenic acids II in 30% yield.[3] These were converted into brassidic and erucic acids respectively by the standard bromination, debromination procedure used by Bowman.

$$\underset{\displaystyle I}{Me(CH_2)_7\cdot CHOH\cdot CHOH\cdot (CH_2)_7CO_2H} + HO_2C(CH_2)_4\cdot CO_2Me \longrightarrow$$

$$\underset{\displaystyle II}{Me(CH_2)_7\cdot CHOH\cdot CHOH\cdot (CH_2)_{11}CO_2H} \longrightarrow Me(CH_2)_7CH{=}CH(CH_2)_{11}CO_2H$$

Erucic acid occurs in the seed fats of Cruciferae and Tropacolacae.

When oleic acid cis III and elaidic acid trans III are electrolysed in the presence of an excess of methyl hydrogen suberate, and the resulting solution worked up as usual, cis- and trans- tetracos-15-enoic acids were isolated in 30% - 35% yield.[8] The cis acid has been shown to be identical with nervonic acid, from the cerebrosides of cattle and man, and selacholic acid from shark and ray liver oils. Both the cis and trans acids have been synthesised by the malonate chain extension of erucic acid[8].

$CH_3[CH_2]_7 \cdot CH{:}CH[CH_2]_7 \cdot CO_2H + HO_2C(CH_2)_6 \cdot CO_2Me$

III

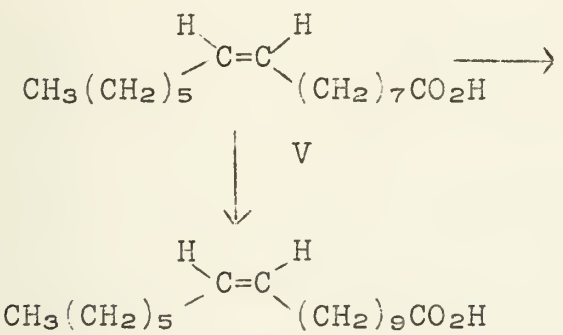
$\searrow$

$CH_3[CH_2]_7 \cdot CH{:}CH[CH_2]_{13}CO_2H$

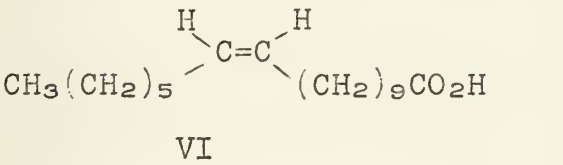
IV

In the latter method a mixture of the cis and trans forms were obtained, and separation was effected by fractional crystallization.

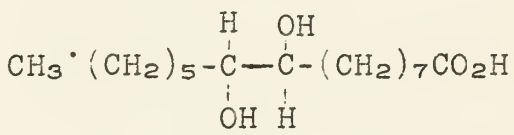
Both the cis and trans forms of octadec-11-enoic VI and IX acid are found to occur in nature. The cis isomer was identified with the haemolytic factor of horse brain. The trans isomer was identified with 'vaccenic acid'. Until recently it was the only natural monoethenoid acid known with a trans configuration. Anodic synthesis of the cis isomer was accomplished by the electrolysis of palmitoleic acid V in the presence of a large excess of methyl hydrogen succinate.[10]



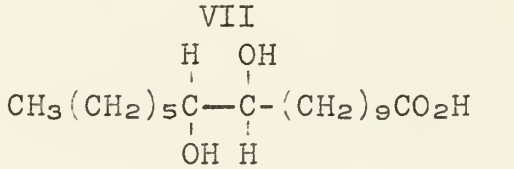
V



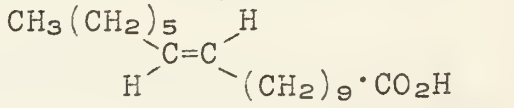
VI



VII



VIII



IX

Hydroxylation of palmitoleic acid by performic acid furnished the threo-9:10 dihydroxypalmitic acid VII. Electrolysis of this acid with excess of methyl hydrogen succinate gave threo-11:12 dihydroxy-stearic acid VIII (23%). The product was converted into the trans-octadec-11-enoic acid IX (42%) by the standard procedure of bromination and debromination. Both of these acids have been synthesised by Strong et al[11].

Half esters of the type $HO_2C[CH_2]_nC{\equiv}C[CH_2]_n \cdot CO_2R$[12,13] have been found to undergo the normal Kolbe reaction, provided $n > 1$. This then provides a flexible route to unsaturated acids since by crossed coupling first at one end of the molecule with a monocarboxylic acid and then, if desired, at the other half with a half ester, acids of different length and with different positions of unsaturation can be obtained. Partial reduction of the acetylenic acid will give the olefinic acid. Depending on the nature of the reducing agent used, the cis or trans acid is obtained respectively[14] Synthesis of oleic acid according to the following scheme has been accomplished by this method.

$$Cl\cdot[CH_2]_4C\vdots CH + Br[CH_2]_4Cl \xrightarrow[liq.NH_3]{Na} Cl[CH_2]_4C\vdots C[CH_2]_4Cl \rightarrow$$

$$NC\cdot[CH_2]_4\cdot C\vdots C[CH_2]_4CN \rightarrow HO_2C[CH_2]_4C\vdots C[CH_2]_4\cdot CO_2H\cdot \rightarrow$$

$$HO_2C[CH_2]_4C\vdots C[CH_2]_4\cdot CO_2Me + CH_3[CH_2]_3\cdot CO_2H \rightarrow$$

$$CH_3[CH_2]_7C\vdots C[CH_2]_4\cdot CO_2H + HO_2C[CH_2]_3CO_2Me \rightarrow$$

$$CH_3[CH_2]_7C\vdots C(CH_2)_7CO_2Me \rightarrow CH_3(CH_2)_7C\vdots C[CH_2]_7\cdot CO_2H \xrightarrow{H_2}$$

$$\begin{array}{ccc} & H \quad\quad H & \\ & \diagdown C{=}C \diagup & \\ CH_3\cdot(CH_2)_7 & & [CH_2]_7\cdot CO_2H \end{array}$$

Oleic acid has been synthesised by many chemists. However, all these syntheses with the exception of Hubers work and the one given above give mixtures of oleic and elaidic acids in which the latter predominates. Only the anodic synthesis and that of Huber[15] are substantially stereospecific.

In recent years it has been realized that during the electrolysis of a fatty acid some esterification with the methanol used as solvent may accompany the coupling process. This side reaction with the solvent may result in the contamination of the product with the starting material in cases where the carbon chain of the original acid is extended by only a few carbon atoms. It has now been observed[16] that this drawback may be avoided by the use of benzyl half esters in place of methyl or ethyl half ester. After cross coupling with a monocarboxylic acid the benzyl ester formed may either be separated by distillation from any methyl ester of the starting acid and be subsequently hydrolysed, or, alternately, converted without isolation into the required acid by hydrogenolysis.

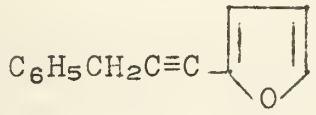
BIBLIOGRAPHY

1. Weedon, Quarterly Rev., 6, 380, 1952.
2. John R. Demuth Seminar University of Illinois, March 13, 1953.
3. D. G. Bounds, R. P. Linstead and B. C. L. Weedon, J. Chem. Soc., (1953) 2393.
4. C. R. Noller and R. A. Bannerot, J.A.C.S., 56, 1563, 1934.
5. Ruzicka, Plattner and Widmer, Helv. Chim. Acta, 25, 604, 1086 (1942).
6. Ahmad and Strong, J.A.C.S., 70, 1699, 1948.
7. R. E. Bowman, J.C.S. (1950), 177.
8. D. G. Bounds, R. P. Linstead and B. C. L. Weedon, J.C.S. (1954) 448.
9. J. B. Hale, W. H. Lycan and Roger Adams, J.A.C.S., 52, 4536, 1930.
10. D. G. Bounds, R. P. Linstead and B. C. L. Weedon, J.C.S. (1954) 4219.
11. Ahmad, Bumpus and Strong, J. Am. Chem. Soc., 1948, 70, 3391.
12. B. W. Baker, R. W. Kierstead, R. P. Linstead and B. C. L. Weedon, J.C.S. (1954) 1804.
13. R. W. Baker, R. P. Linstead and B. C. L. Weedon, J.C.S. (1955) 2218.
14. Crombe, Quart. Rev., 1952, 6, 128.
15. W. Frederic Huber, J.A.C.S. (1951) 73, 2730.
16. R. P. Linstead, B. C. L. Weedon and B. Wladislaw, J.C.S. (1955) 1097.

POLYACETYLENIC COMPOUNDS FROM PLANTS OF THE COMPOSITAE FAMILY

Reported by Philip N. James January 13, 1956

The first acetylenic compound to be discovered in nature was carlina oxide[1], whose structure (I) was confirmed by synthesis[2]. Later, from another source, a group of Russian workers isolated the lachnophyllum ester[3], whose structure (II) and configuration were established by extensive degradative studies.

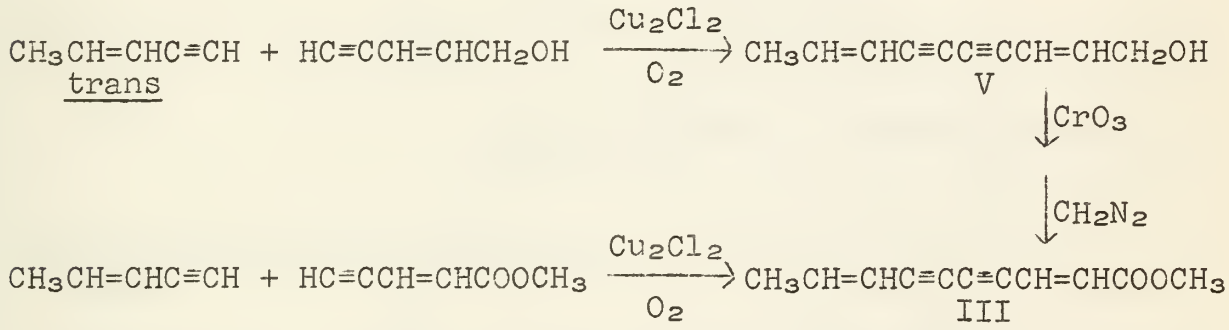


I

$CH_3CH_2CH_2C{\equiv}CC{\equiv}CCH{=}CHCOOCH_3$

II

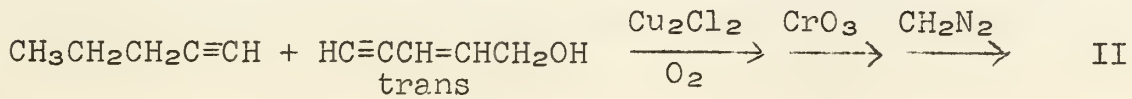
In 1941, Sorensen and Stene[4] isolated the matricaria ester from the scentless mayweed, and from numerous degradation studies assigned to this compound the structure III. They noticed that this compound underwent rearrangement to an isomer upon irradiation with ultraviolet light. A later study of the compound by means of ultraviolet spectroscopy[5] confirmed structure III. This compound was synthesized by Bruun[10] using Glaser's coupling reaction[25]. Both the 2-cis-8-trans and all trans isomers were produced, but neither was identical with the



natural ester. The 2-cis-8-trans isomer, however, was identical with the irradiation isomer of the natural ester, and, from energy considerations, these workers selected the all cis isomer for the natural product. In later work[12], the 2-cis-8-trans isomer was discovered in nature.

The starting materials in these reactions became synthetically available largely through the work of Heilbron's group[24], and the ultraviolet data, which permit surprisingly accurate deductions with respect to the structures of polyynes, were accumulated from several sources[4-24, 26-31].

Bruun also synthesized the trans isomer of II by the following scheme[6]. This isomer was subsequently discovered in nature[18].



A hexahydromatricaria ester apparently possessing a cumulene structure has also been isolated[7]. On the basis of spectral comparisons, the structure IX has been assigned to this "composit cumulene I".

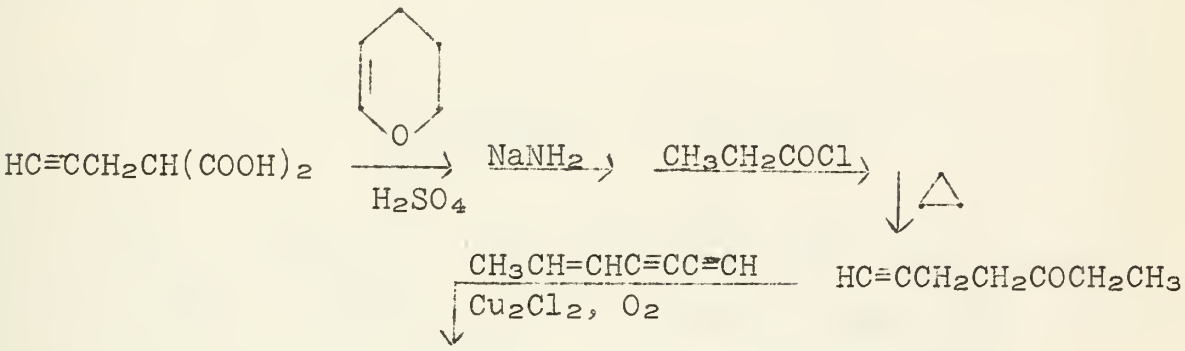
$CH_3CH_2CH_2CH_2CH_2CH{=}C{=}C{=}CHCOOCH_3$ IX

A dehydromatricaria ester having the formula $C_{11}H_8O_2$ was isolated and characterized by Sorensen's group[8]. From preliminary investigations, only structures X and XI seemed plausible for the compound. Synthesis of the trans isomers of

$CH_3CH{=}CHC{\equiv}CC{\equiv}CC{\equiv}CCOOCH_3$ X $CH_3C{\equiv}CC{\equiv}CC{\equiv}CCH{=}CHCOOCH_3$ XI

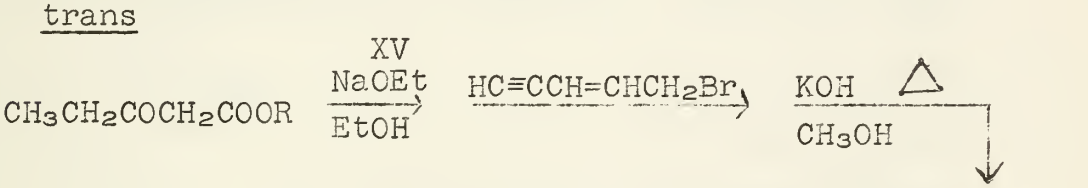
both[11,28] showed that neither was the natural ester, but spectral comparisons of these and other related synthetic compounds indicated that the natural ester possessed the structure cis XI.

From the same source as above, a ketone with the formula $C_{14}H_{14}O$ was isolated[8]. Preliminary investigations and spectral data[8,29] ruled out many possible structures, XV and XVI finally remaining. Bohlmann[29] synthesized these and determined that the natural ketone possessed structure XVI.



$CH_3CH{=}CHC{\equiv}CC{\equiv}CC{\equiv}CCH_2CH_2COCH_2CH_3$
trans

XV



$CH_3C{\equiv}CC{\equiv}CC{\equiv}CCH{=}CHCH_2CH_2COCH_2CH_3$
trans

XVI

Both isomers of α,β-dihydromatricaria ester have been prepared[13], and the 8-cis isomer has been discovered in nature[12].

All trans matricarianol (V)[14], its acetate[17], and a cis isomer of the acetate[17] have also been isolated from Compositae plants.

From another species of this family a series of compounds have been isolated[20] and structures tentatively assigned to them:

$CH_3CH{=}CHC{\equiv}CC{\equiv}CC{\equiv}CC{\equiv}CCH{=}CH_2$	XIX
$C_6H_5C{\equiv}CC{\equiv}CCH{=}CHCH_2OCOCH_3$	XX
$CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCH{=}CHCH{=}CH_2$	XXI
$C_6H_5C{\equiv}CC{\equiv}CC{\equiv}CCH{=}CHCH{=}CHCH_3$	XXIII
$CH_2{=}CHCH{=}CHC{\equiv}CC{\equiv}CC{\equiv}CCH{=}CHCH_2OCOCH_3$	XXIV

Structure XIX was assigned on the basis of the comparison between the ultraviolet spectrum of the natural product and those of several closely related synthetic compounds[20,23,30]. Structure XX was confirmed by synthesis from phenylacetylene[21]. Structure XXI was also confirmed by synthesis and by comparison of maleic anhydride adducts[31].

$$(C_6H_5)_3P + CH_2{=}CHCH_2Br \longrightarrow (C_6H_5)_3\overset{\oplus}{P}CH_2CH{=}CH_2 \xrightarrow{LiC_4H_9} (C_6H_5)_3P{=}CHCH{=}CH_2$$

$$\text{all } \underline{\text{trans}}\ V \xrightarrow{MnO_2} CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCHO \xrightarrow{(C_6H_5)_3P{=}CHCH{=}CH_2} \text{XXI}$$

Structure XXIII was assigned on the basis of spectral comparison and hydrogenation studies[21] as was structure XXIV[22]. Another highly unstable substance has also been isolated, and structure XXV, representing a tris-dehydro XXI, is consistent with the limited data available[23].

$CH_3C{\equiv}CC{\equiv}CC{\equiv}CC{\equiv}CC{\equiv}CCH{=}CH_2$ XXV

For other studies related to naturally-occurring polyacetylene compounds, see references 32 and 33.

REFERENCES

1. F. Semmler, Chem. Ztg., 13, 158 (1889).
2. A. Pfau, J. Pictet, P. Plattner and B. Suoc, Helv. Chim. Acta, 18, 935 (1935).
3. W. Wiljams, V. Smirnov and V. Goljmow, J. Gen. Chem. (U.S.S.R.), 5, 1195 (1935).
4. N. A. Sorensen and J. Stene, Ann., 549, 80 (1941).
5. R. T. Holman and N. A. Sorensen, Acta Chem. Scand., 4, 416 (1950).
6. T. Bruun, C. M. Haug and N. A. Sorensen, Acta Chem. Scand., 4, 850 (1950).
7. N. A. Sorensen and K. Stavholt, Acta Chem. Scand., 4, 1080 (1950).
8. K. Stavholt and N. A. Sorensen, Acta Chem. Scand., 4, 1567 (1950).
9. N. A. Sorensen and K. Stavholt, Acta Chem. Scand., 4, 1575 (1950).
10. T. Bruun, P. K. Christensen, C. M. Haug, J. Stene and N. A. Sorensen, Acta Chem. Scand., 5, 1244 (1951).
11. P. K. Christensen and N. A. Sorensen, Acta Chem. Scand., 6, 602 (1952).
12. K. K. Baalsrud, D. Holme, M. Nestvold, J. Pliva, J. S. Sorensen and N. A. Sorensen, Acta Chem. Scand., 6, 883 (1952).
13. P. K. Christensen and N. A. Sorensen, Acta Chem. Scand., 6, 893 (1952).
14. G. M. Tronvold, M. Nestvold, D. Holme, J. S. Sorensen and N. A. Sorensen, Acta Chem. Scand., 7, 1375 (1953).

15. L. Skattebol and N. A. Sorensen, Acta Chem. Scand., 7, 1388 (1953).
16. J. S. Sorensen, T. Bruun, D. Holme and N. A. Sorensen, Acta Chem. Scand., 8, 26 (1954).
17. D. Holme and N. A. Sorensen, Acta Chem. Scand., 8, 34 (1954).
18. D. Holme and N. A. Sorensen, Acta Chem. Scand., 8, 280 (1954).
19. J. S. Sorensen and N. A. Sorensen, Acta Chem. Scand., 8, 284 (1954).
20. J. S. Sorensen and N. A. Sorensen, Acta Chem. Scand., 8, 1741 (1954).
21. T. Bruun, L. Skattebol and N. A. Sorensen, Acta Chem. Scand., 8, 1757 (1954).
22. J. S. Sorensen and N. A. Sorensen, Acta Chem. Scand., 8, 1763 (1954).
23. J. S. Sorensen, D. Holme, E. T. Borlaug and N. A. Sorensen, Acta Chem. Scand., 8, 1769 (1954).
24. Researches on Acetylene Compounds:
Paper I: K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 39 (1946).
Paper XLVIII: E. R. H. Jones, B. L. Shaw and M. C. Whiting J. Chem. Soc., 3212 (1954).
Studies in the Polyene Series:
Paper I: E. Barraclough, J. W. Batty, I. M. Heilbron and W. E. Jones, J. Chem. Soc., 1549 (1939).
Paper LI: H. B. Henbest, E. R. H. Jones and T. C. Owen, J. Chem. Soc., 2765 (1955).
See also: E. R. H. Jones, M. C. Whiting, J. B. Armitage, C. L. Cook and N. Entwhistle, Nature, 168, 900 (1951).
25. C. Glaser, Ann., 154, 137 (1870).
26. E. F. L. J. Anet, B. Lythgoe, M. H. Silk and S. Trippett, J. Chem. Soc., 309 (1953).
27. B. Lythgoe, Lecture: "Some Naturally Occurring Polyacetylenes," delivered at a joint meeting of the Royal Institute of Chemistry and the Society of Chemistry and Industry held at Marischal College at 7:30 P. M., Friday, January 13, 1956. Announced in Proc. Chem. Soc., November 1955.
28. F. Bohlmann and H. J. Mannhardt, Chem. Ber., 88, 429 (1955)
29. F. Bohlmann, H. J. Mannhardt and H. G. Viehe, Chem. Ber., 88, 361 (1955).
30. E. R. H. Jones, J. M. Thompson and M. C. Whiting, Acta Chem. Scand., 8, 1944 (1954).
31. F. Bohlmann and H. J. Mannhardt, Chem. Ber., 88, 1330 (1955).
32. I. M. Heilbron, E. R. H. Jones, P. Smith and B. C. L. Weedon, J. Chem. Soc., 54, (1946); I. M. Heilbron, E. R. H. Jones and F. Sondheimer, J. Chem. Soc., 1586 (1947).
33. F. Bohlmann and H. G. Viehe, Chem. Ber., 88, 1245 (1955).

KINETIC CONFORMATIONAL ANALYSIS OF CYCLOHEXANE DERIVATIVES

Reported by Carol K. Sauers January 13, 1956

Introduction

The stereochemistry of substituents on six-membered saturated rings was not generally understood until results of recent work both theoretical and experimental became known. Hassel and his coworkers[2] have determined the conformations of cyclohexane and many of its derivatives from analyses of x-ray and electron diffraction data on both the solid and vapor states. Pitzer, Beckett and Spitzer[1] have elucidated the geometry of cyclohexane from thermodynamic calculations. It has been generally assumed and is borne out by the experimental evidence mentioned above, that in polysubstituted cyclohexanes, equatorial positions will be preferred by all substituents and that the more bulky ones will occupy equatorial positions if there is a competition for these positions.

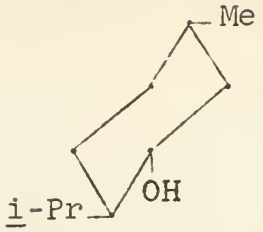
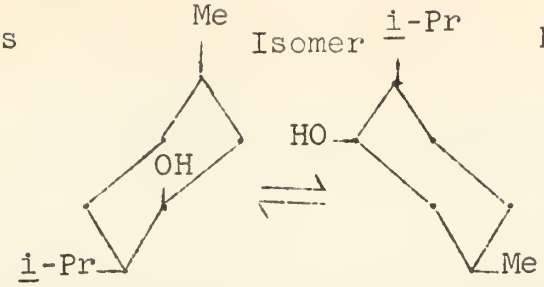
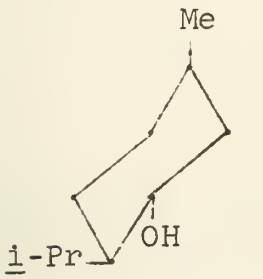
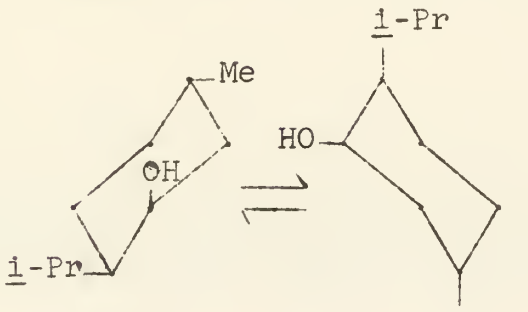
Barton[3] has pointed out that a small difference in the free energy content (ca. 1 kcal./mole at room temperature) will insure that a molecule appears by physical methods of examination and by thermodynamic considerations to be substantially in only one conformation. But, because one conformation of a molecule is more stable does not mean that the molecule is compelled to react as if it were in this conformation. In fact, Curtin has noted a number of depressed rates of chemical reactions resulting from necessary conformation changes from stable to less stable isomers during the rate determining step and has labeled these cases "the axial effect".[4]

Conformation and Reactivity

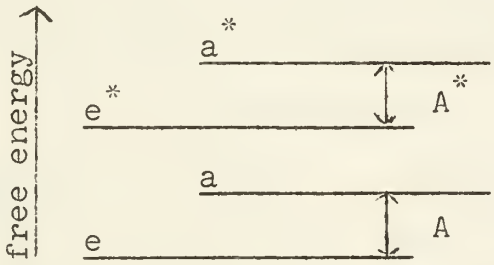
In 1951, Birch remarked that conformation analysis for study of the stability and reactivity of saturated or partly saturated cyclic systems promises to have the same degree of importance as the use of resonance in aromatic systems.[5] The large volume of research reported on conformation and reactivity, especially in the steroid and terpene fields, verifies this prediction. (Reviews in addition to the above are noted in reference 6).

For example, in the esterification of cyclohexanols and the hydrolysis of these esters, equatorially oriented groups react far more readily than the axial epimers. Vavon[7] has shown that trans 2- and trans 4- alkyl cyclohexanols are more reactive than the cis isomers. The rate ratio for basic hydrolysis of 2-isopropylcyclohexyl hydrogen succinates at 39° is trans : cis = 6.0 : 0.15.

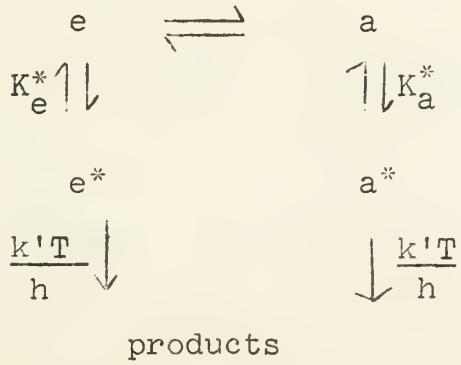
Moreover, in an interpretation of Read and Grubb's data[8] on the rates of esterification of the menthols with p-nitrobenzoyl chloride in pyridine at 25°, Eliel[9] has attributed the following differences in reactivity to the conversion of two of the axial alcohols into less stable equatorial alcohol conformations for reaction.

Isomer		Rel. Rates	Isomer		Rel. Rates
I		16.5	III		3.1
II		12.3	IV		1.0

Recently Winstein and Holness[10] have placed conformational analysis of cyclohexane derivatives on a quantitative basis in a study of the 4-t-butyl and 3-t-butyl cyclohexanols. If a free energy diagram applicable to the axial and equatorial isomers of a cyclohexane compound is constructed, the following facts become apparent:



1. That the relative amounts of reaction through e^* and a^* are independent of A^*. 2. But, the observed rates of reaction are related to the conformational distribution of the ground state; for we see that for unimolecular reactions:



where:
K_e^* and K_a^* are equil. const.
k' is Boltzmann's const.
h is Planck's const.
* stands for Transition State
e is equatorial
a is axial

The rate of formation of these products, dx/dt is given by:[16]

$$dx/dt = k'TK_e^*/h\,[e] + k'TK_a^*/h\,[a]$$

Which upon dividing by [e + a] gives:

$$dx/dt/\ [e + a] = k'TK_e^*/h \cdot Ne \ + \ k'TK_a^*/h \cdot N_a$$

Or,

$$k = k_eNe + k_aN_a \quad (1)^{10,11}$$

Where k is the observed rate of reaction, k_e and k_a are the rates for each conformation and N_e and N_a are the mole fractions.

It will also be seen that:

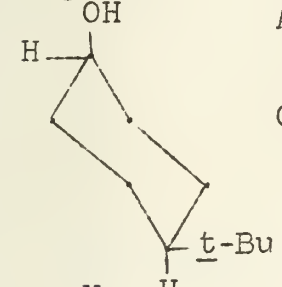
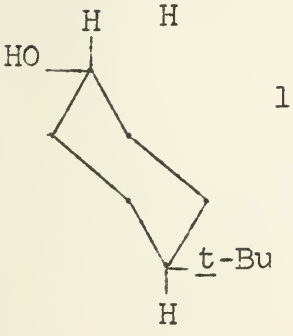
$$F_a - F_e = 2.303\ RT \log (N_e/N_a) \equiv A. \quad (2)$$

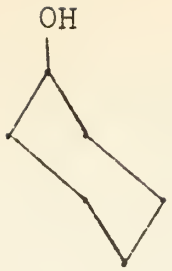
If k_e and k_a can be determined for "conformationally pure" compounds, then using these values for the same reaction on "conformationally mixed" compounds will lead to knowledge of N_e and N_a.

Curtin and Stolow have derived equation (1) without the use of transition state theory from equilibrium considerations alone.[12]

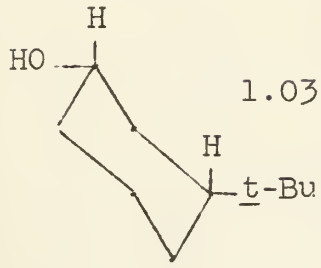
For the purpose of obtaining the k_e and k_a values for various reactions, Winstein and Holness prepared cis and trans 4-t-butyl and 3-t-butyl cyclohexanols. They measured the rates of saponification of the acid phthalates, chromic acid oxidation and solvolysis of the p-toluenesulfonates. These results along with Vavon's[13] work on the acid catalyzed dehydration of the alcohols are reported in the following table.

Table I, Relative Rates

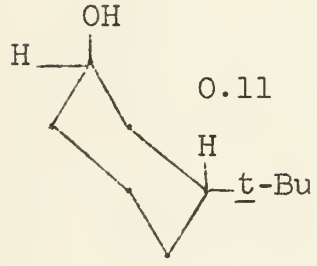
Compounds	Sapn. Acid Phth. 50°	CrO_3 25°	CrO_3 50°	Solvolysis 50° EtOH	Solvolysis 50° AcOH	Solvolysis 50° HCOOH	Dehydr. 140°-160° [13]
	0.11	2.97	2.55	3.90	3.24	3.58	3.5
	1.00	1.00	1.00	1.00	1.00	1.00	1.0



1.02 1.24 1.41 1.29 1.24 1.23 1.16



1.03 0.96



0.11 3.45

Applying these results to those of other workers, notably Vavon[14] and Huckel,[15] Winstein and Holness were able to construct the following table of "A values".

Table II, Group A Values

Group	Solvent	Temp., °C	A, kcal./mole
t-Bu			5.4
i-Pr	H_2O	39	3.3
n-Bu	"	"	2.6
n-Pr	"	"	2.1
Ethyl	"	"	2.1
Methyl			1.8
OTs	EtOH, AcOH, HCOOH	50	1.7
$OCOC_6H_4COO^-$	H_2O	39	1.2
OH	75% AcOH	40	0.8

BIBLIOGRAPHY

1. C. W. Beckett, K. S. Pitzer, R. Spitzer, J. Am. Chem. Soc., 69, 2488 (1947).
2. O. Hassel, B. Ottar, Acta. Chem. Scand. I, 929 (1947); O. Hassel, H. Viervoll, ibid., I, 149 (1947); O. Hassel, Research, 3, 504 (1950).
3. D. H. R. Barton, Experientia, 6, 316 (1950).
4. D. Y. Curtin, Rec. Chem. Prog., 15, 111 (1954) and references contained therein.
5. A. J. Birch, Ann. Repts., XLVIII, 192 (1951).

6. S. J. Angyal, J. A. Mills, Rev. Pure and Appl. Chem. (Australia) 2, 185 (1952); O. Hassel, Quart. Rev., 7, 221 (1953); D. H. R. Barton, J. Chem. Soc., 1027 (1953); H. D. Orloff, Chem. Rev., 54, 347 (1954); W. Klyne, "Progress in Stereochemistry" Vol. I, Chapter 2, Academic Press Inc., New York (1954) and reference 4.
7. G. Vavon, Bull. soc. chim. Fr., (4) 49: 937 (1931).
8. J. Read, W. J. Grubb, J. Chem. Soc., 1779 (1934).
9. E. L. Eliel, Experientia, 9, 91 (1953).
10. S. Winstein, N. J. Holness, J. Am. Chem. Soc., 77, 5562 (1955).
11. E. L. Eliel, C. A. Lukack, R. S. Ro, Technical Report from Notre Dame, p. 4 (1955).
12. D. Y. Curtin, R. Stolow, private communication.
13. G. Vavon, M. Barbier, Bull. soc. chim. Fr. (4) 49: 567 (1931).
14. G. Vavon, Bull. soc. chim. Fr. (4) 49: 989 (1931).
15. W. Hückel, et.al., Ann., 533, 128 (1937).
16. S. Glasstone, K. J. Laidler, H. Eyring, "The Theory of Rate Processes" 1st ed., p. 14, McGraw Hill Book Co., Inc., New York (1941).
17. F. H. Westheimer, A. Novich, J. Chem. Phys., 11, 506 (1943).
18. M. L. Bender, J. Am. Chem. Soc., 73, 1626 (1951); 75, 5596 (1953); M. L. Bender, R. D. Ginger and K. C. Kemp, J. Am. Chem. Soc., 76, 3350 (1954).

SEMINAR TOPICS

CHEMISTRY 435 II SEMESTER 1955 56

The Structure of Ajmaline
R. G. Schultz, February 10..... 1

The Alkylation of Mesomeric Anions
R. A. Scherrer, February 10..... 7

Conversion of Primary Amines to Alcohols
B. M. Vittimberga, February 17..... 11

Vapor Phase Chromatography
B. D. Wilson, February 17..... 15

The 1,4-Elimination Reaction With Cleavage
W. De Jarlais, February 24..... 19

The Absolute Configuration of Morphine
D. S. Matteson, March 2..... 23

Alkylations With Alcohols Under Basic Conditions
Joe A. Adamcik, March 2..... 27

Colchicine: Aspects of Structure and Synthesis
J. H. Rassweiler, March 9..... 31

Ferrocene as an Aromatic Nucleus
Kenneth Conrow, March 16..... 35

Application of Mass Spectrometry to Organic Chemistry
Philip N. James, March 16..... 39

The Unsaturation of Cyclopropane Rings
Norman Shachat, March 23..... 43

Aliphatic Hydroxy Sulfonic Acids and Sultones
J. S. Dix, March 23..... 47

Nucleophilic Substitution of Vinyl Halides
Willis E. Cupery, April 6..... 50

Non-Polymer-Forming Reactions of Vinyl Halides
H. Scott Killam, April 6..... 54

Alkaline Ferricyanide Oxidations
C. W. Schimelpfenig, April 20..... 57

The Structure of Novobiocin
Kaye L. Motz, April 20..... 61

Ozonation Studies of Aromatic Hydrocarbons and Heterocycles
M. S. Konecky, April 27..... 64

Isomerization in the Flavanoids
Jerome Gourse, May 4..... 71

Vitamin B_{12}
L. R. Haefele, May 11..... 74

Reactions of Cyclooctatetraene and its Derivatives
W. A. Remers, May 11..... 78

Some Aspects of the Mechanisms of Catalytic Hydrogenation
C. K. Sauers, May 18..... 82

Organic Peroxides
J. C. Little, May 18..... 88

THE STRUCTURE OF AJMALINE

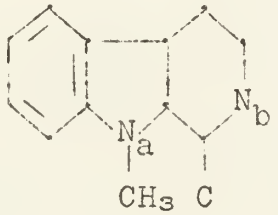
Reported by R. G. Schultz February 10, 1956

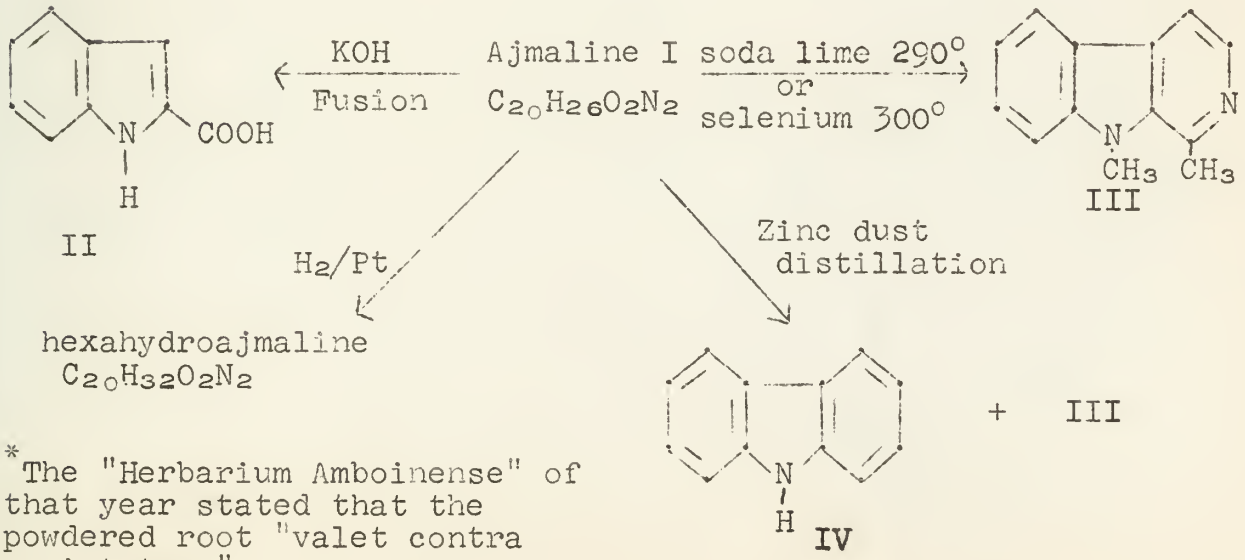
Ajmaline is an alkaloid isolated from several species of the Rauwolfia family of shrubs.[1,2] The physiological effects of crude extracts of the roots of the Rauwolfia family have been known in Europe since 1741*, but until recently attracted little attention. The pharmacology of ajmaline has been investigated,[3] and it was found, in contrast to the related reserpine, that ajmaline was an hypertensor and an intestinal stimulant.

The molecular formula, $C_{20}H_{26}O_2N_2$, was determined early and some preliminary structural work done,[1,4,5] but it remained for Robinson and coworkers and Woodward and Schenker to elucidate the structure completely.[6,7,8,9]

Ajmaline takes up three moles of hydrogen over platinum to give completely saturated hexahydroajmaline. Both nitrogens are tertiary. The infra red and ultra violet spectra are characteristic of dihydroindoles, and color reactions are typical of N-alkyl substituted anilines. O,O-Diacetyl and dibenzoyl derivatives can be prepared showing that the oxygens are present as hydroxyls. From this information it may be concluded that ajmaline has six rings.

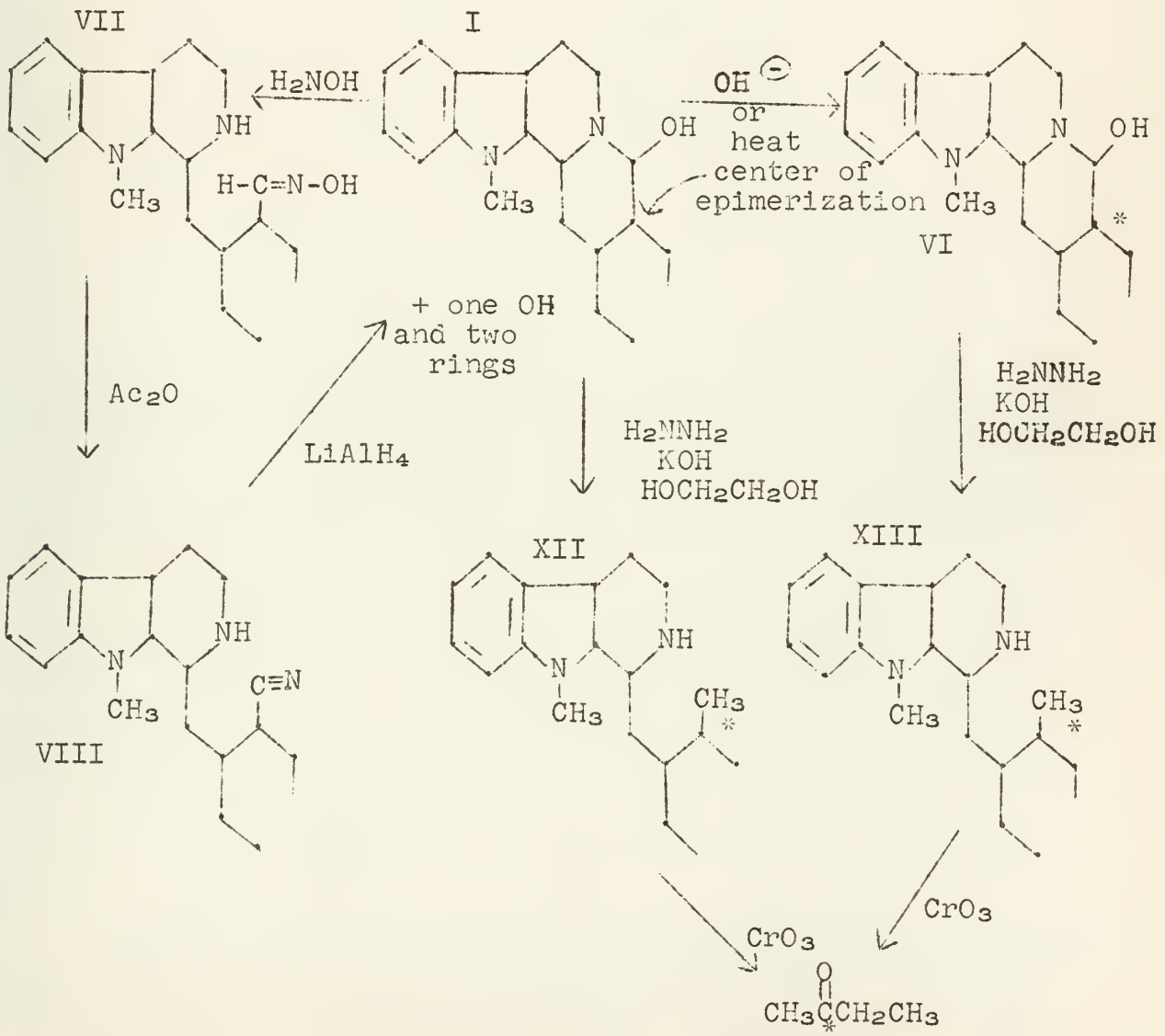
Ajmaline (I) on potassium hydroxide fusion yields indole-2-carboxylic acid (II).[5] On treatment with soda lime or selenium N-methylharman (III) is formed, and on zinc dust distillation carbazole (IV) and N-methylharman are isolated. Ajmaline then has a partial structure

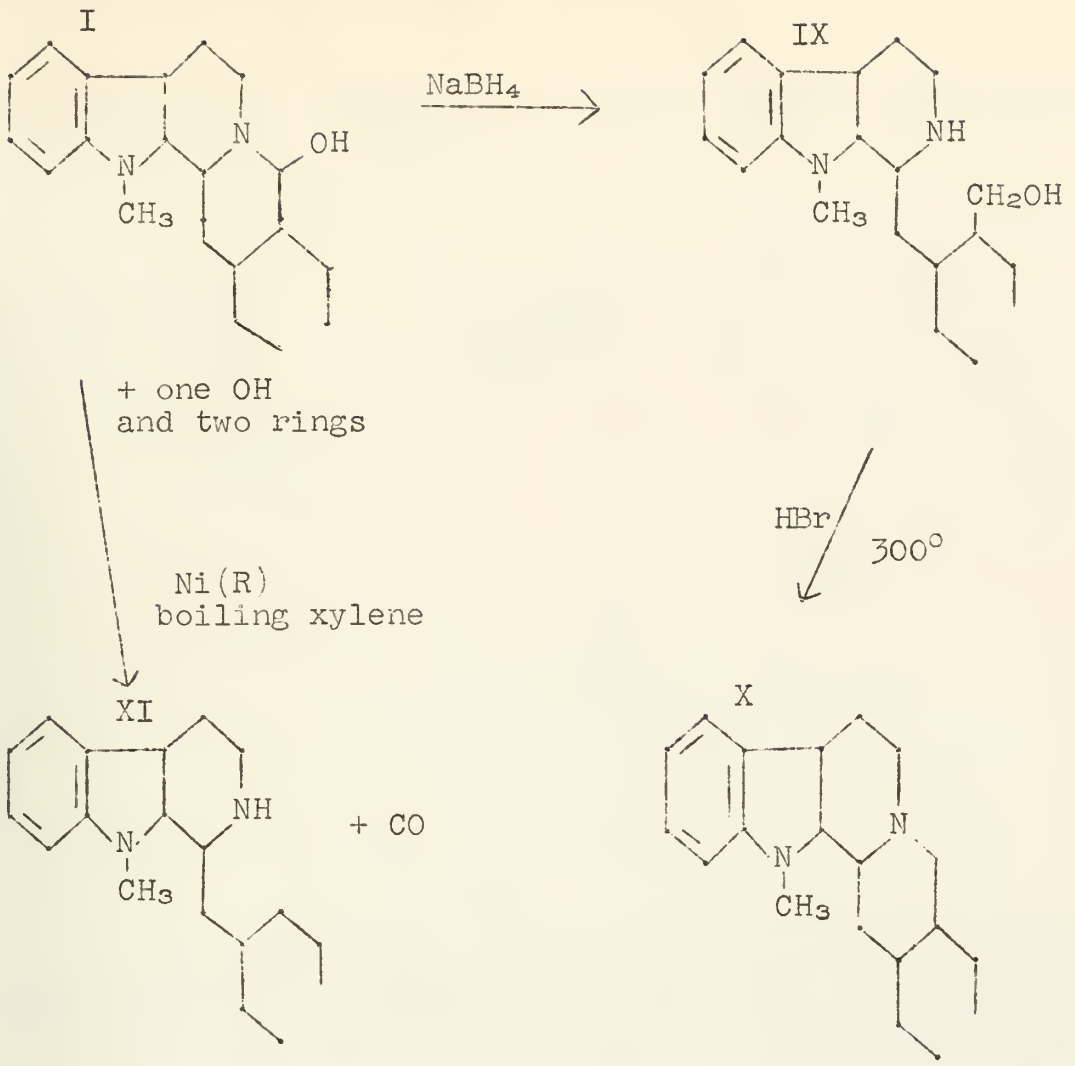




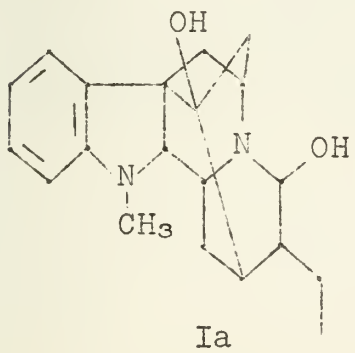
*The "Herbarium Amboinense" of that year stated that the powdered root "valet contra anxietatem."

Ajmaline may be converted to isoajmaline (VI) by alkali or heat. Reduction of ajmaline (I) or isoajmaline (VI) by the Huang-Minlon modification of the Wolff-Kishner method yields desoxydihydroajmaline (XII) and desoxydihydroisoajmaline (XIII) respectively. Oxidation of either XII or XIII yields methyl ethyl ketone. On oxime (VII) can be prepared from ajmaline and hydroxylamine. This oxime can be converted to the nitrile (VIII) by treatment with acetic anhydride, and ajmaline regenerated by reduction of the nitrile with lithium aluminum hydride. Reduction of ajmaline with sodium or potassium borohydride affords dihydroajmaline (IX) in which N_b is secondary and two hydroxyls are present. Treatment of IX with HBr at 300° yields desoxyajmaline (X) in which N_b is again tertiary and only one hydroxyl is present. Finally Raney nickel in boiling xylene decarbonylates ajmaline to decarbonoajmaline (XI) which contains one hydroxyl and a secondary amino group. This work can be rationalized if a carbinol amine, -N-CHOH-, is postulated. (Schenker also found that heating ajmaline monoacetate to 200° formed an N-acetyl aldehyde. -N-CHOAc $\xrightarrow{200°}$ -N-Ac OHC-) The partial structure of ajmaline (I) may now be extended as in the following scheme:

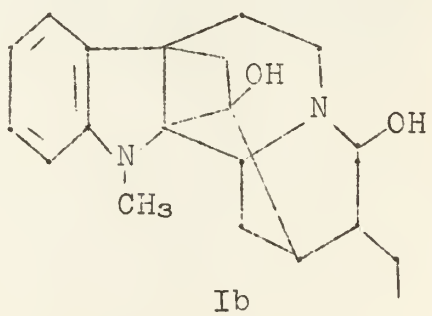




Robinson[6,7,8] considers the second hydroxyl to be bridge-head tertiary in ajmaline since it doesn't undergo displacement reactions with several reagents including thionyl chloride, and since it is not oxidized by CrO_3. On the basis of this and the other data, Robinson proposed two possible structures for ajmaline, Ia and Ib.



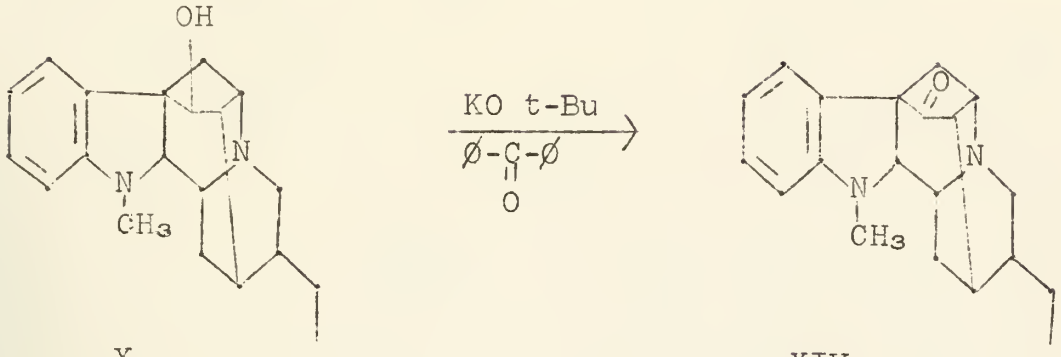
Ia



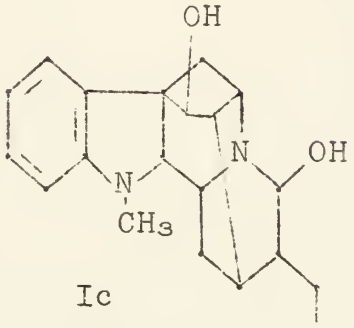
Ib

However the second hydroxyl might be secondary, since it is easily acetylated and benzoylated and indeed, Schenker[9] has been able to oxidize desoxyajmaline (X) with potassium t-butoxide and benzophenone to yield a ketone (XIV) in 85% yield which has an infra red spectrum characteristic of a

cyclopentanone (1745 cm.$^{-1}$). He then proposed the structure Ic for ajmaline.



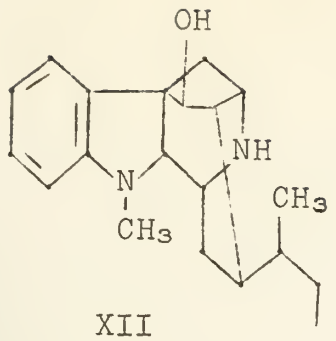
X XIV



Ic

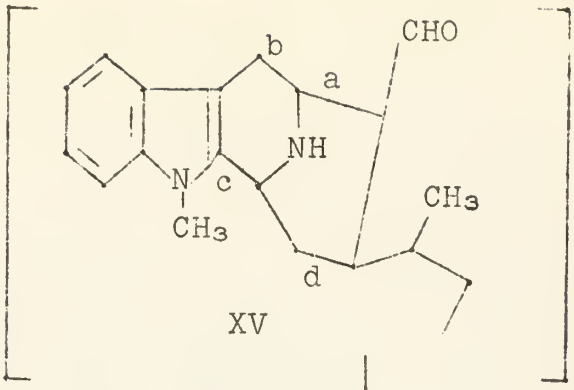
The dehydrogenation studies of Robinson on desoxydihydroajmaline were also explained by Schenker. It was postulated that desoxydihydroajmaline (XII) on treatment with palladium on carbon rearranged to the intermediate aldehyde (XV) and thence by cleavage at a and d to N-methyl harman (III) (6%), by cleavage at a to $C_{20}H_{26}N_2$ (XVI) (7%), by cleavage at c to $C_{20}H_{24}N_2$ (XVII) (15%), and by cleavage at b to $C_{20}H_{24}N_2$ (XVIII) (1%).

Schenker[9] has treated dihydroajmaline (IX) with lead tetraacetate and alkaline silver oxide to obtain a lactone of postulated structure XIX, and with lead tetraacetate to obtain an hemiacetal (XX) which can then be dehydrated to an enol ether (XXI) with acetic anhydride and heat. The structure of Woodward and Schenker (Ic) appears to be the best of those postulated.



XII

Pd/C
240°



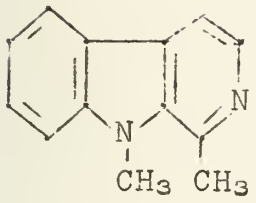
XV

a,d

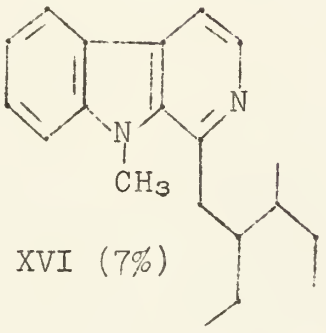
a

b

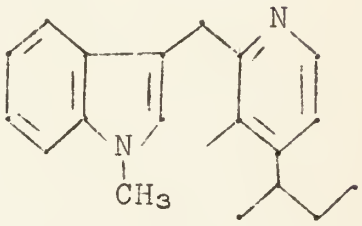
c



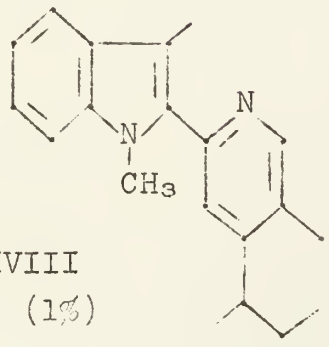
III (6%)



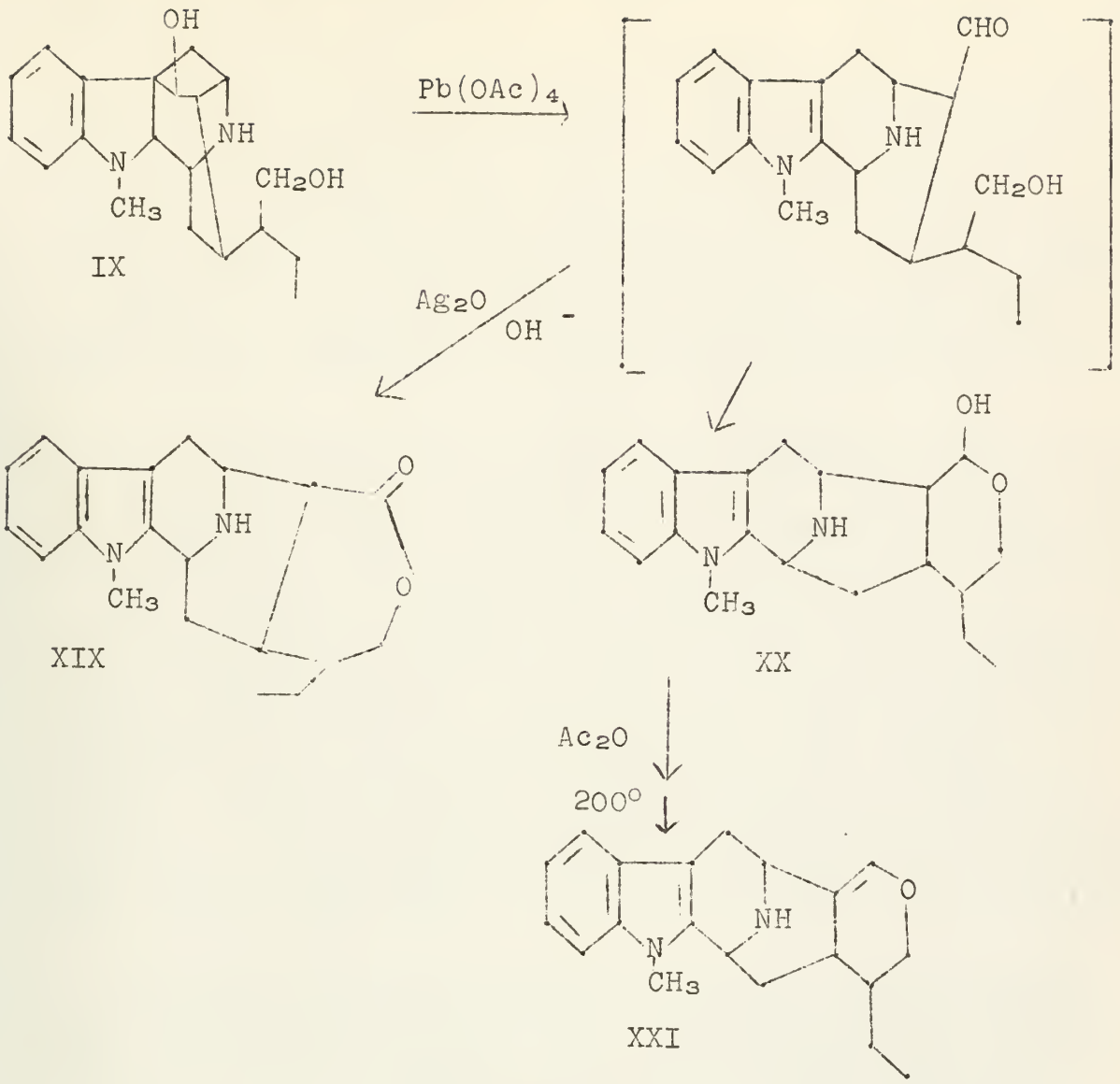
XVI (7%)



XVII (15%)



XVIII
(1%)



BIBLIOGRAPHY

1. S. Siddiqui and R. H. Siddiqui, J. Indian Chem. Soc., 8, 667 (1931).
2. C. Djerassi, et.al., J. Am. Chem. Soc., 76, 4463 (1954); 77, 6687 (1955).
3. R. N. Chopra et.al., Indian J. Med. Research, 21, 261 (1933); 24, 1125 (1937); 29, 763 (1941); 30, 319 (1942).
4. S. Siddiqui and R. H. Siddiqui, J. Indian Chem. Soc., 9, 539 (1932); 12, 37 (1935); 16, 421 (1939).
5. A. Chatterjee and S. Bose, Experientia, 9, 254 (1953); J. Indian Chem. Soc., 31, 17 (1954).
6. F. A. L. Anet, D. Chakravarti, R. Robinson and E. Schlittler, J. Chem. Soc., 1242 (1954).
7. R. Robinson, Chem. and Ind., 285 (1955).
8. F. C. Finch, J. D. Hobson, R. Robinson, Chem. and Ind., 653 (1955).
9. K. A. Schenker, 7th Summer Seminar in the Chemistry of Natural Products, Univ. of New Brunswick, 1955.

THE ALKYLATION OF MESOMERIC ANIONS

Reported by R. A. Scherrer February 10, 1956

This seminar concerns the prediction of products from the reactions of mesomeric anions. The problem exists for such cases because two or more structural isomeric products can be formed, depending on which atom of the anion is attacked. It is well known that the relative stability of the various products cannot always be used to predict their relative rates of formation; at times the less stable isomer is formed and at other times the more stable isomer results. In addition, for a given reaction, a change of reaction conditions or reagents may bring about a change in product ratio to favor the more or the less stable product.

A rigorous solution to the problem depends on the ability to estimate the structure and stability of the transition states leading to the various products. The product ratio of two products formed competitively will depend only on their relative rates of formation, and hence on the difference in free energy of the transition states ($\triangle \triangle F^{\ddagger}$) leading to these products. Hammond[1] has proposed a method of establishing the structure of the transition state from the overall thermodynamics of the reaction. For a highly exothermic reaction, the transition state has a structure closely resembling that of the starting material. For a highly endothermic reaction the transition state will resemble the product. This correlation is valid if the free energy of activation is not high for the exothermic reaction or for the reverse of the endothermic reaction. The assumption is also made that the more nearly alike two structures are, the closer their energies will be.

Another method of estimating transition state structure is from reaction theory derived from kinetic data, steric data, structure-medium-reactivity relationships and the like. Thus, for example, from all the data on displacement reactions of alkyl halides we can draw with fair certainty the structure of the transition state for the reaction of hydroxide ion with methyl bromide.

These principles can be applied to rationalize the data on product composition and rates for several reactions recently reported by Kornblum[2].

Nitrite ion reacts with alkyl halides to give a mixture of nitrite ester and nitroalkane. In the reaction of 2-iodooctane with silver nitrite it has been shown that both products are produced with inversion of configuration[3]. With this same reagent, the order of reactivity of alkyl halides is $3^{\circ} \gg 2^{\circ} > 1^{\circ}$. The tertiary halides give mostly alkyl nitrite while primary halides give mostly nitroalkane (Table I).

The study of substituted benzyl bromides in which electrical effects may be varied with a constant steric effect provides further data on product composition. As one goes from p-NO_2- to p-MeO- benzyl bromide and as the carbon atom

undergoing valence change becomes more cationic, the yield of nitrite ester relative to nitroalkane increases and the relative rates are again characteristic of an ionization process induced by an electrophilic attack of silver ion on halogen. (Table I)

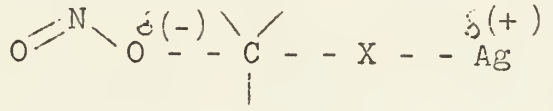
Table I

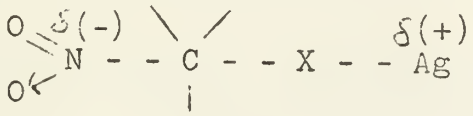
Reaction of alkyl halides with $AgNO_2$

compound	relative rates	% yield $RNO_2/RONO$	reference
1-bromobutane (1-iodo)	1 (1)	73/13	4
2-bromobutane (2-iodo)	4 (9)	19-25/27-37	5
t-butyl bromide	1500	0-5/65	5
p-NO_2-benzyl bromide	.09	84/16	2
benzyl bromide	1	70/30	
p-CH_3-benzyl bromide	16	52/48	
p-CH_3Obenzyl bromide	>16	39/61	

From the above data we can postulate a transition state for the reaction of silver nitrite with alkyl halides. There are two variables in the transition state which must be considered: a) the degree of ionization of the C-X bond, (or the degree of silver to halogen bond formation) and b) the degree of bonding of nitrite to carbon.

Let us consider first the case in which a) (above) is small. This corresponds to the situation with primary alkyl halides and p-NO_2-benzyl bromide. This is so because the positive charge that would be induced on formation of a silver-halogen bond could not be stabilized to a great extent. Nitrite ion is needed as a nucleophilic agent to complete the reaction. A high degree of bond formation between nitrite ion and carbon is needed in the transition state to displace the halogen. There are two transition states which can be drawn for this displacement of halogen:

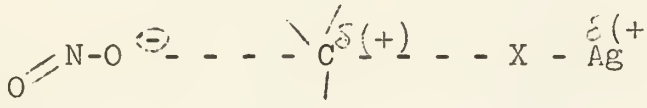
I  (leading to alkyl nitrite)

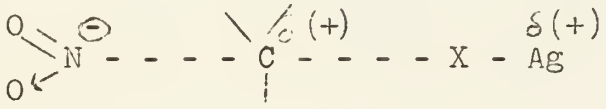
II  (leading to nitroalkane)

The relative differences in free energy of these transition states will determine the relative rate of formation of each product. The main factors contributing to the difference in free energies of these transition states are 1) the difference in energy of the C--N and C--O bonds 2) the difference in resonance energy of the nitro group and the nitrite ester group 3) differences in solvation energy, 4) steric hindrance, and 5) electrostatic forces. One and two,

above, are reflections of the stability of the products. Since nitroalkane is ~3 Kcal. more stable than an alkyl nitrite ref (6), and assuming the other differences are small in comparison, the free energy of the transition state II will be lower than I, and nitroalkane will be formed predominately.

Now let us consider the case in which the carbon-halogen bond is broken to a considerable degree in the transition state, as with tertiary halides and p-MeO-benzyl bromide. Bond formation of nitrite ion to carbon is less important here, since the carbonium ion being formed is stabilized by resonance or hyperconjugation. We can draw two transition states for this reaction:

III 

IV 

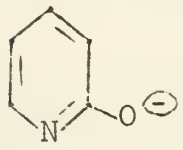
The main factors determining difference in free energy of these transition states are the solvation energies and electrostatic forces. Exact calculation of these energies is not now possible, and therefore no prediction of the relative amounts of alkyl nitrite and nitroalkane can be made. Note that there is no direct relation between the stabilities of the products and the relative stabilities of the transition states.

It is observed that for the reaction just described, the yield of alkyl nitrite is much higher than nitroalkane. We can then say that III must have a lower free energy than IV.

Two generalizations concerning the reactions of mesomeric anions can now be made. If the transition state involves a high degree of bonding between the anion and the alkylating group, as in I and II, the stability of the products will determine how the reaction proceeds. If the transition state has a high degree of cationic character, as in III and IV, the product cannot be predicted.

Silver salts of mesomeric anions will tend to react <u>via</u> a transition state resembling III and IV, and alkali metal salts will, in general, tend to react <u>via</u> a transition state resembling I and II. This explains the sometimes observed differences in product. (Table II)

Table II

Anion	Cation	Alkyl halide	Yield	Ref.
	Ag^+	C_2H_5I	80% O-R 0% N-R	7
	K^+	C_2H_5I	0% O-R 70% N-R	
	Ag+	CH_3I	50% N-R	
$CN^{\ominus}$	Ag^+	2Me-1-iodobutane	60% N-R	8a
	Ag^+	$(CH_3)_3SiI$	80% N-R	b
	Na^+	n-C_4H_9Br	80% C-R 1% N-R	c
$C_6H_5N{:}\,CH\,O^{\ominus}$	Ag^+	C_2H_5I	74% O-R	9
p-$NO_2C_6H_5NCCH_3$	K^+	C_2H_5I	84% N-R	10
$NO_2^{\ominus}$	Ag^+	2-iodooctane	17-25% O-R 15-20% N-R	3
	Na^+	2-iodooctane	30% O-R 63% N-R	6

References

1. G. S. Hammond, J. Am. Chem. Soc., 77, 334 (1955).
2. N. Kornblum et.al., ibid., 77, 6269 (1955).
3. N. Kornblum, L. Fishbein and R. A. Smiley, ibid., 77, 6261, 6266 (1955).
4. N. Kornblum, B. Taub and H. E. Ungnade, ibid., 76, 3209 (1954).
5. N. Kornblum et.al., ibid., 77, 5528 (1955).
6. Calculated from heats of combustion.
7. H. von Pechmann and O. Baltzer, Ber., 24, 3148 (1891) C. Rath, Ann., 489, 107 (1931).
8. a) H. Rupe and K. Glenz, Ann, 436, 184 (1929).
   b) J. J. McBride, Jr. and H. C. Beachell, J. Am. Chem. Soc., 74, 5247 (1952).
   c) R. Adams and C. S. Marvel, ibid., 42, 310 (1920).
9. J. L. Simonsen and R. Storey, J. Chem. Soc., 95, 2106 (1909).
10. M. A. Sattar, J. Indian Chem. Soc., 32, 489 (1955).

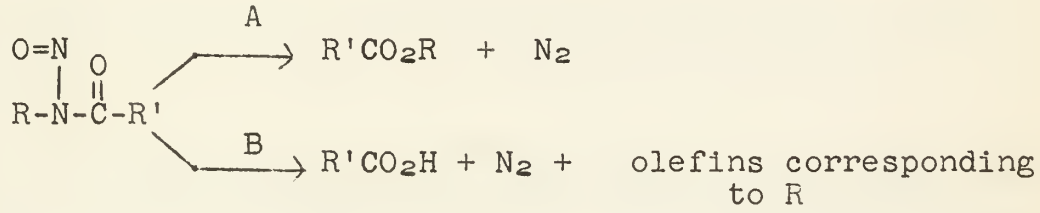
CONVERSION OF PRIMARY AMINES TO ALCOHOLS

Reported by B. M. Vittimberga February 17, 1956

For many years, the only available method for the conversion of primary amines to the corresponding alcohols involved a reaction with nitrous acid. This method was not a good preparative procedure; low yields and mixtures of isomers were often obtained.[1,2,3]

It had been reported[4,5] that when N-alkyl-N-nitrosoamides were heated, they decomposed to form esters. Since that time, little work has been done to investigate this reaction further. Recent[6,7,8,9,10] investigations on this decomposition have shown it to be a convenient means of transforming amines, in good yields, to corresponding esters, relatively free of isomers.

The N-alkyl-N-nitrosoamides were found to undergo decomposition with the elimination of nitrogen by the paths A and B,



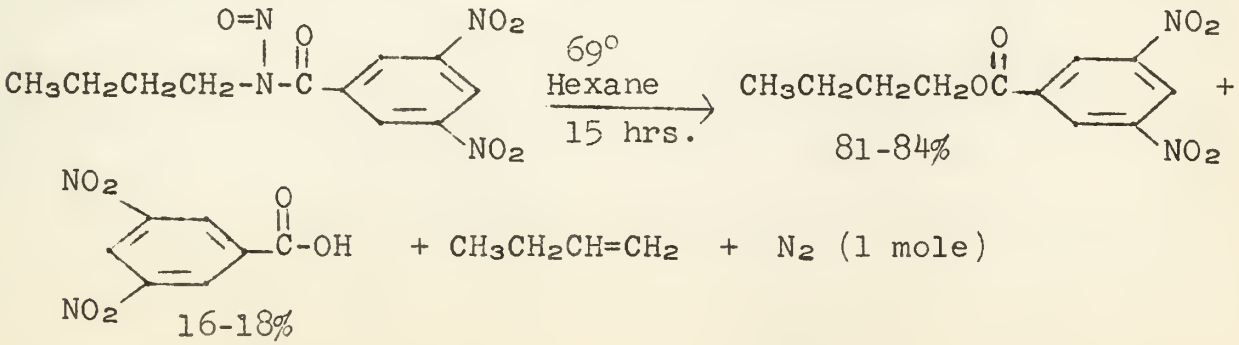
the relative importance of which depends on the reaction conditions.

The thermal stabitity of different N-nitrosoamides was found to vary as follows:

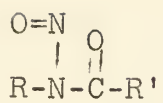
Type of Compound	Temp. of N_2 elimination
Nitrosoamides of primary carbinamines*	60-80°
Nitrosoamides of aliphatic secondary carbinamines	20-30°
Nitrosoamides of tertiary carbinamines	about -10°

*The term carbinamine refers to the C-NH_2 grouping as compared to the C-OH of carbinols. Primary etc. refer to the carbon atom.

Nitrosoamides of primary carbinamines produce the highest yields of the corresponding esters. An example of this is the decomposition of N-(n-butyl)-N-nitroso-3,5-dinitrobenzamide in hexane.



Other examples are:

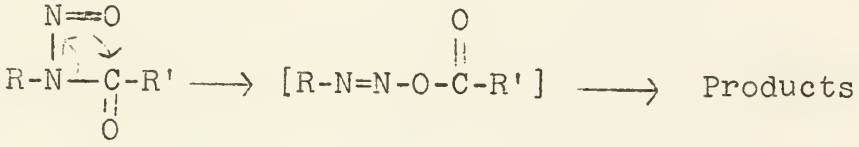


R	R'	Solvent	Temp.	Yield Ester	Yield Acid	Isomers Butyl ester n	iso	sec	ter
n-Butyl	Methyl	Heptane	77°	67	18	99		1	
Isobutyl	3,5-Dinitrophenyl	Hexane	69°	66	33		95.5	3.5	1
sec-Butyl	Phenyl	Pentane	25°	23	64			100	

Nitrosoamides of aliphatic secondary carbinamines follow path B more closely and give lower yields of ester and proportionately higher yields of olefin and acid. Tertiary carbinamines give the lowest yields of esters.

Variation of the acyl group has little effect on this decomposition reaction. Essentially the same results were obtained with nitroacetamides, benzamides, and dinitrobenzamides.

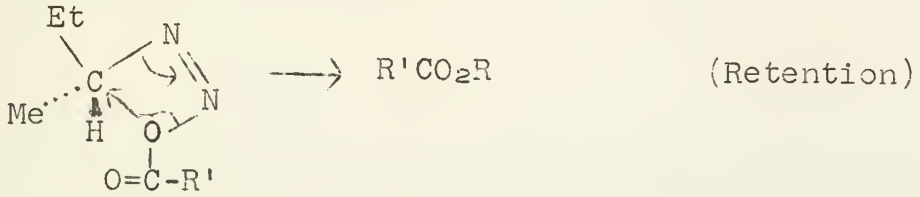
The first step in the mechanism of this decomposition is thought to be the formation of a diazo ester as was shown to be the case in the aryl series.[11,12] In the aliphatic series this diazo ester is very unstable and decomposes.



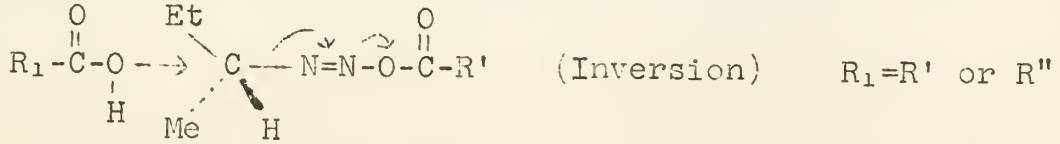
The nitrogen elimination step can proceed by a unimolecular or bimolecular mechanism with retention or inversion of configuration at R depending on the reaction conditions.

In order to explain the experimental observations the following mechanisms have been proposed:

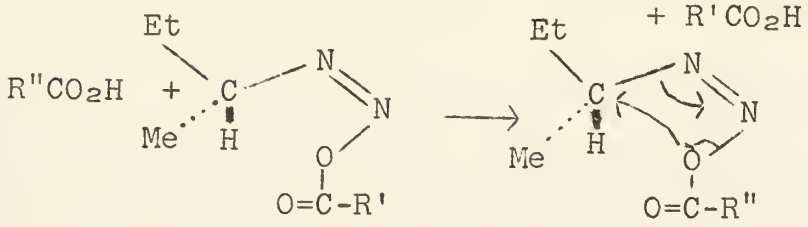
A. Unimolecular elimination



B. Bimolecular elimination

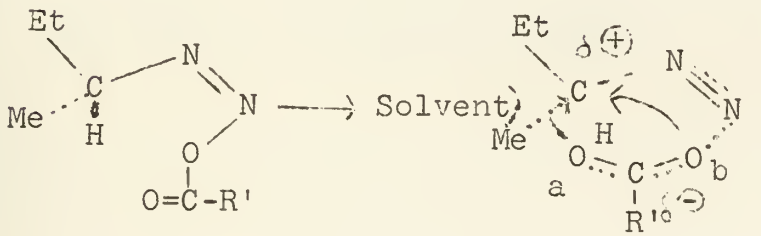


C. Acyl transfer followed by elimination



$R''CO_2R$ (Retention)

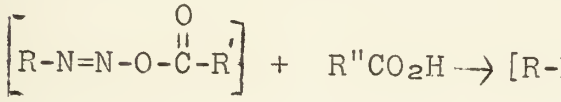
D. Solvolysis- Unimolecular elimination

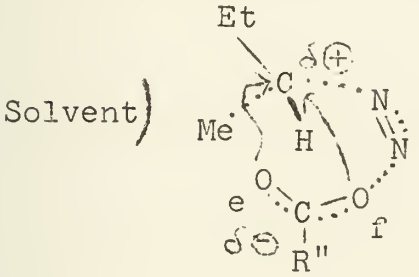


a → $R'CO_2R$ (Inversion)

b → $R'CO_2R$ (Retention)

E. Acyl transfer-Solvolysis-Unimolecular elimination

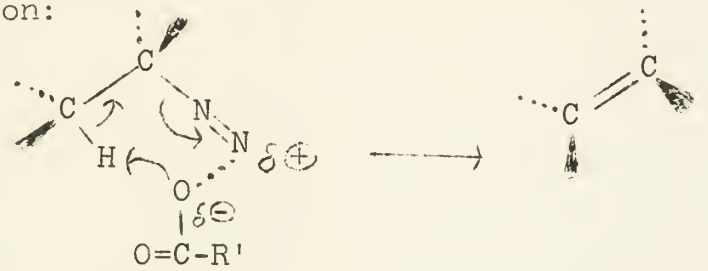




e → $R''CO_2R$ (Inversion)

f → $R''CO_2R$ (Retention)

The following mechanism is postulated for olefin formation:



+ $R'CO_2H + N_2$

The decomposition of N-(n-butyl)-N-nitroacetamide, N-(n-butyl)-N-nitroso-p-toluenesulfonamide, and N-cyclohexyl-N-nitrosourethan is thought to proceed by a similar elimination reaction.[9]

BIBLIOGRAPHY

1. F. C. Whitmore and D. P. Langlois, J. Am. Chem. Soc., 54, 3441 (1932).
2. F. C. Whitmore and R. S. Thorpe, ibid., 63, 1118 (1941).
3. D. W. Adamson and J. Kenner, J. Chem. Soc., 838 (1934).
4. H. V. Pechmann, Ber., 31, 2640 (1898).
5. M. F. Chancel, Bull. soc. chim. France, (3) 13, 125 (1895).
6. K. Heyns and W. v. Bebenburg, Ber., 86, 278 (1953).
7. E. H. White, J. Am. Chem. Soc., 76, 4497 (1954).
8. E. H. White, ibid., 77, 6008 (1955).
9. E. H. White, ibid., 77, 6011 (1955).
10. E. H. White, ibid., 77, 6014 (1955).
11. R. Huisgen, Ann., 574, 184 (1951) and preceding papers.
12. D. H. Hey, J. Stuart-Webb and G. H. Williams, J. Chem. Soc., 4657 (1952) and preceding papers.

VAPOR PHASE CHROMATOGRAPHY

Reported by B. D. Wilson 17 February 1956

Vapor phase chromatography (VPC) differs from conventional types of chromatography only in that the mobile fluids are volatilized under the conditions used. For this reason, the tool largely has developed in the realm of organic chemistry, for it is here the largest number of volatile compounds are to be found.

The method is fast, generally reproducible, requires only small samples (5-100 µl. of liquid; 1-10 ml. of gas), and as many as 18 components are reported[1] as having been separated in one analysis. Azeotrope formation does not interfere as it does in distillation. Accuracy is on the order of 1%. Concentrations as low as 4 ppm. have been accurately measured.[2] However, 1 part per 5,000 is more common with the detector generally employed.[3]

As with liquid phase chromatography, VPC is of two classes; adsorption and partition.

Adsorption gas chromatography: This is a process of adsorbing the vapor on some solid surface and then selectively desorbing the components by some means. The desorption methods which have been devised are:

(1) Fractional desorption by heat.[4-6]

(2) Elution from the adsorbent by a carrier gas.[7-9]

(3) Displacement by a more strongly adsorbed vapor.[3,10-12]

The adsorbent used is almost exclusively activated charcoal. The use of silica gel, alumina, zeolite, sand, or glass beads has been reported.

Methods (2) and (3) require a carrier gas. Carbon dioxide or nitrogen is most often used for this purpose. Air, hydrogen, or helium sometimes is used.

The detector device is a thermal conductivity cell.

Method (1) was the earliest developed. It entails slowly heating the column with a mobile heater. It is a rather slow process, as well as having all the limitations of method (2).

Method (2) gives asymmetric peaks, with frequent tailing, making resolution difficult. This is traced back to the non-linear adsorption isotherms produced by elution from charcoal. The elution method is limited to being adaptable to separation of relatively non-polar substances boiling below 150°C. at atm. pressure.[13] Neither of these methods is much used now,

having been superseded by method (3). This is because the displacement technique is ideally applicable to the Langmuir type adsorption isotherms obtained.[12,14]

In the displacement technique, the adsorbed vapors are desorbed by a more strongly adsorbed vapor in the carrier gas. Ethyl acetate, diethyl malonate, or bromobenzene is most commonly used. Displacement does not give the characteristic peaks of the elution methods, but rather gives a stepwise graph. The height of the step is a characteristic of the compound; the width is a measure of the amount present. The order of displacement is approximately that of the relative boiling points.[12]

The displacement technique, though useful, suffers from two serious drawbacks: (a) The column packing is not re-usable; it must be replaced after each run. (b) Compounds with similar thermal conductivities (e.g., isomers) give identical step heights, and, if displaced one after the other, while being separated, are indistinguishable on the graph.[14]

Gas-Liquid partition chromatography: Suggested in 1941 in Martin and Synge's classic paper[15] introducing partition chromatography, the method was introduced by the work of Martin and James[16,17] in 1951-2. Theory was developed on three assumptions:[17,18]

(a) The partition coefficient between two phases is a constant.

(b) Diffusion of gases within a single phase along the length of the column is negligible.

(c) The partial pressures of substances to be separated are negligible compared to that of the carrier gas.

Gas-liquid partition theory differs from liquid-liquid theory only in that the mobile phase is compressible, leading to a gas velocity gradient down the column.[17] Because of the lower viscosity of the mobile phase, relatively longer columns can be used, with a corresponding gain in efficiency. Also, there is the advantage that methods for the determination of a change in composition of a gas stream are generally simpler than those for a liquid stream.[1]

Studies relating gas-liquid partition chromatography to distillation show it to be similar to a very efficient extractive distillation.[18] A good fractionation column has a HETP value of ~1 cm. VPC has HETP values of ~0.1 cm. (1,000-2,000 theoretical plates on a 4 ft. column[17]).

In partition work, the gas phase (N or He), carrying the vapors, flows over an inert solid (celite) coated with the liquid (static) phase. While somewhat limited by theoretical considerations, the choice of a proper liquid phase is mostly empirical.[19] A whole host of substances have been used. Di-(3,5,5-trimethylhexyl) phthalate ("dinonyl phthalate" of the trade) seems to be used more often than the others.

The order of elution depends on the Henry coefficient of the substance.[19]

Temperature must be controlled, although the operating range is 0-230° C. The boiling point of the liquid phase ought to be at least 100 degrees greater than the column temperature. A general rule is to keep the column temperature 40 degrees above the boiling point of the most volatile component.[5] Pressures as low as 20 mm. have been used.

For qualitative analysis, the retention volume (that volume of the mobile phase that must be passed before the particular elution peak is reached) is used, since it is a characteristic of the compound. Using a constant rate flow of carrier gas, the retention time is generally the parameter measured. This retention time (volume) is analogous to R_f values of liquid-liquid partition chromatography.

For quantitative analysis, one measures the area under each peak. Accuracy can be greatly improved by the use of an internal standard.[20]

Partition chromatography gives linear isotherms, which are ideally suited to the elution technique involved.[12,14] The reason for various types of isotherms is that in partition chromatography, vapor distribution depends only on solution effects (ideal at these low concentrations), while adsorption chromatography deals with the interface effects of adsorption.[21]

The limit of VPC methods lies in the detection device. While thermal conductivity is now most often used, there are several other promising techniques: (a) surface potential method[3] (b) gas density balance method.[22]

VPC (usually partition) has been used in the separation of permanent gases, hydrocarbons (aliphatic, cycloaliphatic, and aromatic), fatty acids through C_{12}, fatty acid methyl esters C_{12}-C_{22}, amines, aromatic bases, halides, alcohols, esters, aldehydes, ketones, and ethers.

To date, no separation of optical isomers has been successful.[22] VPC is applicable to such things as:

I. Control

A. Purity of gaseous anesthetics.

B. Perfume industry.

C. Petroleum industry.

II. Check raw materials and solvents for impurities.

III. Preparation of pure substances in small amount. In theory, this can be scaled up.

IV. Analysis of intermediate and final products in gaseous reactions.[23,24]

V. Identification of volatile oils, perfumes, plasticizers, etc. in commercial products.

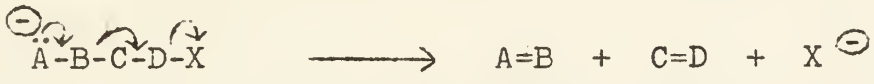
BIBLIOGRAPHY

1. D. H. Lichtenfels, S. A. Fleck and F. H. Burow, Anal. Chem., 27, 1510 (1955).
2. J. H. Griffiths and C. S. G. Phillips, J. Chem. Soc., 3446 (1954).
3. J. Griffiths, D. James and C. Phillips, Analyst, 77, 897 (1952).
4. N. M. Turkel'taub, J. Anal. Chem. U.S.S.R., 5, 200 (1950).
5. N. H. Ray, J. App. Chem. (London), 4, 21 (1954).
6. N. C. Turner, Petroleum Refiner, 22, 140 (1943).
7. G. Hesse and B. Tschachotin, Naturwissenschaften, 30, 387 (1942).
8. N. H. Ray, J. App. Chem. (London), 4, 82 (1954).
9. J. Janák, Chem. Listy, 47, 464 (1953); cf. C.A. 48, 3196h (1954). This is paper no. 1 in a series of 12. For no. 12, see C.A. 50, 104b (1956).
10. S. Claesson, Arkiv. Kemi. Min. Geol., 23A, No. 1 (1946).
11. C. S. G. Phillips, Dis. Far. Soc., 7, 241 (1949).
12. D. H. James and C. S. G. Phillips, J. Chem. Soc., 1600 (1953).
13. H. W. Patton, J. S. Lewis and W. I. Kaye, Anal. Chem., 27, 170 (1955).
14. D. Harvey and D. E. Chalkey, Fuel, 34, 191 (1955).
15. A. J. P. Martin and R. L. M. Synge, Biochem. J., 35, 1359 (1941).
16. A. T. James and A. J. P. Martin, ibid., 48, vii (1951).
17. A. T. James and A. J. P. Martin, ibid., 50, 679 (1952).
18. A. T. James and A. J. P. Martin, Analyst, 77, 915 (1952).
19. A. I. M. Keulemans, A. Kuantes and P. Zaal, Anal. Chim. Acta, 13, 357 (1955).
20. A. B. Littlewood, C. S. G. Phillips and D. T. Price, J. Chem. Soc., 1480 (1955).
21. B. W. Bradford, D. Harvey and D. E. Chalkey, J. Inst. Petroleum, 41, 80 (1955).
22. A. J. P. Martin, Kolloid Zeitschrift, 136, 5 (1954).
23. C. J. Hardy, Analyst, 79, 726 (1954).
24. J. H. Knox, Chem. and Ind., 1631 (1955).
25. M. I. T. Org. Chem. Sem. Abst., II Sem. 1954-5, p. 342.

THE 1,4-ELIMINATION REACTION WITH CLEAVAGE

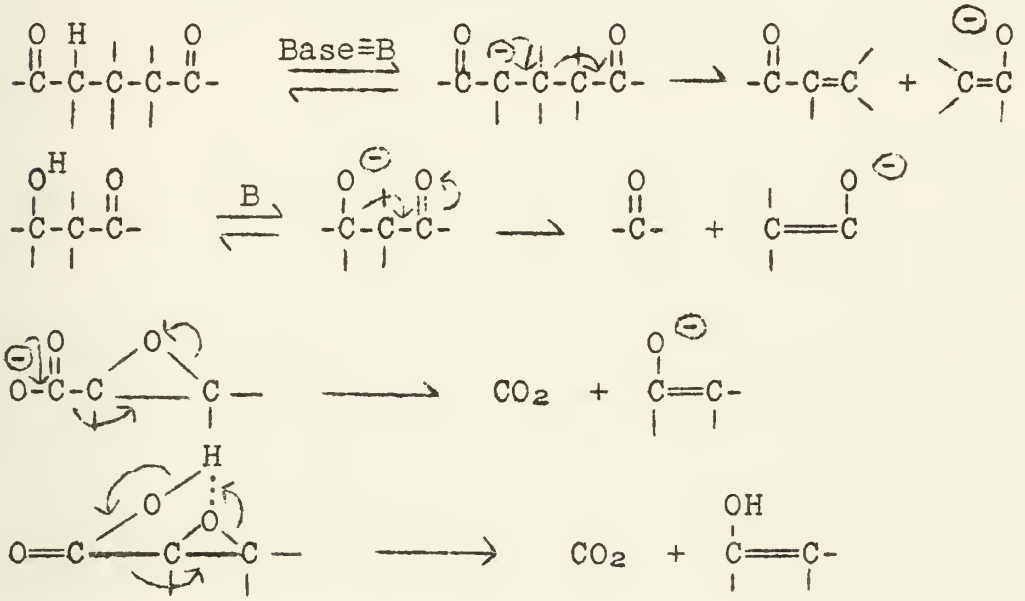
Reported by W. De Jarlais February 24, 1956

A considerable number of reactions, when examined closely, fit the mechanistic picture formulated as follows:



The atom A must of course be capable of forming a double bond with B. By far the greater number of reactions of this type involve an anionic oxygen as atom A. An additional requirement is that the anion expelled be a relatively weak base. Steric factors such as increased substitution on the atoms B and C aid the reaction.

Familiar examples of reactions fitting this mechanism are, the reverse Michael, the reverse aldol and the reverse Claisen reactions as well as the decarboxylation of glycidic acids. These may be formulated:



Perhaps somewhat less familiar is the decarboxylation of the anions of certain β-bromoacids. For example, a successful method for the preparation of β-bromostyrene depends upon the elimination of carbon dioxide and bromide ion from the anion of α,β-dibromohydrocinnamic acid. This reaction has been shown to be stereospecific and shows a rate dependent on the concentration of the anion.[1,2]

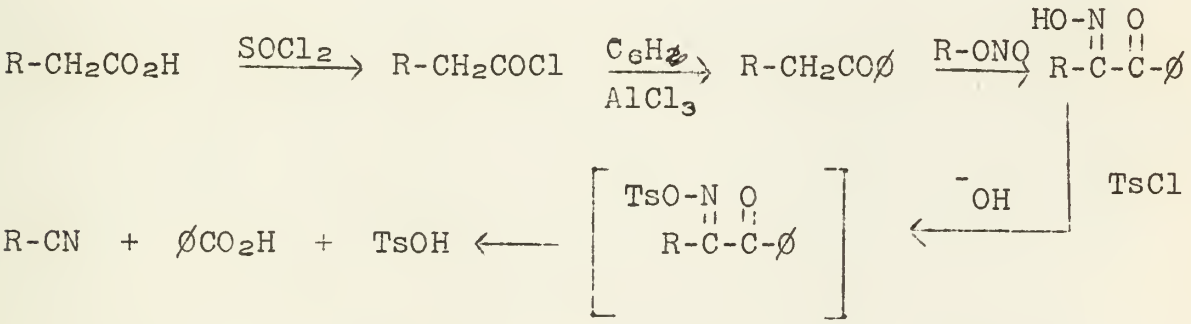
The importance of a relatively weak base as the anion X^- is shown by the fact that the p-toluenesulfonate of α-hydroxy-β,β-dimethyl-γ-butyrolactone is cleaved to the sodium salt of β,β-dimethylacrylic acid, formaldehyde and sodium p-toluenesulfonate by treatment with two equivalents of sodium hydroxde at 90°, while the unesterified lactone under the same conditions does not yield any formaldehyde.[3]

An attempt to prepare 2,2-dimethyltrimethylene oxide form 2,2-dimethyl-3-bromo-1-propanol by a potassium hydroxide catalyzed Williamson reaction gave only formaldehyde and

isobutylene.[4] Similarly, it was found that the methiodide of the Mannich base of isobutyrophenone on treatment with alkali gave isobutylene, benzoic acid and trimethylamine.[5]

Many of the reactions for the formation of diazomethane are of this type. For example, diazomethane may be prepared by the action of potassium hydroxide on nitrosomethylurethane or N-nitroso-N-methylurea or by the reaction of alkoxide ion with N-nitroso-β-methylaminoisobutyl methyl ketone.[6] It may also be prepared by the reaction of N-nitroso-N-methyl-acetamide with potassium hydroxide solution; the yield is 73%.[7] A reaction which might be considered to be "pseudo" of this type is the recently revealed preparation of diazo-methane from the corresponding N-nitroso-N-methyl-p-toluene-sulfonamides.[8] The yields are good (usually from 80-90%). The reaction is carried out in the usual manner. The nitrosocompound, dissolved in ether is added to a solution of potassium hydroxide in alcohol or, if alcohol free diazo-methane is desired, carbitol is used instead of alcohol and the diazomethane codistilled with ether. The real advantage in this method lies in the fact that the nitrosocompound is in this case, stable, and may be stored in stoppered brown bottles for long periods of time without decomposition.

An interesting application of the 1,4-elimination re-action with cleavage is a method for the degradation of long chain fatty acids.[9] The method was specifically designed for the determination of radioactive carbon by degrading the acid one carbon at a time. An iron pyrolytic method has been used for this purpose but the product is not suitable for further degradation.[10] In addition, an experiment with carboxyl labelled octanoic acid led to a specific activity that was only 95% of theory for the carboxyl group. The Barbier-Wieland method gave only average yields and led to a dilution of the activity of 13 to 1. A bromine-silver salt method has been used but again a lower than expected activity was found. The Schmidt degradation gives good yields but extraneous carbon dioxide causes difficulties. The following method gave good results.



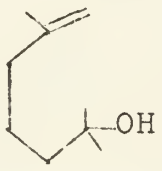
The yields ran about 75% overall.

The compound I (see below) when treated with 40% aqueous potassium hydroxide gave 5-methyl-5-hexenoic acid (II) in 82% yield.[11] The infrared spectrum shows the bands of the methylene double bond (893 cm.$^{-1}$, 1655 cm.$^{-1}$). Upon catalytic hydrogenation (platinum-glacial acetic acid) a mole of hydrogen

was taken up. The resulting dihydro acid was identified by the melting point of its benzyl thiouronium salt as 5-methylhexanoic acid. Ozonolysis of the product from the treatment of I with alkali gave formaldehyde and a 70% yield of 5-ketohexanoic acid. There can be little doubt that the reaction product is II.

I II

Treatment of the methane sulfonate of 2-hydroxymethyl-2-methyl-cyclopentanone (I) with methyl magnesium iodide gave a compound $C_9H_{18}O$ which on the basis of its origin and properties is assigned the structure III below. The compound assigned structure III shows the band of the hydroxyl (3450 cm.$^{-1}$) group and the two bands of the methylene double bond in the infrared as well as an atom of active hydrogen by a Zerevitinov determination. This compound takes up a mole of hydrogen on catalytic hydrogenation and an atom of oxygen when treated with perbenzoic acid. Here, again then, the reaction involves a 1,4-elimination with cleavage of the carbocyclic system.

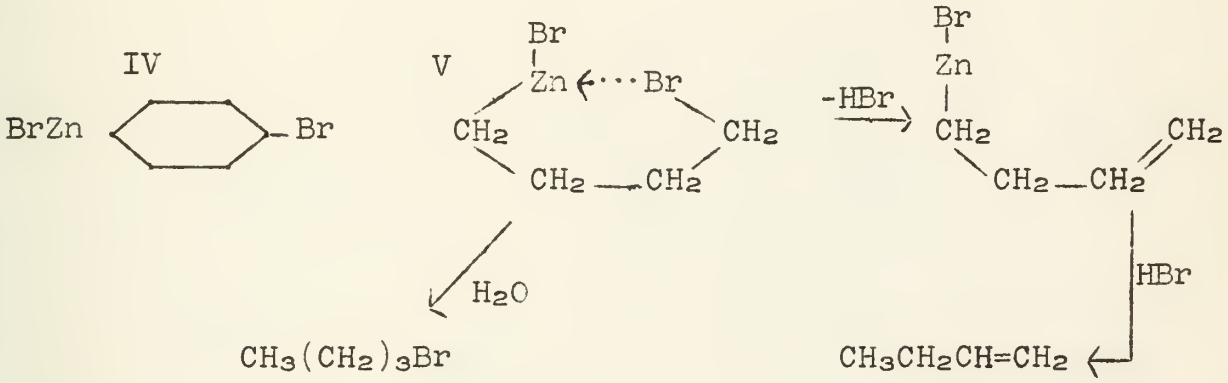


III

The reaction of I with lithium aluminum hydride gave an 85% yield of 2,2-dimethylcyclopentanone and therefore is not analogous to the above two reactions of I.

It has been reported that the debromination of dibromides can proceed by a reaction of 1,4-elimination with cleavage. For example, Vogel[12] reported that debromination with zinc dust of 1,2-dibromocyclobutane-3,4-dicarboxylic acid gave muconic acid. Much more extensive investigations of this type of dehalogenation reaction have been made by Grob and Baumann.[13] They prepared the "cis" and "trans" 1,4-dibromo and diiodo-cyclohexanes and treated them with solutions of sodium metal in decalin. They obtained benzene and cyclohexene plus an 8% yield of biallyl. Furthermore, small amounts of 2,4-hexadiene and 1,3-cyclohexadiene were found. No indication of the presence of bicyclo-[2. 2. 0]-hexane could be found. Conditions were then sought in which the yield of biallyl would be increased. If the dibromide was treated with magnesium in ether only traces of biallyl were formed. With zinc dust in alcohol 20 to 40% diallyl was obtained. The best yields were obtained by the use of dioxane and zinc dust. The yield of biallyl from either of the two iodides was 90% and from the dibromides 70%. This reaction is remarkable in that

steric effects do not seem to play an important role. This is in contrast to the case of loss of carbon dioxide and bromide ion from the anions of the dibromodihydrocinnamic acids. It is, however, not so unreasonable, if one makes the assumption that the compound IV is an intermediate. The condition then for the smooth coupling of two trans-eliminations is that the molecule be able to arrange itself so that the four carbon atoms involved lie in the same plane. This is obviously impossible no matter whether one has the "cis" or "trans" dihalide. It should, however, be possible in the open chain 1,4-dibromobutane. Consequently, it might be expected that this dibromide would react more rapidly than the cyclic dibromides. However, 1,4-dibromobutane gave only a 10% yield of ethylene after 20 hours of reaction time. Much of the dibromide is recovered and butyl bromide and 1-butene are found. This can be rationalized by the cyclic intermediate, V, below



BIBLIOGRAPHY

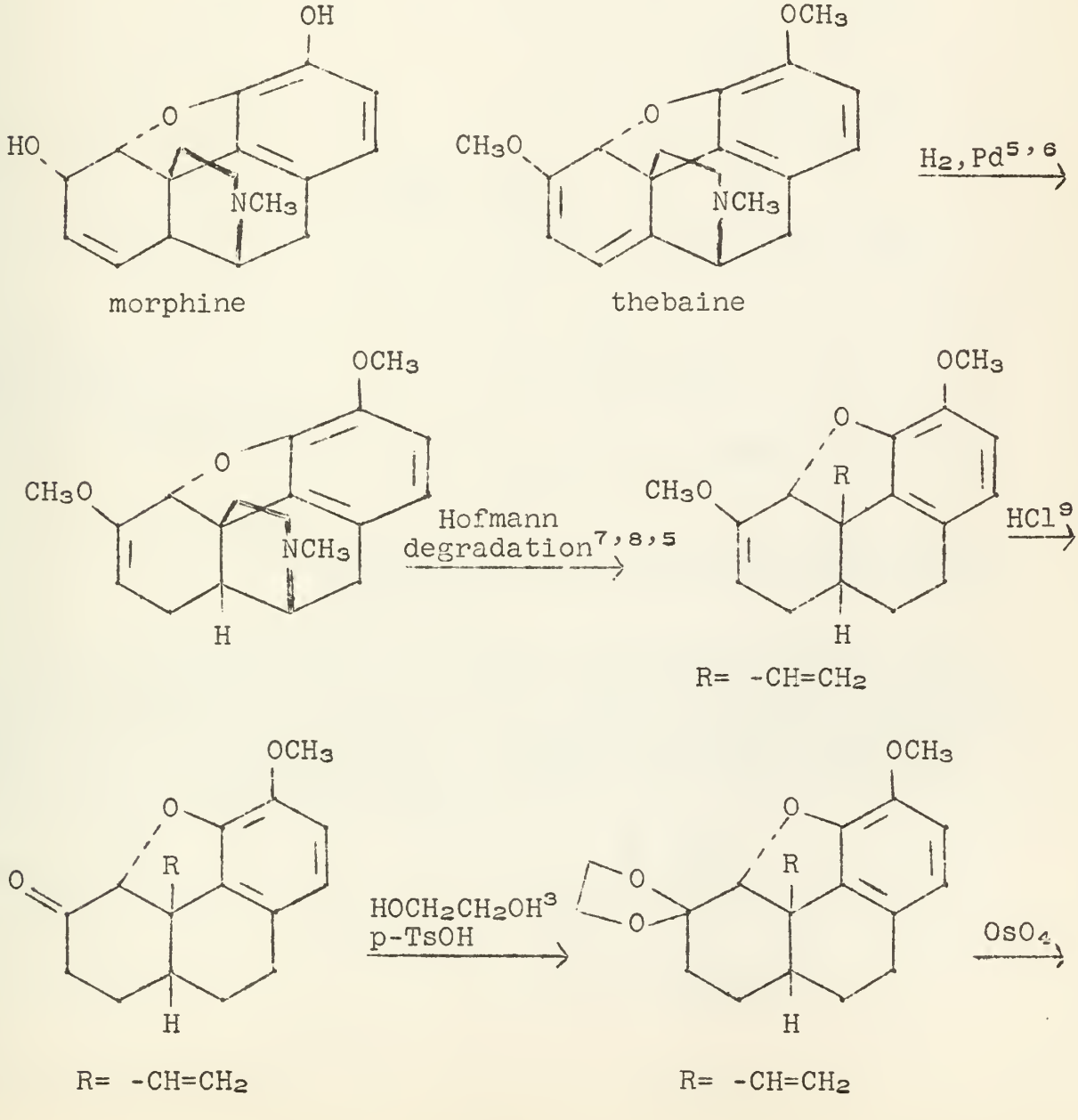
1. E. Grovenstein and D. E. Lee, J. Am. Chem. Soc., 75, 2639 (1953).
2. S. J. Cristol and W. P. Norris, ibid., 75, 2645 (1953).
3. H. Bretschneider and H. Hass, Monatsh., 81, 954 (1950).
4. S. Searles and M. J. Gortatowski, J. Am. Chem. Soc., 75, 3030 (1953).
5. H. R. Snyder and J. H. Brewster, ibid., 71, 1061 (1949).
6. "Organic Synthesis", Coll. Vol. III, J. Wiley and Sons, Inc. New York, N. Y.
7. K. Heyns and O. F. Wayrsch, Ber., 86, 76 (1953).
8. J. De Boer and H. J. Backer, Rec. Trav. Chim., 73, 229, 682 (1954).
9. W. G. Dauben, E. Hoerger and J. W. Petersen, J. Am. Chem. Soc., 75, 2347 (1953).
10. A. Zabin, J. Biol. Chem., 189, 355 (1951).
11. A. Eschenmoser and A. Frey, Helv. Chim. Acta, 35, 1660 (1952).
12. E. Vogel, Angew. Chem. 66, 305 (1954).
13. C. A. Grob, W. Bauman, Helv. Chim. Acta, 38, 594 (1955).

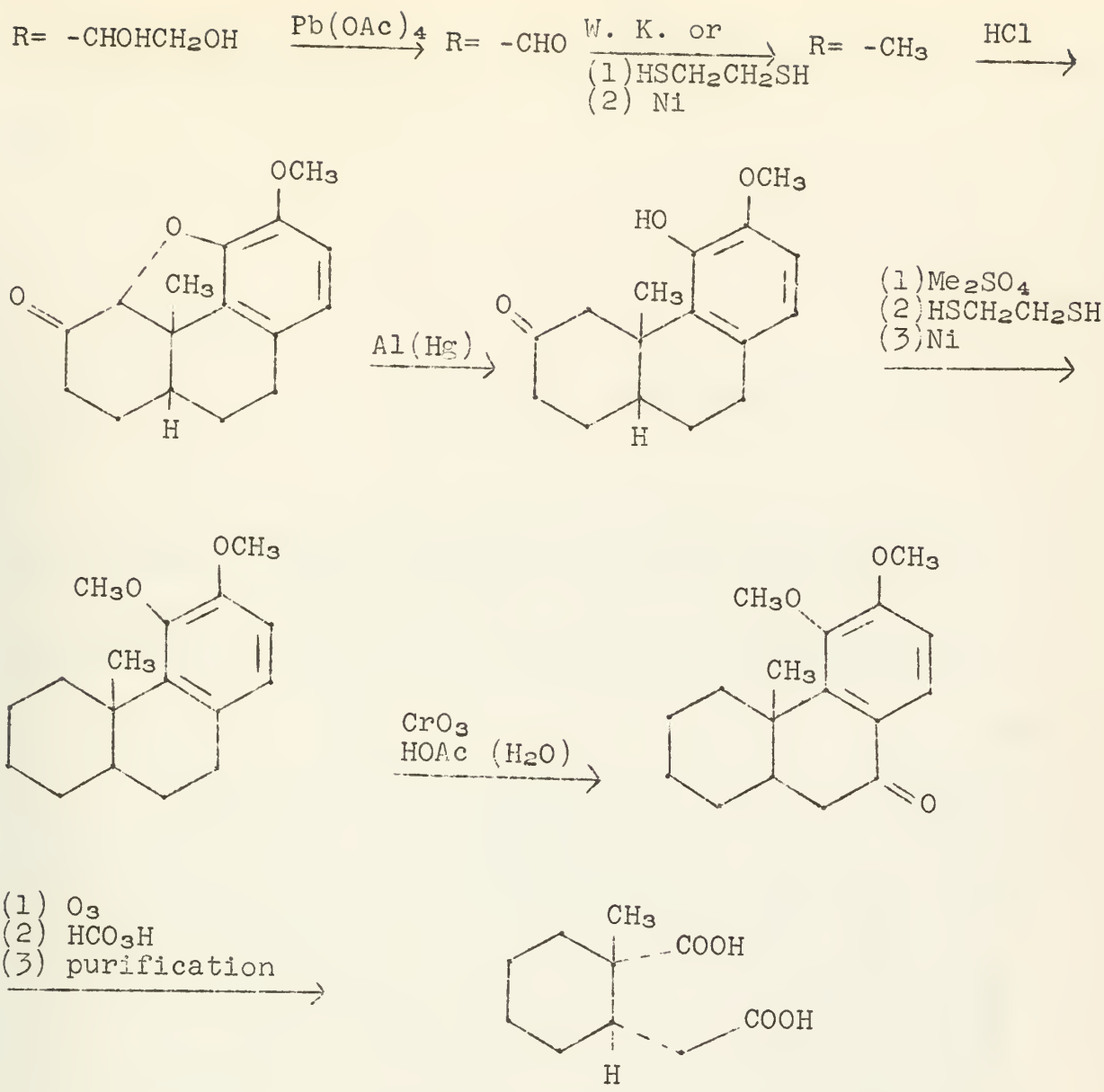
THE ABSOLUTE CONFIGURATION OF MORPHINE

Reported by D. S. Matteson March 2, 1956

A knowledge of the relationships between configurations of natural products is useful to those who like to speculate on biosynthetic pathways. Emil Fischer adopted D-glyceraldehyde as a standard to which other configurations were referred. That the Fischer convention for writing D-glyceraldehyde is actually correct[1,2] has been shown by calculations and physical measurements, including X-ray diffraction. Thus the absolute configurations of all compounds which have been related to this standard are known.

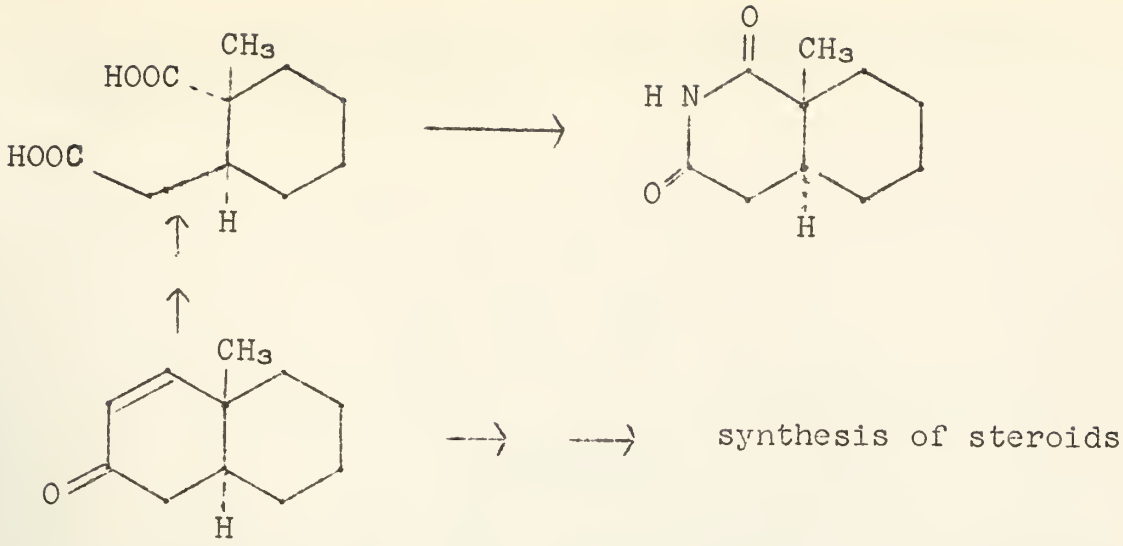
Morphine alkaloids have recently been degraded to simple compounds of known absolute configuration by two independent methods.[3,4] The method of Kalvoda, Buchschacher and Jeger[3] is outlined below.





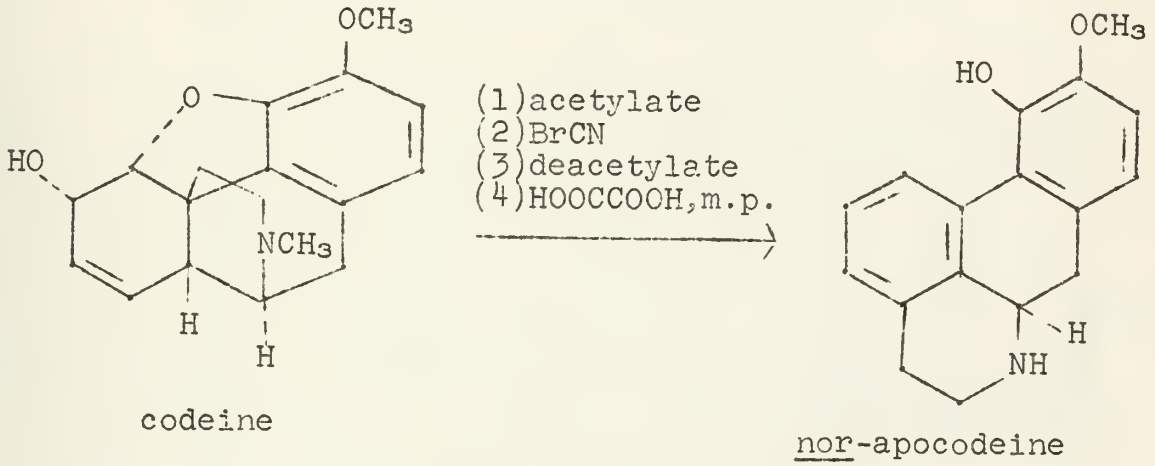
(-)-cis-[2-methyl-2-carboxycyclohexyl-(1)]-acetic acid

The stereoisomeric [2-methyl-2-carboxycyclohexyl-(1)]-acetic acids have also been used in the proofs of the absolute configurations of abietic acid,[10] cevine (veratrum alkaloids),[11] ergosterol[12] and β-eudesmol (a bicyclic sesquiterpene).[13] The absolute configurations of these acids have been established by relating them to steroids.[13,11]



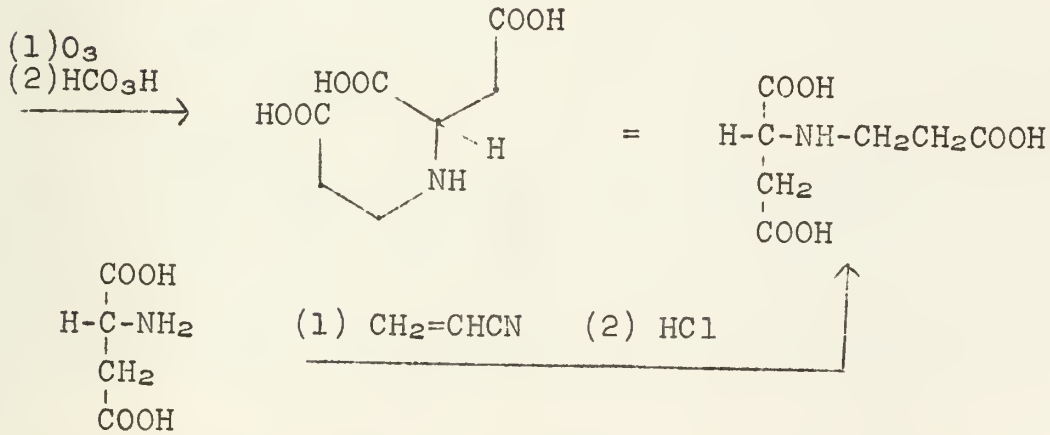
The absolute configuration of the steroid series has been established by several methods.[14,15,16,17,18,19,20]

Corrodi and Hardegger have proved the absolute configuration of morphine by a much simpler degradation.[4]



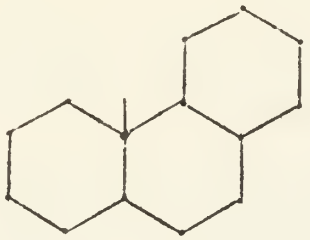
codeine

nor-apocodeine



D-aspartic acid[21]

It should be noted that the morphine alkaloids, triterpenes, steroids and veratrum alkaloids all contain a common structural element.



REFERENCES

1. W. Kuhn, Z. El. Chem. 56, 506 (1952).
2. J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, Nature 168, 271 (1951).
3. J. Kalvoda, P. Buchschacher and O. Jeger, Helv. Chim. Acta 38, 1847 (1955).
4. H. Corrodi and E. Hardegger, Helv. Chim. Acta 38, 2038 (1955).
5. H. Wieland and M. Kotake, Ann. 444, 69 (1925).
6. L. F. Small, H. M. Fitch and W. E. Smith, J.A.C.S. 58, 1457 (1936).
7. L. J. Sargent and L. F. Small, J. Org. Chem. 16, 103 (1951).
8. H. Wieland and M. Kotake, Ber. 58, 2009 (1925).
9. H. Rapoport and G. B. Payne, J.A.C.S. 74, 2630 (1952).
10. D. Arigoni, J. Kalvoda, H. Heusser, O. Jeger and L. Ruzicka, Helv. Chim. Acta 38, 1857 (1955).
11. F. Gautschi, O. Jeger, V. Prelog and R. B. Woodward, Helv. Chim. Acta 38, 296 (1955).
12. H. Heusser, E. Beriger, R. Anliker, O. Jeger and L. Ruzicka, Helv. Chim. Acta 36, 1918 (1953).
13. B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, J.A.C.S. 76, 313 (1954).
14. W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, Helv. Chim. Acta 36, 325 (1953).
15. J. A. Mills, J.C.S. 4976 (1952).
16. B. Riniker, D. Arigoni and O. Jeger, Helv. Chim. Acta 37, 546 (1954).
17. J. W. Cornforth, I. Youhotsky and G. Popjak, Nature 173, 536 (1954).
18. S. Bergström, Helv. Chim. Acta 32, 3 (1949).
19. S. Bergstrom, A. Lardon and J. Reichstein, Helv. Chim. Acta 32, 1617 (1949).
20. M. Viscontini and P. Miglioretto, Helv. Chim. Acta 38, 930 (1955).
21. P. Brewster, E. D. Hughes, C. K. Ingold and P. A. D. S. Rao, Nature 166, 178 (1950).

ALKYLATIONS WITH ALCOHOLS UNDER BASIC CONDITIONS

Reported by Joe A. Adamcik March 2, 1956

Examples of the use of alcohols as alkylating agents under basic conditions have long been known. Haller's alkylation of camphor[1], for example, dates from 1891. Unfortunately many of the older methods are not of great preparative use because of the low yields and mixtures of products obtained.

Haller and Minguin[1,2] observed the alkylation of camphor by the action of an alcohol and its alkoxide. Cyclohexanone has also been alkylated by n-butyl alcohol and sodium butoxide to produce a low yield of 2-butyl cyclohexanone[3].

Another example of the alkylation of active methylene compounds is the observation of Carroll[4,5,6] that the reaction of β, γ-unsaturated alcohols and ethyl acetoacetate in the presence of a basic catalyst such as sodium acetate produced, among other products, alkenylacetones. An allylic shift was usually, but not always, involved in the reaction. An example is the reaction of cinnamyl alcohol with ethyl acetoacetate[6]:

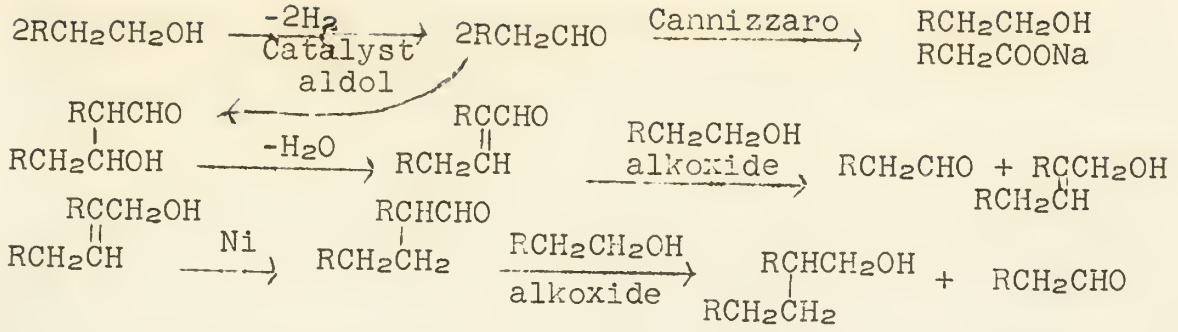
$$PhCH{=}CH{-}CH_2OH + CH_3COCH_2COOEt \longrightarrow Ph{-}\underset{\displaystyle CH_2COCH_3}{\overset{\displaystyle |}{CH}}{-}CH{=}CH_2 \qquad (33\%)$$

The yields of ketone were generally poor however. A similar alkylation of ethyl malonate yielded unsaturated acids. In the case of cinnamyl alcohol the yield of acid was 66%. Saturated alcohols did not alkylate.

The Guerbet reaction[7], conducted by heating a primary alcohol with its alkoxide gives as the major products the salt of the acid corresponding to the original alcohol, hydrogen, and the condensation product in approximate accordance with the following equation:

$$2\ RCH_2CH_2OH + RCH_2CH_2ONa \longrightarrow \underset{\displaystyle RCH_2CH_2}{\overset{\displaystyle RCHCH_2ONa}{|}} + RCH_2COONa + 2H_2$$

With secondary alcohols, cleavage products are produced instead of the acid. The use of a copper vessel or copper bronze as a catalyst is helpful.[3] It has recently been shown[8,9,10] that the use of nickel rather than copper and removal of water from the reaction mixture leads to a higher yield with less formation of the undesired acid. In this manner, alcohols as low boiling as n-butyl have been successfully condensed at atmospheric pressure in yields of about 70%.[9] n-Propyl alcohol has also been condensed[10], but the yield is not stated. Mixed condensations have also been successful. The mechanism of the Guerbet reaction has been discussed[9,11]. The major route to the main products seems to be:

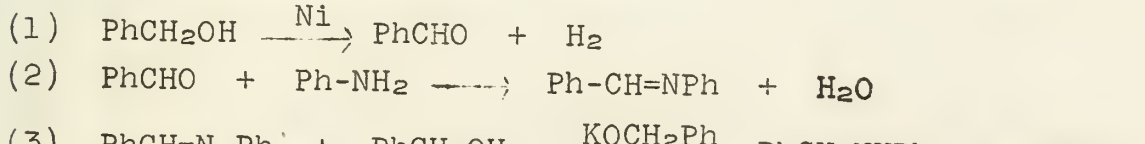


Pyrroles[12,13,14,15] and indoles[16] and some of their derivatives have also been alkylated by alcohols under basic conditions. Examples are the formation of 2,4-dimethyl-3,5-diethylpyrrole by reaction of 2,4-dimethylpyrrole with sodium ethoxide in ethanol in a sealed tube at 220° and the formation of skatole by treatment of indole with methanolic sodium methoxide at 210-220°.

Certain phenols are methylated in low yield by treatment with methanolic sodium methoxide at high temperature. Beta-naphthol, for example, gives 1-methyl-2-naphthol.[17]

As one would expect, an alcohol which is branched in the 2-position cannot be condensed in the Guerbet manner. However, reaction of 2-ethylhexanol with its alkoxide at 300° in the presence of copper bronze has been reported to give approximately equimolar amounts of 2-ethylhexanoic acid and bis-(2-ethylhexyl)-ether.[18] A similar observation has been made in the case of cinnamyl alcohol.[3] These interesting O-alkylations find analogy in the observation of Lund[19] that isopropyl ethers are sometimes produced in the Meerwein-Ponndorf-Verley reduction of α,β-unsaturated ketones.

Nef[20] early reported N-ethylation of aniline by treatment with sodium ethoxide at high temperature. The yield was poor however and the reaction was of little preparative use. Recently Pratt and Frazza[21] have reported the N-alkylation of anilines with certain primary alcohols in high yields. Benzyl alcohols gave yields in the range of 80-90%, and n-hexyl and n-decyl alcohols gave yields only slightly lower. Aliphatic amines did not undergo the reaction. The procedure involved refluxing with Universal Oil Products Company (U. O. P.) nickel a xylene solution of excess alcohol, the aniline, and potassium alkoxide. Water was continuously removed by means of a Dean-Stark apparatus. It was observed that the presence of nickel was unnecessary at high temperatures, as refluxing a mixture of benzyl alcohol, aniline, and potassium benzoxide gave a 94% yield of N-benzyl aniline. The course of the reaction was represented as follows:



The effect of substituents on the rate of the reaction were consistent with the assumption that step (3) was rate controlling and that its mechanism was similar to that proposed for the Meerwein-Ponndorf-Verley reduction.[22]

It should be noted that Rice and Kohn[23] have described a method for N-alkylation of aniline and benzidine in high yield by refluxing an alcohol with the amine in the presence of a large amount of Raney nickel catalyst. This procedure is successful for many lower aliphatic primary alcohols as well as for benzyl alcohol. They write a mechanism somewhat similar to the above except that the reduction step involves catalytic hydrogenation of the intermediate. It is of interest that U. O. P. nickel is not sufficiently active to cause this reaction to proceed. Other examples of N-alkylation with alcohols in the presence of Raney nickel have been reported, for example, the work of Clapp and coworkers[24,25] in the alkylation of piperazines.

The first base-catalyzed alkylation of a hydrocarbon with an alcohol was reported by Becker and coworkers[26] in 1953. The reaction of 2,3,4,5-tetraphenylcyclopentadiene with ethanolic sodium ethoxide at high temperature gave an 84% yield of 1-ethyl-2,3,4,5-tetraphenylcyclopentadiene. The alkylation of fluorene has been reported by Schoen and Becker[27] and Sprinzak[28]. For example, ethanolic sodium ethoxide and fluorene give 9-ethyl fluorene in 83% yield. Benzyl alcohol, the normal primary alcohols from C_1 to C_7 inclusive and also C_{18} have been condensed to give the corresponding 9-alkylfluorenes in 58-99% yields. The mechanism proposed is similar to that proposed for the N-alkylation of amines, with a fulvene intermediate rather than an anil.

BIBLIOGRAPHY

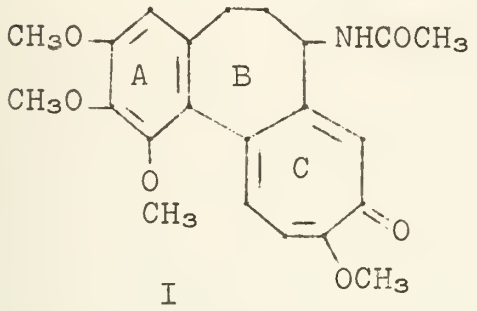
1. A. Haller, Compt. rend. 112, 1490 (1891).
2. A. Haller and P. Minguin, Compt. rend. 142, 1309 (1906).
3. C. Weizmann, E. Bergmann and L. Haskelberg, Chemistry and Industry 56, 587 (1937).
4. M. F. Carroll, J. Chem. Soc. 1266 (1940).
5. M. F. Carroll, J. Chem. Soc. 704 (1940).
6. M. F. Carroll, J. Chem. Soc. 507 (1941).
7. M. Guerbet, Compt. rend. 128, 511 (1899).
8. Clare A. Carter, U. S. Patent 2,457, 866, Jan. 24, 1949; Chem. Abstr. 43, 3437i (1949).
9. E. F. Pratt and D. G. Kubler, J. Am. Chem. Soc. 76, 52 (1954).
10. J. Bolle and L. Burgeois, Compt. rend. 233, 1466 (1951). J. Bolle, Compt. rend. 233, 1628 (1951).
11. H. Machemer, Angew. Chem. 64, 213 (1952).
12. H. Fischer and E. Bartholomäus, Z. physiol. Chem. 77, 185 (1911).
13. H. Fischer and E. Bartholomaus, Z. physiol. Chem. 80, 6 (1912).
14. H. Fischer and H. Rose, Z. physiol. Chem. 87, 38 (1913).
15. U. Colociachi and C. Bertoni, Atti accad. Lincei 21, I, 653; ibid. 21, II, 450, 518; G. Plancher and T. Zambonini, ibid. 21, I, 598; Chem. Abstr. 7, 1183 (1913).

16. R. H. Cornforth and R. Robinson, J. Chem. Soc. 680 (1942).
17. J. W. Cornforth, R. H. Cornforth and R. Robinson, J. Chem. Soc. 683 (1942).
18. C. Weizmann, E. Bergmann and M. Sulzbacher, J. Org. Chem. 15, 54 (1950).
19. H. Lund, Ber. 70, 1520 (1937).
20. J. U. Nef, Ann. 318, 140 (1901).
21. E. F. Pratt and E. J. Frazza, J. Am. Chem. Soc. 76, 6174 (1954).
22. W. von E. Doering and T. C. Aschner, J. Am. Chem. Soc. 75, 393 (1953).
23. R. G. Rice and E. J. Kohn, J. Am. Chem. Soc. 77, 4052 (1955).
24. L. T. Plante and L. B. Clapp, J. Org. Chem. 21, 86 (1956).
25. L. T. Plante, W. G. Lloyd, C. E. Schilling and L. B. Clapp, J. Org. Chem. 21, 82 (1956).
26. S. M. Linder, E. I. Becker and P. E. Spoerri, J. Am. Chem. Soc. 75, 5972 (1953).
27. K. L. Schoen and E. I. Becker, J. Am. Chem. Soc. 77, 6030 (1955).
28. Y. Sprinzak, J. Am. Chem. Soc. 78, 466 (1956).

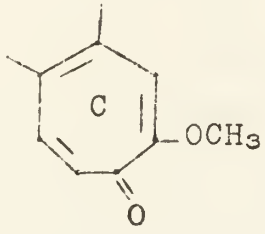
COLCHICINE: ASPECTS OF STRUCTURE AND SYNTHESIS

Reported by J. H. Rassweiler March 9, 1956

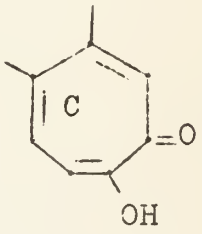
The alkaloid colchicine is an important tool in physiological research[1]. It was isolated in crystalline form in 1884, but the first postulated structure was that of Windaus in 1924[7]. In 1945, Dewar[3] proposed what is now considered the correct structure (I). The final problem, the relative location of the methoxy and carbonyl groups in ring C,



I



II

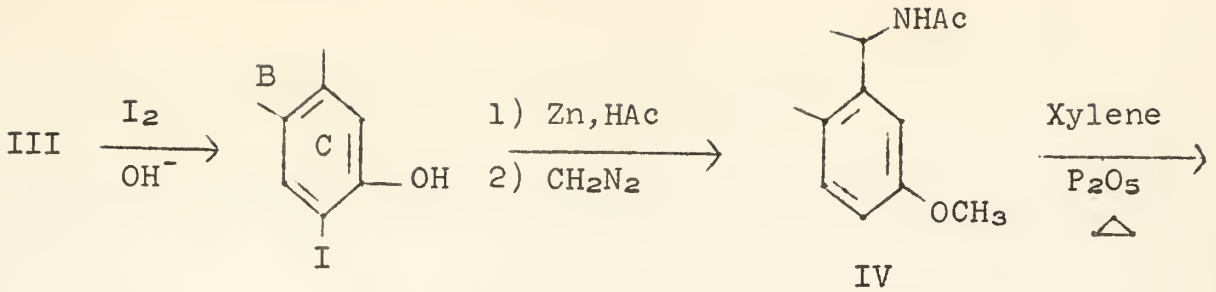


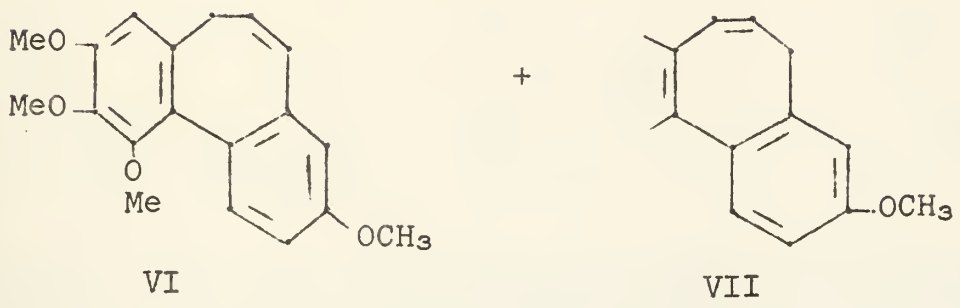
III

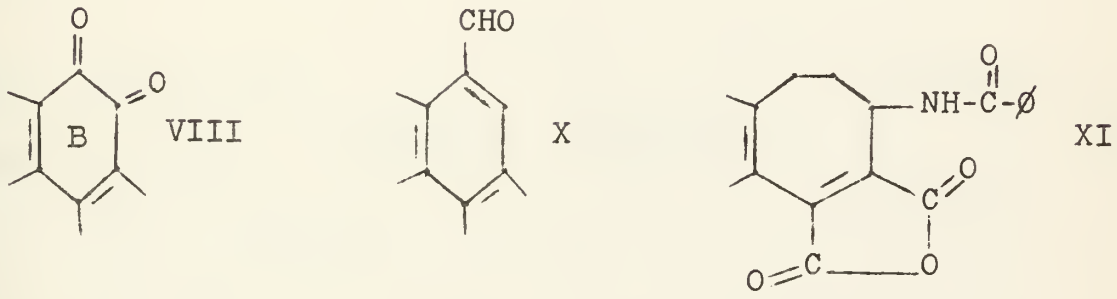
was reported by Rapoport last summer[5]. To date, however, there has not been a complete synthesis of I.

Most of the structural information has been obtained from degradation work. I, on hydrolysis, yields colchiceine III which, on treatment with diazomethane, gives two isomeric methyl ethers, I and isocolchicine II[1]. Windaus[7] treated I with hot alkaline permanganate to obtain 3,4,5-trimethoxyphthalic acid, proving the benzenoid character of ring A. Degradation of III to the deaminocolchinol methyl ethers[8,9] VI, VII; the oxidation of VI to the quinone[4] VIII; and the independent synthesis of these compounds proved the bridged biphenyl system of ring B and the positions of the ring A methoxyl groups. The three carbon bridge of VI was proved by treatment with OsO_4 then lead tetraacetate with the isolation of X, an internal condensation product of the dialdehyde[10]. Two other series of colchicine degradation products[7,11,12] giving N-benzoylcolchinic anhydride XI and some substituted phenanthrene ring systems conclusively proved the 7-membered character of ring B.

Ring C in Dewar's formula I is a tropolone. This was established in several ways. N-Acetylcolchinol[8] IV and allocolchicine[13,14] XII were obtained by the expected ring contraction. Finally, Rapoport's[5] work and many others observed similarities of the C ring reactions to those of

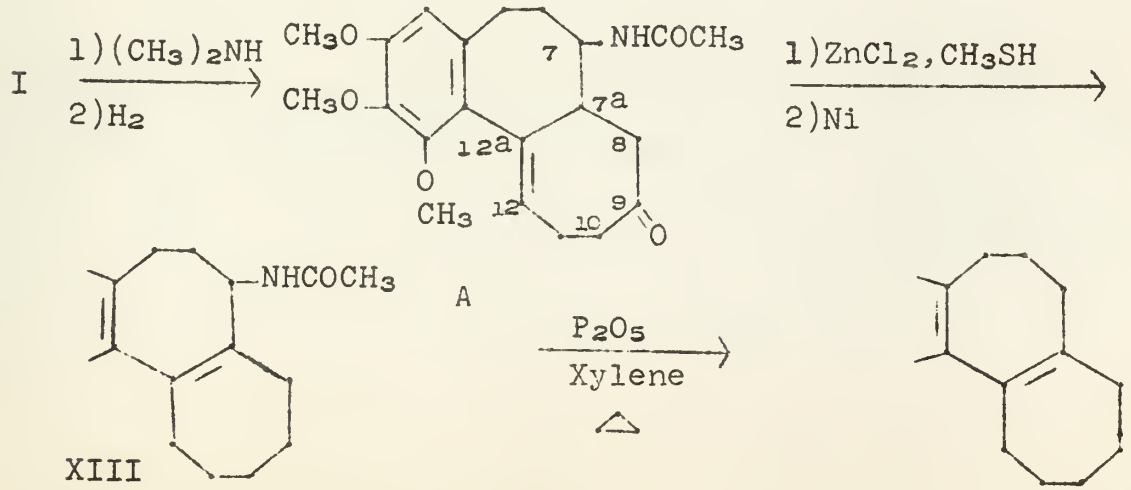


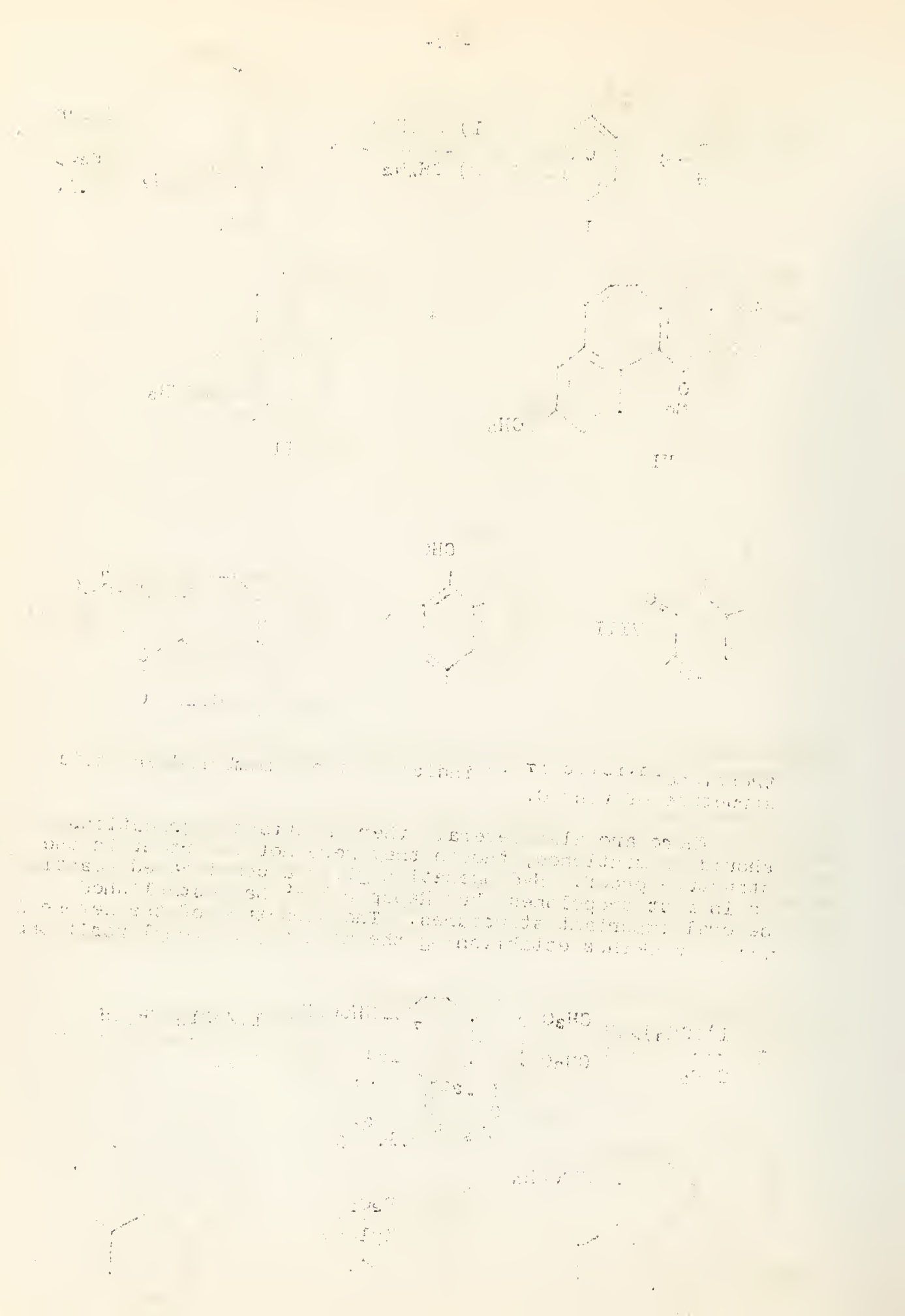




tropolones[2,15,16,17,18] indicated the 7-membered aromatic structure of ring C.

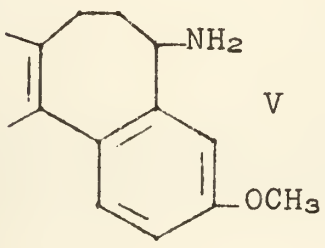
There are also several other important degradations which should be mentioned, though they were not important in the structure proof. Hydrogenation gives a complicated reaction[6,18] as in most tropolones, but Rapoport[5,19] has established several important structures. The structure of the ketone A was proved[5] thus establishing the methoxy, carbonyl positions in



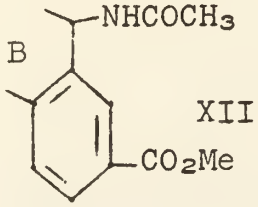


I. I also undergoes photoisomerism to α,β,γ lumicolchicines[20], one of whose structure is postulated as XX.

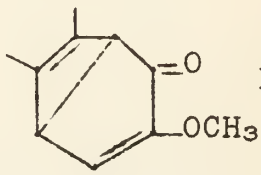
Although less important, some mention must be made of the principle synthetic work to date. The synthesis of colchinol methyl ether V and its identification with the degradation



V

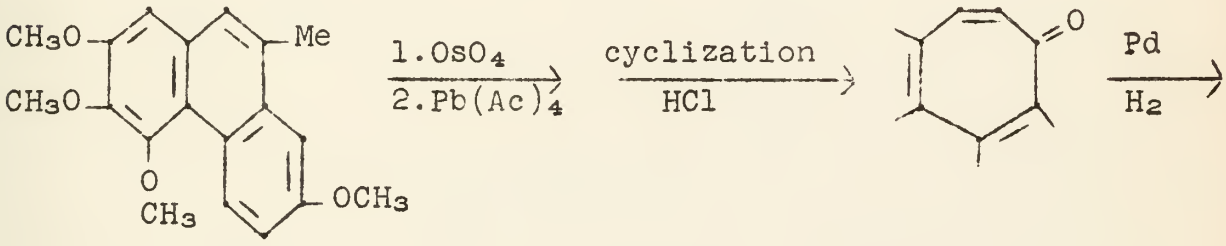


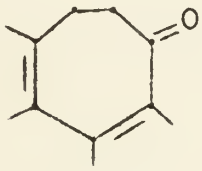
XII



XX

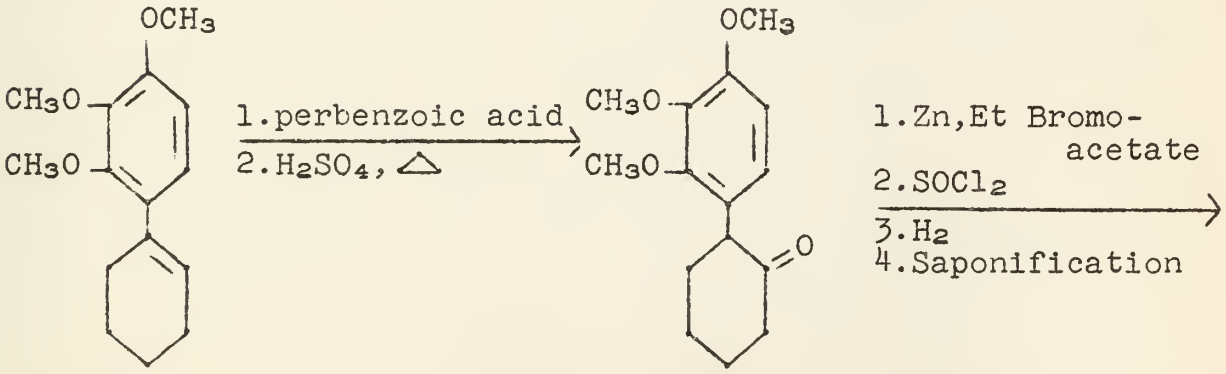
product was basic to the structure proof. Two somewhat similar methods were used[4,21]; the best probably was Cook's[4]. Synthesis of the deaminocolchinic anhydride also was successful[26].

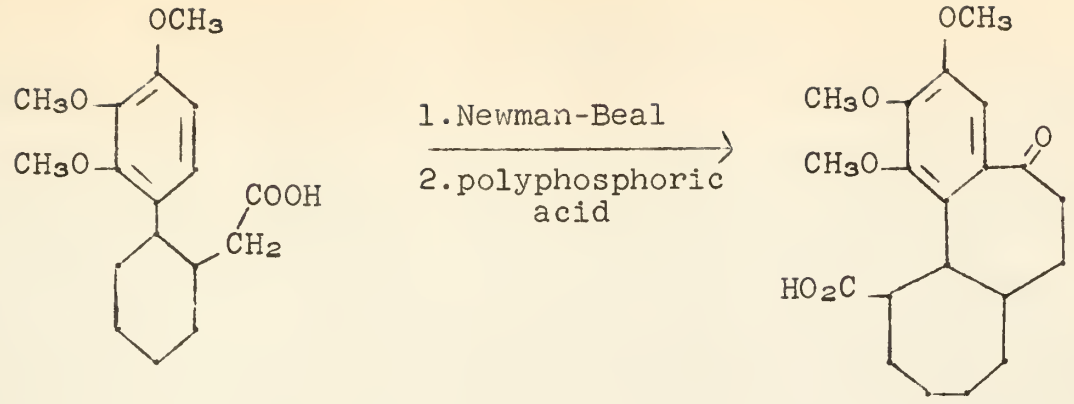




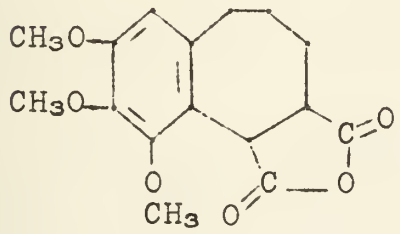
dl- V

The skelation of I was prepared by Gutsche[22], but this could not be converted to the actual alkaloid. TheA-B[23] and

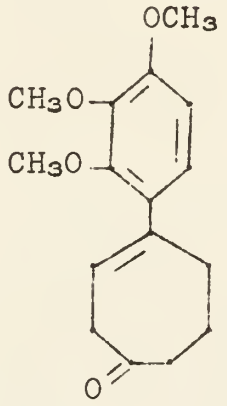




the A-C ring[24] systems have been synthesized, coumarin derivatives acting as intermediates[25], but again the complete molecule has not been obtained.



A - B



A - C

BIBLIOGRAPHY

1. O. I. Eigsti, P. Dustin, Colchicine, Iowa State College Press 1955.
2. H. Fernholz, Ann. 576, 131 (1952).
3. M. J. S. Dewar, Nature, 155, 141 (1945).
4. J. Cook, J. Chem. Soc., 1951, 1397 (1951).
5. H. Rapoport, 7th Summer Seminar on Chem. Natural Products, U. of New Brunswick, Aug. 16-19, 1955.
6. V. Bursian, Ber, 71, 245 (1938).
7. A. Windaus, Ann, 439, 59 (1924).
8. J. Cech et.al., Coll. Czech. Chem. Comm., 14, 532 (1949).
9. J. Cook, J. D. London, J. Chem. Soc., 1945, 176 (1945).
10. J. D. Loudon, J. Chem. Soc., 1947, 746 (1947).
11. J. Koo, G. E. Ullyot, J. Am. Chem. Soc., 72, 4840 (1950).
12. J. Cook, J. Chem. Soc., 1950, 537 (1950).
13. F. Santavy, Helv. Chim. Acta, 31, 821 (1948).
14. H. Fernholz, Angew Chim., 59A, 218 (1947).
15. J. Loudon, Quart. Revs., 5, 99 (1951).
16. A. Uffer, Helv. Chim. Acta, 35, 2135 (1952).
17. F. Santavy, Coll. Czech. Chim. Comm., 14, 145 (1949).
18. O. S. Tarbell, J. Am. Chem. Soc., 72, 240 (1950).
19. H. Rapoport, J. Am. Chem. Soc., 76, 3693 (1954).
20. E. J. Forbes, J. Chem. Soc., 1955, 3864 (1955).
21. H. Rapoport, J. Am. Chem. Soc., 73, 1414 (1951).
22. G. D. Gutsche, J. Am. Chem. Soc., 76, 1771 (1954).
23. J. Koo, J. Am. Chem. Soc., 75, 1625 (1953).
24. J. E. Loewenshal, J. Chem. Soc., 1953, 3962 (1953).
25. V. Boekelheide, J. Am. Chem. Soc., 74, 1558 (1952).
26. J. Koo, J. Am. Chem. Soc., 75, 720 (1953).

FERROCENE AS AN AROMATIC NUCLEUS

Reported by Kenneth Conrow March 16, 1956

Since the original demonstration that ferrocene is an unusual aromatic system, a great deal of work has been done to investigate its chemistry. The simplest demonstration of the aromatic character of the cyclopentadiene rings of the ferrocene molecule is found in their non-reactivity toward maleic anhydride and toward hydrogen over Adams' catalyst.[1] A convincing example of the resistance of the ferrocene system to catalytic reduction is found in the preferential reduction of the benzene rings in bis-indenyl iron to bis-(tetramethylene-cyclopentadienyl) iron.[2]

The simplest aromatic substitution reactions are not observed with ferrocene because of its ready oxidation to the ferricinium ion. Thus nitration, halogenation and sulfonation under the usual conditions lead to the destruction of the molecule. However, a dilute solution of 100% sulfuric acid in acetic anhydride[3] or sulfur trioxide in pyridine[4] have served to sulfonate ferrocene without concurrent oxidation.

Friedel-Crafts acylations are quite successful in the ferrocene series and have led to the majority of the reported types of derivatives of ferrocene. With acetic anhydride in anhydrous hydrogen fluoride an 87% yield of monoacetyl ferrocene is obtained.[3] With excess aluminum chloride and acetyl chloride in methylene chloride, a 71% yield of diacetyl ferrocene is obtained.[5] Phthalic anhydride similarly gives o-carboxybenzoyl-ferrocene, and β-chloropropionyl chloride gives β-chloropropionylferrocene.[1] Competition experiments between anisole and ferrocene with aluminum chloride and acetyl chloride give acetyl ferrocene exclusively.[6]

In view of the ease of most acylations it is surprising to find that oxalyl chloride fails to acylate ferrocene.[5,7] Friedel-Crafts alkylations are reported not to occur with propylene or isobutylene in anhydrous hydrogen fluoride (conditions which alkylate benzene). However, cyclopentenyl ferrocene is formed under these conditions. This reaction may be formally regarded as the degradation of the ferrocene molecule followed by alkylation of another molecule by the cyclopentadiene produced.[3] It is also reported that isopropyl chloride, ethyl bromide and benzyl chloride fail to alkylate ferrocene with aluminum chloride in carbon disulfide.[17]

Ferrocene also reacts with aldehydes in anhydrous hydrogen fluoride. Formaldehyde gives a product whose molecular weight and analysis agree with the binuclear $(C_6H_4)_2Fe(CH_2)_2Fe(C_5H_4)_2$.[3] Attempts at chloromethylation of ferrocene have given only polymethyleneferrocene.[6]

Mercuration of ferrocene proceeds smoothly at room temperature with mercuric acetate to give mixtures of starting material, mono-mercurated and di-mercurated ferrocene in approximately equal amounts.[4,7] Reduction of monochloro-mercuriferrocene with thiosulfate gives the interesting diferrocenyl mercury.[4,7] Reaction of these mercuri derivatives

with halogens give haloferrocenes, otherwise unobtainable.[4,9]

Ferrocene reacts with butyl lithium to form mono and di-lithium derivatives of ferrocene.[4,7,14] The acids formed on carbonation are identical with those from hypohalite oxidation of the acetyl ferrocenes.[7] Triphenylsilyl ferrocenes have also been prepared from these lithium intermediates.[14] With O-benzyl hydroxylamine, aminoferrocene is obtained.[4,10]

Another very successful reaction has been the arylation of ferrocene with aromatic diazonium salts.[7,8,12,13] A large variety of substituted phenyl ferrocenes have been prepared in this way, though once again the generality is limited by the ease of oxidation of ferrocene. Thus 2,4-dinitrophenyl diazonium salt is reduced to dinitrobenzene and no arylated ferrocene is obtained.[12] This reaction is enjoyed by neutral ferrocene as well as ferricinium ion and has been done under a variety of conditions, so that there is some doubt about the mechanistic analogy with the free radical Gomberg-Bachmann reaction.

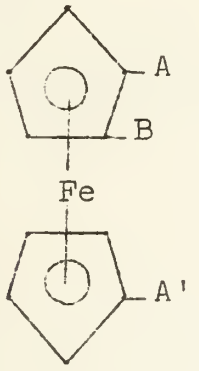
The above reactions almost invariably give mixtures of mono-, di- and sometimes poly- substituted ferrocenes. Di-substituted ferrocenes are usually assumed to be hetero-annular. The first reported proof of this is the identity of the bis-benzhydryl ferrocene from dibenzoyl ferrocene (by reaction with phenyl lithium followed by reduction with titanous sulfate) with the bis-benzhydryl ferrocene from benzhydryl cyclopentadiene.[15] Similarly diphenyl ferrocene from aniline diazonium salt and ferrocene is identical with diphenyl ferrocene from phenylcyclopentadiene.[12] Infra-red evidence for heteroannular substitution in the disubstituted derivatives is based on the observation that bands at 9 and 10μ seem to be characteristic of an unsubstituted cyclo-pentadienyl ring in the molecule.[5]

Many transformations in the side chain of ferrocene have been accomplished to yield a variety of derivatives not available by direct substitution. Several of these have already been mentioned. Oxidation of the acetyl substituent to the acid has been accomplished by hypohalite[5] and by iodine in pyridine.[18] Amino ferrocene can be obtained from ferrocene carboxylic acid *via* the Curtius rearrangement, though the Hofmann rearrangement of the amide and the Beckmann rearrangement of the oxime of acetyl ferrocene both failed to give this product.[16] Reduction of acetyl ferrocene with $LiAlH_4$ gives 89% of the corresponding carbinol, whose acetate may be pyrolysed to give vinyl ferrocene. Various copolymers of vinyl ferrocene have been prepared.[16] Reduction of the acetyl group to the ethyl group has been accomplished with zinc amalgam and hydrochloric acid[16] and with hydrogen over Pt.[5]

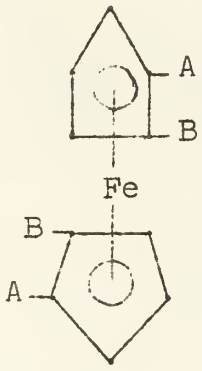
Reaction of 1,1'-diacetyl ferrocene with ethyl magnesium bromide yields a di-tertiary carbinol, each carbinol carbon being asymmetric.[17] Two isomers (assumed to be 1) meso (DL) and 2) racemic (DD + LL)) were obtained but the latter has not been resolved. Since use of methyl magnesium iodide yields but one isomer, belief that isomerism is indeed of the type

indicated is substantiated. Dehydration of bis-(2-hydroxy-2-butyl) ferrocene gives a mixture of isomers also. These are formulated on the basis of cis-trans asymmetry.[17]

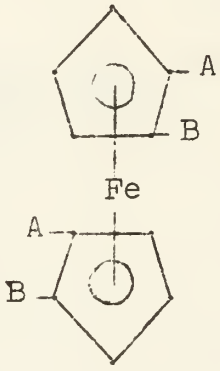
A different sort of isomerism should also offer interest in the ferrocene system. Compounds of type I are not superimposable on their mirror images and should be resolvable. Compounds of type II should also be distinguishable: "cis" form a is a meso form, while "trans" form b is a racemate.[6]



I



IIa



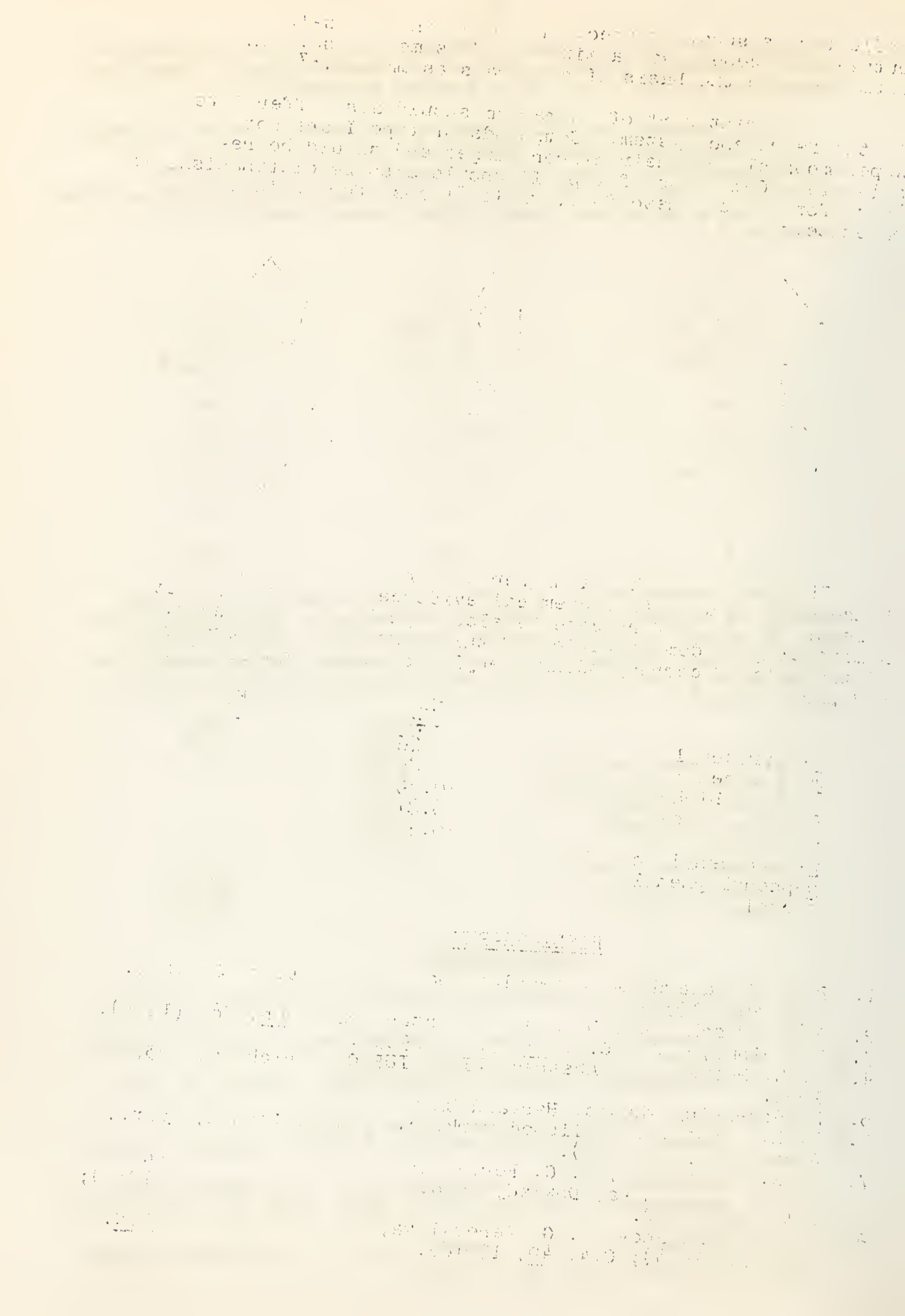
IIb

That ferrocene has a higher electron density than has benzene is evident from chemical evidence of the comparitive ease of attack on ferrocene by electrophilic substituents. A more elegant demonstration of this comes from a comparison of the pK's of corresponding phenyl and ferrocenyl anilines and phenols.[11]

	pK_b	pK_a
p-ferrocenyl aniline	9.66	
m-ferrocenyl aniline	9.85	
p-amino biphenyl	10.89	
amino ferrocene	8.81	
aniline	10.14	
p-ferrocenyl phenol		11.79
p-phenyl phenol		11.04
phenol		11.33

BIBLIOGRAPHY

1. R. B. Woodward, M. Rosenblum and M. C. Whiting, J.A.C.S. 74, 3458 (1952).
2. E. O. Fischer and D. Seus, Z. Naturforsch. 9b, 386 (1954).
3. V. Weinmayr, J.A.C.S. 77, 3009 (1955).
4. A. N. Nesmeyanov, Abstract XIVth IUPAC, Zurich, p. 193, 1955.
5. M. Rosenblum, Thesis, Harvard Univ., 1953.
6. P. L. Pauson, unpublished work; c.f. P. L. Pauson, Quart. Revs., 9, 391 (1955).
7. A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and O. A. Nesmeyanova, Doklady Akad. Nauk. USSR 97, 459 (1954); C.A. 49, 9633f.
8. A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, ibid. 99, 539 (1954); C.A. 49, 15918c.



9. A. N. Nesmeyanov, E. G. Perevalova, O. A. Nesmeyanova, ibid. 100, 1099 (1955).
10. A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and L. S. Shilovtawa, ibid. 102, 531 (1955).
11. A. N. Nesmeyanov, E. G. Perevalova and R. V. Golovnya, ibid. 103, 81 (1955).
12. G. D. Broadhead and P. L. Pauson, J. Chem. Soc., 367 (1955).
13. V. Weinmayr, J.A.C.S. 77, 3012 (1955).
14. R. A. Benkeser, D. Goggin and G. Scholl, J.A.C.S. 76, 4025 (1954).
15. P. L. Pauson, J.A.C.S. 76, 2187 (1954).
16. F. S. Arimoto and A. C. Haven, Jr., J.A.C.S. 77, 6295 (1955).
17. R. Riemschneider and D. Helm, Ber. 89, 155 (1956).
18. V. Weinmayr, U.S. 2,683,157; C.A. 49, 10364a (1954).

APPLICATIONS OF MASS SPECTROMETRY TO ORGANIC CHEMISTRY

Reported by Philip N. James March 16, 1956

Positive rays were first discovered by Goldstein in 1886, and J. J. Thomson developed the first machine for their analysis. Since these investigations, the field of positive ray analysis has developed along two different lines[1]. The first, pioneered by Aston and called mass spectrography, uses photographic recording for the accurate determination of isotopic masses. It is the second branch, called mass spectrometry, which is of primary interest to the organic chemist. In this branch, pioneered by Dempster, an ion current recording device is used for the accurate measurement of the relative abundances of the ions present in the positive ray.

A mass spectrometer consists of the following parts[2]: 1.) sample handling and introduction system, 2.) ion source, 3.) mass analyzer, and 4.) ion current detector. Only the first of these need concern us, since the remaining parts are standard for most chemical work. The problem in the design of the sample handling system is the production and introduction of a vapor characteristic of the sample, but this is essentially a problem in vacuum technique. Thus, it is obvious that gases and low-boiling liquids are easily analyzed by the spectrometer, while high-boiling liquids, solids, and mixtures present difficult problems.

Undoubtedly the most important industrial application of the mass spectrometer has been the analysis of hydrocarbon mixtures[3,4]. Such analyses are complicated by the fact that a molecule rarely yields a simple mass spectrum. For example, methane can give rise to all of the following species: CH_4^+, CH_3^+, CH_2^+, CH^+, C^+, and H^+. The extension of this complication to hydrocarbons of higher molecular weight is obvious. The usefulness of the machine resides in the fact that each compound produces a characteristic fragmentation ("cracking") pattern.

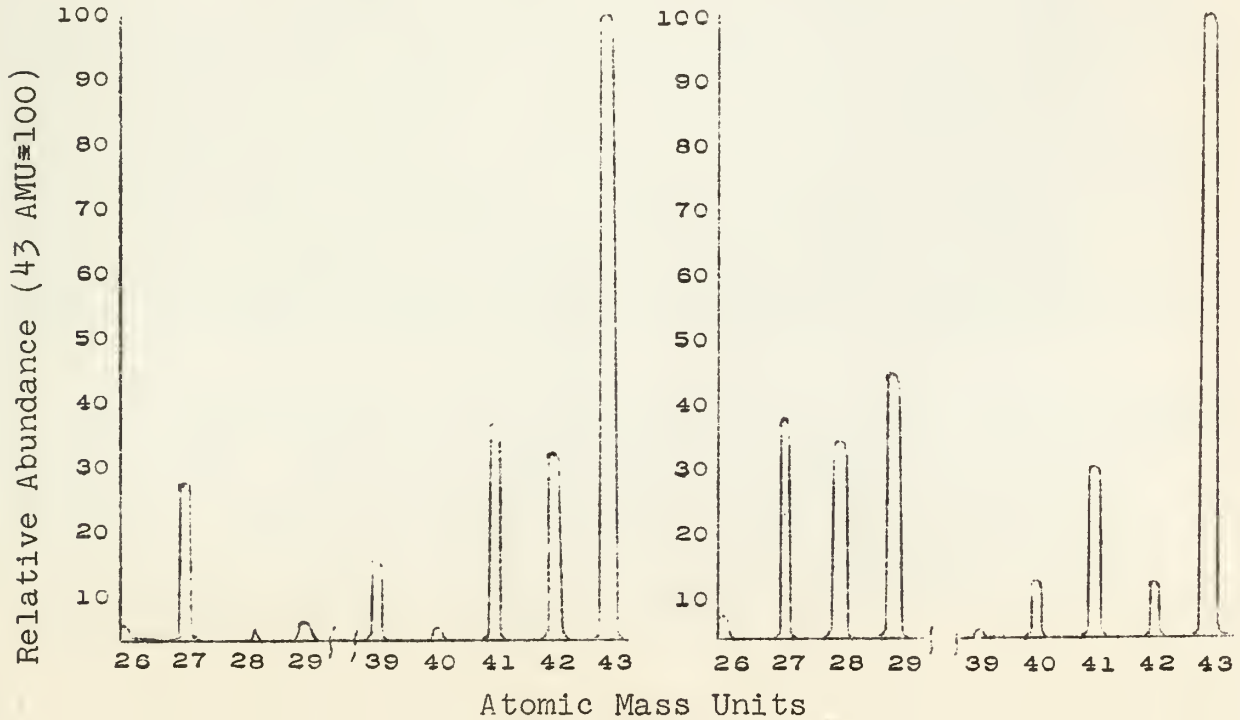


Figure 1: Comparison of Portions of the Mass Spectra of iso-Butane (left) and n-Butane (right). (See p. 39, bottom.)

Typical examples are the partial spectra of n-butane and iso-butane shown in Fig. 1[5]. In the complete specta, it can be seen that the most abundant species for each compound lies not at mass 58 ($C_4H_{10}^+$), but at mass 43, equivalent to $C_3H_7^+$, indicating that the easiest path for both molecules on electron bombardment is the rupture of a CH_3-C bond. The band at mass 29 in the iso-butane spectrum could correspond to a rearrangement peak[6], an isotope effect peak, or a peak due to doubly charged $C_4H_{10}^{++}$ ions. There is also a weak band at mass 31.9 corresponding to a metastable ion transition.

From the spectra, it is obvious that a mixture of the two isomers could be quantitatively analyzed by a measurement of, for example, the ratio of the relative intensities at masses 42 and 43. A similar technique has been applied to much more complex hydrocarbon mixtures. By a combination of mass spectrometry with infrared spectroscopy, the time required for the quantitative analysis of typical refinery samples has been reduced from about 10 days (for a low-temperature fractionation method) to 4-5 hours, and the accuracy compares favorably with that obtained using more tedious methods. With high molecular weight and highly complex mixtures, the calculations become so complicated that data are usually reported as compound types rather than specific compounds. Table I gives a partial list of the types of compounds which have been successfully analyzed by mass spectrometry[7].

Table I: Compounds Successfully Analyzed by the Mass Spectrometer

Hydrocarbons		Oxygen Compounds	
Paraffins	C_1-C_9	Aldehydes	C_1-C_5
Olefins	C_2-C_5	Ketones	C_2-C_3
Diolefins	C_3-C_5	Esters	C_2-C_4
Naphthenes	C_5-C_7	Acids	C_2
Aromatics	C_6-C_{10}	Lactones	
Acetylenes	C_2-C_4	Alcohols	C_1-C_4
		Ethers	C_2-C_4
Alkyl Halides			
Alkyl Chlorides	C_1-C_4	Sulfur Compounds	
Alkyl Iodides	C_1-C_4	Mercaptans	C_1-C_4
Freon		Sulfides	C_1-C_4
Dichlorodifluoromethane		Disulfides	C_1-C_3
		Thiophene	
		2 and 3-Methylthiophenes	

Mass spectrometry is a natural medium for the use of tracer techniques[8,9,10] using stable isotopes, such as C^{13}, N^{15}, O^{18}, H^2, and S^{34}. The main consideration is that, for ease of analysis, the labelled atom must be converted to a gaseous molecule. The usual gases for the elements mentioned are, respectively, CO_2, N_2, CO_2, H_2, and SO_2, although in some applications, it may be easier or more convenient to use other gases containing the required element[10].

The ions which are measured in the mass spectrometer are produced by bombarding the neutral vapor with electrons. If the energy of the electrons is gradually increased from zero, it is noted that ions do not appear until a certain electron energy is reached. This electron energy is called the appearance potential, and is characteristic for the particular ionic species being measured[4,7,9,11,12]. The magnitude of the appearance potential is related both to the ionization potential of the neutral fragment and to the dissociation energy of the bond whose rupture led to the neutral fragment. Thus, both ionization potentials and bond energies may be obtained from mass spectral data. The results check closely with those obtained by other methods.

A few instances of the analysis of solids have been reported, but the data are not extensive enough at this time to permit an evaluation of the method. The use of high resolution mass spectrometers for this purpose, however, promises to have wide application in the fields of natural products, polymers, and biochemistry[14].

In gas phase reactions, particularly those involving free radicals, the mass spectrometer may be used to follow the fate of short-lived intermediates, giving an insight into the mechanism of the reaction which is difficult to obtain in any other way[4,7,9,11,12]. The particular advantage in using this technique for free radicals lies in the fact that radicals generally have much lower ionization potentials than molecules, and lower electron energies may be used for the ionization.

The machine has also been used industrially as a process monitoring device[3]. A sample may be piped continuously from a vapor phase reaction mixture into the mass spectrometer, thus providing a continuous check on the progress of the reaction.

The mass spectrometer provides an excellent method for the detection of leaks in vacuum systems[9,11], having the advantage over other methods that leaks in metal systems may be found in this way. The system is connected to a mass spectrometer, and a test probe of helium is applied along the exterior of the system. A leak is indicated by the appearance of helium peaks in the spectrum.

The instrument provides a useful method for the measurement of low vapor pressures[13] since determinations are rapid and convenient, and the results are not affected by traces of volatile impurities in the sample. The method has been used for a number of hydrocarbons with vapor pressures in the range 10^{-3} to 10 mm. of mercury.

REFERENCES

1. F. W. Aston, Mass Spectra and Isotopes, Second Ed., Longmans, Green and Co., New York, 1942.
2. M. G. Ingraham and R. J. Hayden, Mass Spectroscopy, Nat. Res. Council, Nat. Acad. Sci. (U.S.), Nucl. Sci. Ser. Rept. No. 14, 1954.
3. C. E. Berry and J. K. Walker, Ann. Rev. Nucl. Sci., 5, 197, (1955).

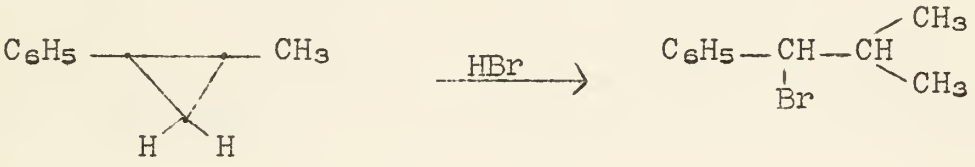
4. G. P. Barnard, Modern Mass Spectrometry, Institute of Physics, London, 1953.
5. Catalog of Mass Spectral Data, Am. Pet. Inst. Res. Proj. 44, Nat. Bur. Stds., Washington 25, D.C.
6. This is a common phenomenon in mass spectra. For an example with aliphatic acids, see G. P. Happ and D. W. Stewart, J. Am. Chem. Soc., 74, 4404 (1952).
7. H. W. Washburn in W. G. Berl (ed.), Physical Methods in Chemical Analysis, Vol. I, pp. 587-639, Academic Press, Inc., New York, 1950.
8. R. F. Glascock, Isotopic Gas Analysis for Biochemists, Academic Press, Inc., New York, 1954.
9. D. W. Stewart in A. Weissberger (ed.), Technique of Organic Chemistry, Second Edition, Vol. I, Part II, pp. 1991-2058, Interscience Publishers, Inc., New York, 1949.
10. W. E. Coleman, B.S. Thesis, Coll. Lib. Arts and Sci., University of Illinois, Urbana, Illinois, 1956.
11. W. J. Dunning, Quart. Revs., 9, 23 (1955).
12. M. Krauss, A. L. Wahrhaftig and H. Eyring, Ann. Rev. Nucl. Sci., 5, 241 (1955).
13. W. A. Sheppard, MIT Seminar in Organic Chemistry, March 12, 1952.
14. Chem. and Eng. News, 33, 3988 (1955).

THE UNSATURATION OF CYCLOPROPANE RINGS

Reported by Norman Shachat March 23, 1956

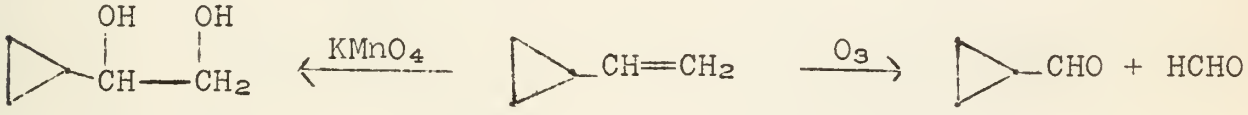
The cyclopropane ring exhibits many of the properties associated with an ethylenic linkage. Much chemical and physical evidence relating to this phenomenon has been compiled. On the basis of this evidence, two reasonable molecular orbital pictures have been postulated for cyclopropane.

Chemically, many similarities exist between cyclopropyl and ethylenic compounds. Cyclopropane can be hydrogenated catalytically under slightly more vigorous conditions than are required for an ordinary double bond.[1,2] Addition of hydrogen halides, which results in ring opening, occurs in accordance with the Markovnikov rule.[3,4,5]



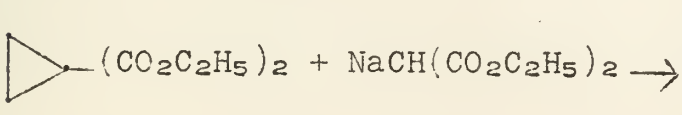
Furthermore, the addition of halogens to yield 1,3-dihalopropanes has been observed.[5,6,7]

In contrast to propylene, which generally gives rise to isopropyl products as a result of ionic reactions, cyclopropane yields only n-propyl compounds under similar conditions.[8,9] The most striking chemical difference between cyclopropane rings and unsaturated compounds is observed in their behavior toward oxidizing agents, as is concisely illustrated by the following reactions of vinylcyclopropane:[10,11,12]



Although vinylcycloporpane does not form an adduct with maleic anhydride at 100°C, it does polymerize readily in the presence of benzoyl peroxide and ultra-violet light.[10]

The ability of unsaturated cyclopropyl compounds to undergo conjugate addition has been demonstrated in a variety of cases.[2,12,13,14] For example, Bone and Perkin observed the following reaction:[15]



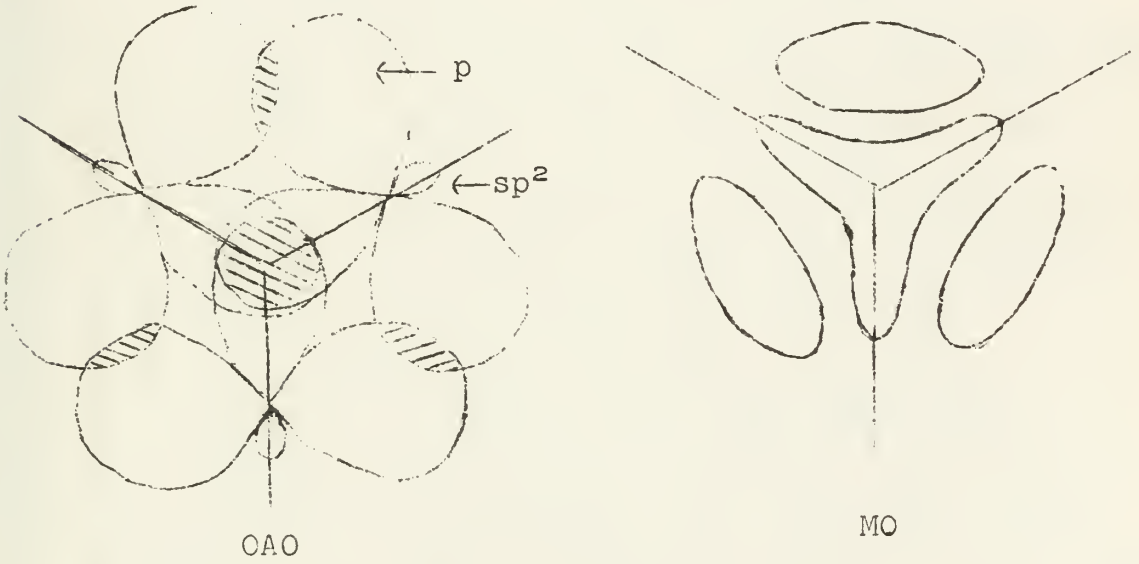
Although benzene condenses with cyclopropyl mesityl ketone in a conjugate manner in the presence of aluminum chloride, the Grignard reagent or ethyl malonate did not combine with the ketone.[16]

Olefins are known to form π-electron coordination complexes with a variety of substances, including Ag^{+}, Cu^{+}, Hg^{++}, platinous salts, iodine, and tetranitromethane. Similarly, cyclopropane forms complexes with chloroplatinic acid,[17] iodine,[18] and tetranitromethane.[19]

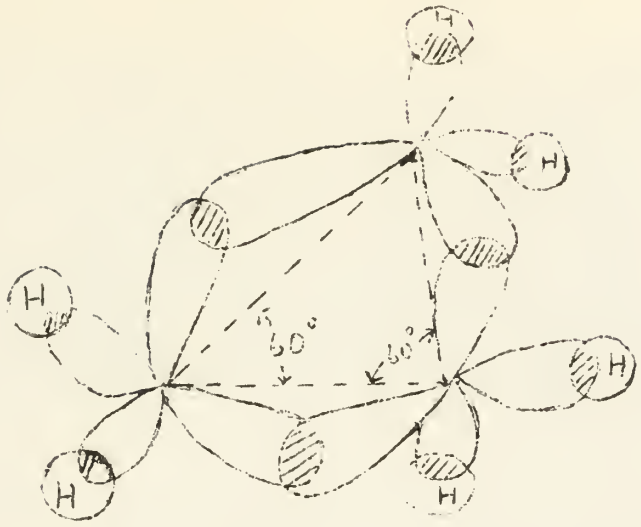
Physical measurements and especially spectral data have supplied much significant information concerning the unsaturated character of cyclopropyl compounds. Ultra-violet absorption studies on a large number of systems containing a cyclopropane ring adjacent to a double bond indicate a conjugative effect.[20-26] However, the bathochromic shift is less in the case of a cyclopropyl conjugated system than for a fully unsaturated one. Recently, it has been demonstrated that a chain of conjugation cannot be transmitted through a cyclopropane ring.[27-30] Infrared spectra, mainly of cyclopropyl ketones, also indicate that the conjugative effect of the cyclopropyl group is less pronounced than that of an ethylenic bond.[16,28,31-33] In addition, it is significant that cyclopropyl compounds exhibit C-H stretching frequencies at 3010 $cm.^{-1}$ and 3090 $cm.^{-1}$, since ethylenic hydrogens also absorb in this region.[33-35]

Other physical measurements such as molecular refraction,[36,37,38] dipole moment,[23,39,40] quenching cross-section of cadmium resonance radiation,[41] and electron diffraction[42,43] have also supplied much important data relating to the π-electron character of cyclopropane rings.

On the basis of the available evidence, Walsh has suggested the following orbital pictures for cyclopropane:[44]



More detailed calculations led Coulson and Moffit to propose the following "bent bond" structure:[45]



OAO

BIBLIOGRAPHY

1. R. Willstatter, J. Bruce, Ber., 40, 4456 (1907).
2. R. Van Volkenburgh et al., J.A.C.S., 71, 172 (1949).
3. N. Kishner, Chem. Abst., 6, 2915 (1912).
4. D. Davidson, J. Feldman, J.A.C.S., 66, 488 (1944).
5. M. S. Kharasch et al., ibid., 61, 2139 (1939).
6. R. A. Ogg, Jr., W. J. Priest, ibid., 60, 217 (1938).
7. G. Gustavson, J. Prakt. Chem., [2], 62, 270 (1900).
8. T. B. Dorris, F. J. Sowa, J.A.C.S., 60, 358 (1938).
9. C. D. Lawrence, C.F.H. Tipper, J. Chem. Soc., 713 (1955).
10. R. Van Volkenburgh et al., J.A.C.S., 71, 3595 (1949).
11. N. J. Demjanov, M. Dojarenko, Ber., 55, 2718 (1922).
12. E. P. Kohler, J. B. Conant, J.A.C.S., 39, 1404,1699 (1917).
13. R. W. Kierstead et al., J.Chem.Soc., 3610 (1952).
14. R. W. Kierstead et al., ibid., 1799 (1953).
15. W. A. Bone, W. H. Perkin, ibid., 67, 108 (1895).
16. R. C. Fuson, F. N. Baumgartner, J.A.C.S., 70, 3255 (1948).
17. C.F.H. Tipper, J. Chem. Soc., 2045 (1955).
18. S. Freed, K. M. Sancier, J.A.C.S., 74, 1273 (1952).
19. O. Filipov, Chem. Zentb., [I], 1057 (1915).
20. R. P. Mariella et al., J.A.C.S., 70, 1494 (1948).
21. R. P. Mariella, R. R. Raube, ibid., 74, 518,521 (1952).
22. A. E. Gillam, T. F. West, J. Chem. Soc., 95 (1945).
23. M. T. Rogers, J.A.C.S., 69, 2544 (1947).
24. E. P. Carr, C. P. Burt, ibid., 40, 1590 (1918).
25. I. M. Klotz, ibid., 66, 88 (1944).
26. J. D. Roberts, C. Green, ibid., 68, 214 (1946).
27. L. I. Smith, E. R. Rogier, ibid., 73, 3840 (1951).
28. R. H. Eastman, ibid., 76, 4115 (1954).
29. R. H. Eastman, J. C. Selover, ibid., 76, 4118 (1954).
30. R. H. Eastman, S. K. Freeman, ibid., 77, 6642 (1955).
31. N. Fuson et al., ibid., 76, 2526 (1954).
32. N. Fuson, M. L. Josien, Compt.Rend., 231, 131,1511 (1950).
33. H. Hart, O. E. Curtis, Jr., J.A.C.S., 78, 112 (1956).
34. S. E. Wiberley, S. C. Bunce, Anal. Chem., 24, 623 (1952).

35. V. A. Slabey, J.A.C.S., 76, 3604 (1954).
36. V. A. Slabey, ibid., 74, 4928 (1952).
37. G. J. Ostling, J. Chem. Soc., 101, 457 (1912).
38. L. Tschugaeff, Ber., 33, 3118 (1900).
39. M. T. Rogers, J. D. Roberts, J.A.C.S., 68, 843 (1946).
40. B. I. Spinrad, ibid., 68, 617 (1946).
41. W. R. Steacie, D. J. Le Roy, J. Chem. Phys., 11, 164 (1943).
42. J. Donohue et al., J.A.C.S., 67, 332 (1945).
43. L. Pauling, L. O. Brockway, ibid., 59, 1223 (1937).
44. A. D. Walsh, Trans. Far. Soc., 45, 179 (1949).
45. C. A. Coulson, W. E. Moffitt, Phil. Mag., 40, 1 (1947).

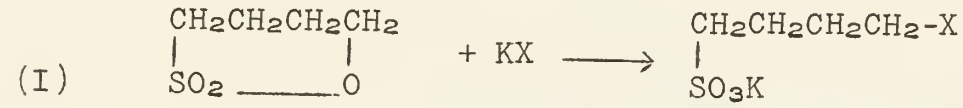
ALIPHATIC HYDROXY SULFONIC ACIDS AND SULTONES

Reported by J. S. Dix March 23, 1956

Reactions of Sultones

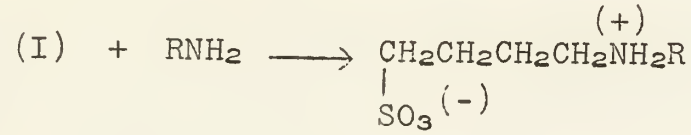
The preparation of aliphatic sultones was first fully reported by Helberger in 1949.[1] He and other workers have described many of their varied reactions:

1. With salts[2]



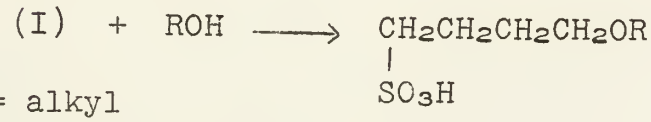
X = halogen, cyanide, carboxylate, phthalimide

2. With ammonia and amines[2]



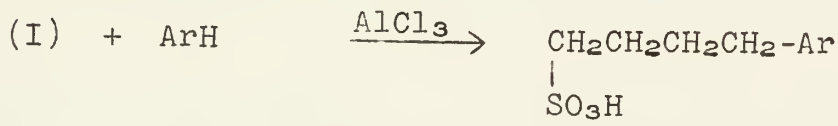
R = phenyl, alkyl, H

3. With alcohols[3]



R = alkyl

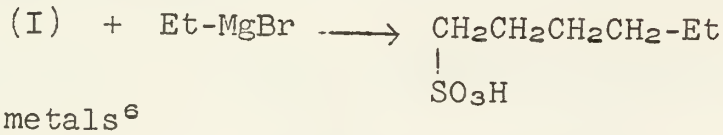
4. With aromatic hydrocarbons[4]



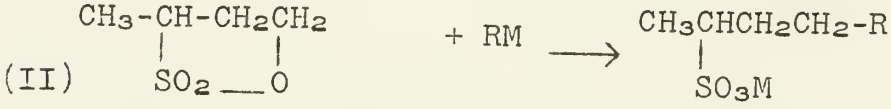
ArH = benzene, p-xylene, p-dichlorobenzene

5. With organometallic compounds

(a) Grignard reagents[5]



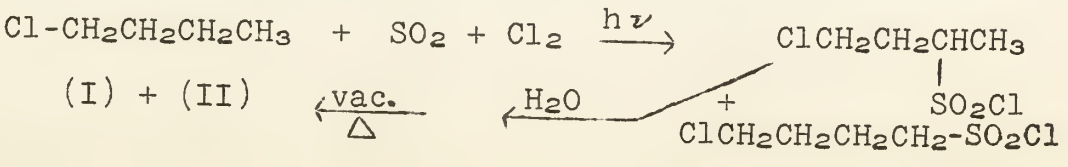
(b) Alkali metals[6]



R = Butyl, M = Li
R = phenyl, 9-fluorenyl, M = Na

Preparations of Sultones

1. Helberger employed the Reed chlorosulfonation reaction with alkyl halides:



Disadvantages are:
(a) Low yields
(b) The sultone isomers are not readily separable
(c) Decomposition of higher molecular weight acids often occurs before sultone formation.

2. Helberger noted that the sultones could be regenerated after hydrolysis to their acids by the vacuum distillation technique used for the halo sulphonic acids, with water being eliminated rather than hydrogen chloride. Previous attempts to prepare aliphatic sultones from their hydroxy acids had failed.[7,8] Helberger's method often causes decomposition of the higher molecular weight acids, however, and is not general.

Very recently a diluting agent technique has been found to be more general and to give higher yields.[9] The diluting agent must fulfill three requirements:
(a) Its boiling point must correspond to the dehydration temperature of about 150°.
(b) It must be miscible with the sultone formed.
(c) It must form an azeotropic mixture with the water which is eliminated.

Xylene has proved most successful thus far.

With this method, γ-and δ-sultones have been formed, as well as the ε-sultone of 5-hydroxypentane-1-sulfonic acid, but attempted elimination of water from 11-undecane-1-sulfonic acid failed. No β-sultone has been formed in this manner, although an unstable intermediate in the sulfonation of styrene by dioxane-sulfur trioxide is thought to be a β-sultone.[10]

Preparations of the acids

No general method is available, but four modes of preparation have been developed:

1. Bisulfite addition to an olefinic alcohol.

A free radical addition,[11] this method is restricted to terminal double bonds:

$$CH_3(CH_2)_7\underset{\underset{OH}{|}}{CH}\text{-}CH{=}CH_2 \;+\; NaHSO_3 \xrightarrow[\text{t-butyl perbenzoate}]{} CH_3(CH_2)_7\underset{\underset{OH}{|}}{CH}CH_2CH_2\text{-}SO_3Na$$

2. Reduction of keto sulfonic acids

These acids can be formed in two ways:

(a) From α,β-unsaturated aldehydes or ketones and sodium bisulfite[9,12]

$$CH_3(CH_2)_{13}CH{=}CH\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{NaHSO_3} CH_3(CH_2)_{13}\underset{\underset{SO_3Na}{|}}{CH}CH_2\overset{\overset{O}{\|}}{C}CH_3$$

(b) From acetoacetic ester, an aldehyde, and sodium bisulfite[9,13]

$$CH_3\overset{O}{\overset{\|}{C}}CH_2COOEt + H\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3 \xrightarrow{OH^-} CH_3\overset{O}{\overset{\|}{C}}-\underset{\underset{COOEt}{|}}{C}=CHCH_2CH_2CH_3$$

(III)

$$III + \overset{Na}{HSO_3} \longrightarrow \xrightarrow[\triangle]{H_2SO_4} CH_3\overset{O}{\overset{\|}{C}}CH_2\underset{\underset{SO_3H}{|}}{C}HCH_2CH_2CH_3$$

The carbonyl group is best reduced with Raney nickel catalyst.

3. The Strecker synthesis of alkyl sulfonates
Disadvantages:
(a) Starting materials are often difficult to obtain
(b) Higher molecular weight halides are less reactive
A special case:[4,14]

$$+ CH_3COCl \xrightarrow{ZnCl_2} CH_3COO(CH_2)_4Cl \xrightarrow{Na_2SO_3} \xrightarrow[H_2O]{H^+} HO(CH_2)_4SO_3H$$

4. Oxidation of hydroxyalkyl mercaptans
Again starting materials represent a disadvantage, but in this case the halides are more reactive toward the reagent.

$$HO\text{-}R\text{-}X + NaSH \longrightarrow HO\text{-}R\text{-}SH \xrightarrow{HNO_3} HO\text{-}R\text{-}SO_3H$$

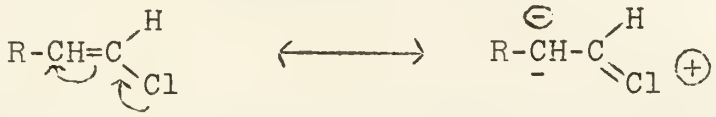
BIBLIOGRAPHY

1. Helberger, Manecke and Fisher, Ann. 562, 23 (1949).
2. Helberger, Manecke and Heyden, ibid., 565, 22 (1949).
3. Helberger, Heyden and Winter, ibid., 586, 147 (1954).
4. Truce and Hoerger, J. Am. Chem. Soc., 76, 5357 (1954).
5. Willems, Bull. soc. chim. Belg., 64, 747 (1955).
6. German patent 894,116 to Bohme Fettchemie (Helberger and Heyden); C.A., 48, 4234e (1954).
7. Marckwald and Frahne, Ber., 31, 1854 (1898).
8. Shriner, Rendleman and Berger, J. Org. Chem. 4, 103 (1939).
9. Willems, Bull. soc. chim. Belg., 64, 409 (1955).
10. Bordwell, Peterson and Rondestvedt, J. Am. Chem. Soc., 76, 3945 (1954); and preceeding papers.
11. Karasch, May and Mayo, J. Org. Chem., 3, 175 (1938).
12. Smith, Norton and Ballard, J. Am. Chem. Soc., 75, 748 (1953).
13. Rashig and Prahl, Ann., 448, 265 (1926).
14. Helberger and Lantermann, ibid., 586, 158 (1954).

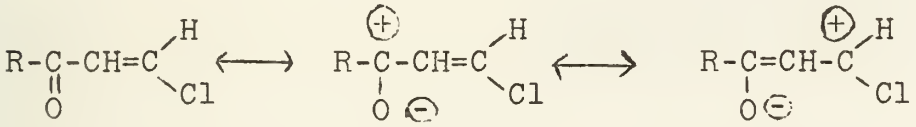
NUCLEOPHILIC SUBSTITUTION OF VINYL HALIDES

Reported by Willis E. Cupery April 6, 1956

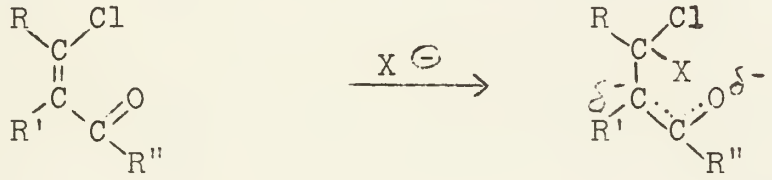
The inertness of vinyl halides toward nucleophilic substitution can be explained in several ways. The carbon atom at which substitution would occur is shielded by π electrons[1], and resonance forms of the type,



should strengthen the C-Cl bond[2] and would result in prohibitive loss of resonance energy in the transition state.[3] When a carbonyl group is introduced at the β-position to the halogen, greatly increased reactivity is observed. In resonance terminology, additional resonance forms more inviting to the nucleophile are possible.[4]



Or, in terms of a transition state, charge is better dispersed.



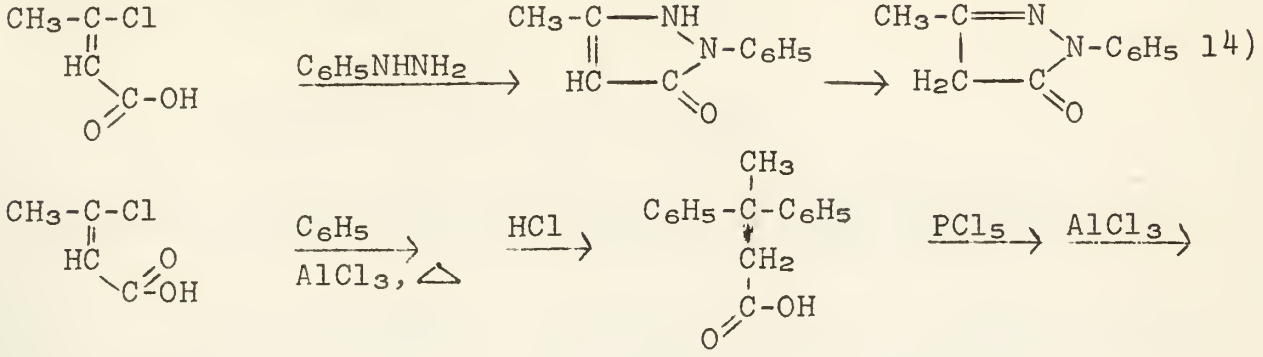
The latter transition state followed by elimination represents a mechanism which is reminiscent of Taft's work on the halogenation of double bonds where addition or substitution may occur.[5] The mechanism together with an assumption that elimination occurs before rotation is used by Jones and Vernon to explain substitution of halogen by thioethanolate in the ethyl β-chloro crotonates with retention of configuration.[6] In models, a slight steric hindrance to rotation appears with thioethanolate which is not present with ethanolate. Only one product is formed with ethanolate.

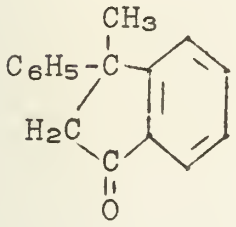
The other extreme transition state, leading to inversion, involves a tendency toward sp hybridization rather than sp^3. One of the two p orbitals takes part in the C-C bond, and the other forms half bonds to the nucleophile and the leaving group.[7] This would explain the reported inversion of β-chloroacrylate during sulfonic acid formation with ammonium sulfite.[8] The work itself is far from clear, so final judgment is best reserved.

There are many very early reports, mainly due to Autenreith, concerning substitution of β-halo-α,β-unsaturated acids, esters, and salts, sometimes under rather strenuous conditions, with benzene sulfinic acid[9], thiophenolate, thioethanolate, phenolate[10], benzyl alcoholate[11], and benzyl and allyl mercaptides.[12] Fritsch in 1897 reported that ethyl trichloroacrylate reacted with two moles of sodium ethoxide with the

displacement of both β-halogen atoms.[13]

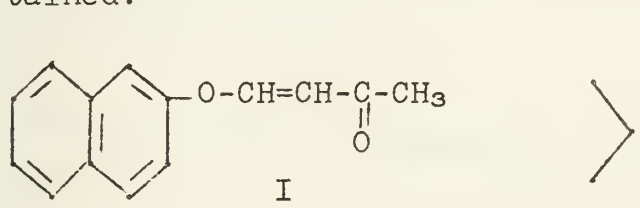
Two syntheses indicative of the usefulness of this grouping are shown below:



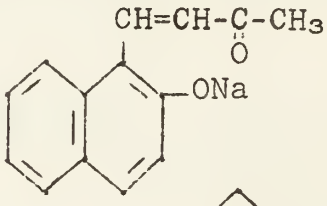


In this case, the reactivity of the β-halide allows more direct preparation of 3,3-diphenyl butyric acid.[15]

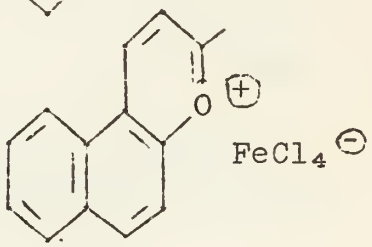
Although early reports of substitution in chloromethylene camphor exist,[16] only recently have β-halo-α,β-unsaturated ketones been extensively studied. Vinyl ethers are easily formed with alkoxides, although under too vigorous conditions with free alcohol, addition also occurs.[17] The Russian workers have treated phenol, p-cresol, and α- and β-naphthol in basic solution with methyl, propyl and isobutyl halovinyl ketones, in yields of 80-87%. With β-naphthol two products were obtained.[18]



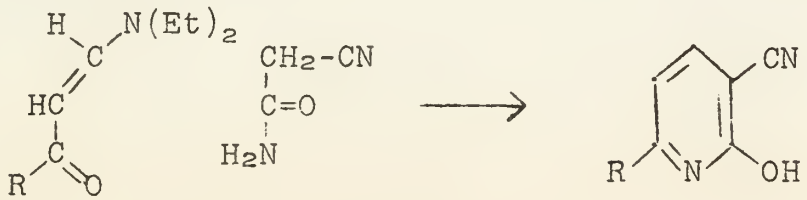
I



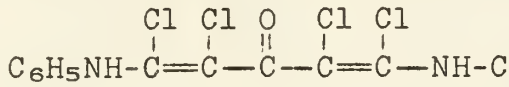
Where the para position in aromatic systems is blocked, the migration proceeds with $FeCl_3$ to give products of the type shown to the right.[19]



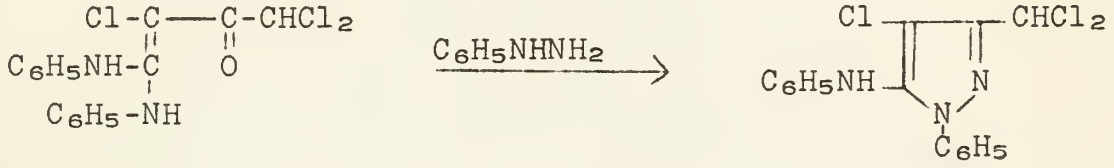
In cyclizations, groups other than halogen have been displaced. I, above, when allowed to react with phenylhydrazine forms β-naphthol and 1-phenyl-3-methyl pyrazole. In the reaction below, a diethylamino group is displaced by an active methylene group:[20]



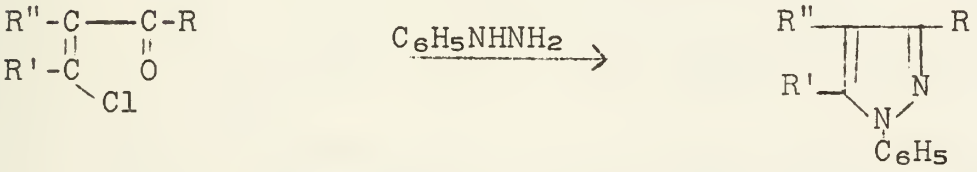
Much of the study on substitution with amines has been carried out on highly halogenated compounds.[4] When two β-chlorine atoms are present, usually they are both displaced, although perchloropenta-1,4-diene-3-one lost only two chlorine atoms and oxidation of the product did not give symmetrical diphenyl urea. The product is probably



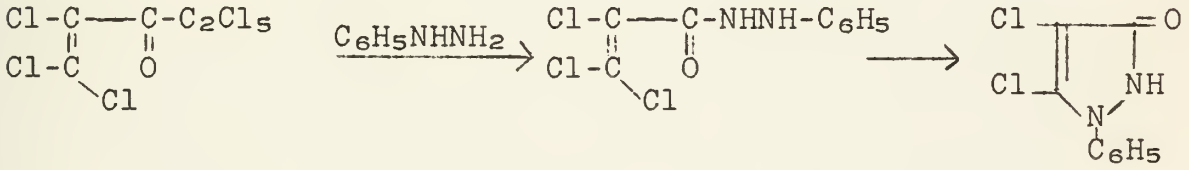
The β,β-dianilino-derivatives can be converted to substituted pyrazoles by the action of phenylhydrazine, e.g.,



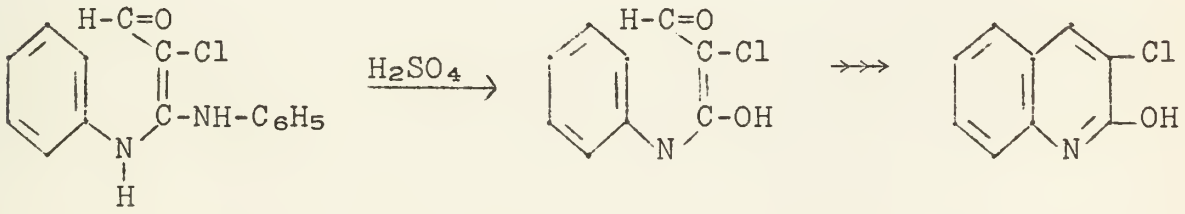
as can the original halogen compounds:



The reaction is poor when R=H or C_6H_5. The dependence on R' and R" is less clear at present. The only unexpected reaction from a series of eight highly halogenated compounds was found with perchloro-1-pentene-3-one, supposedly by the following route:

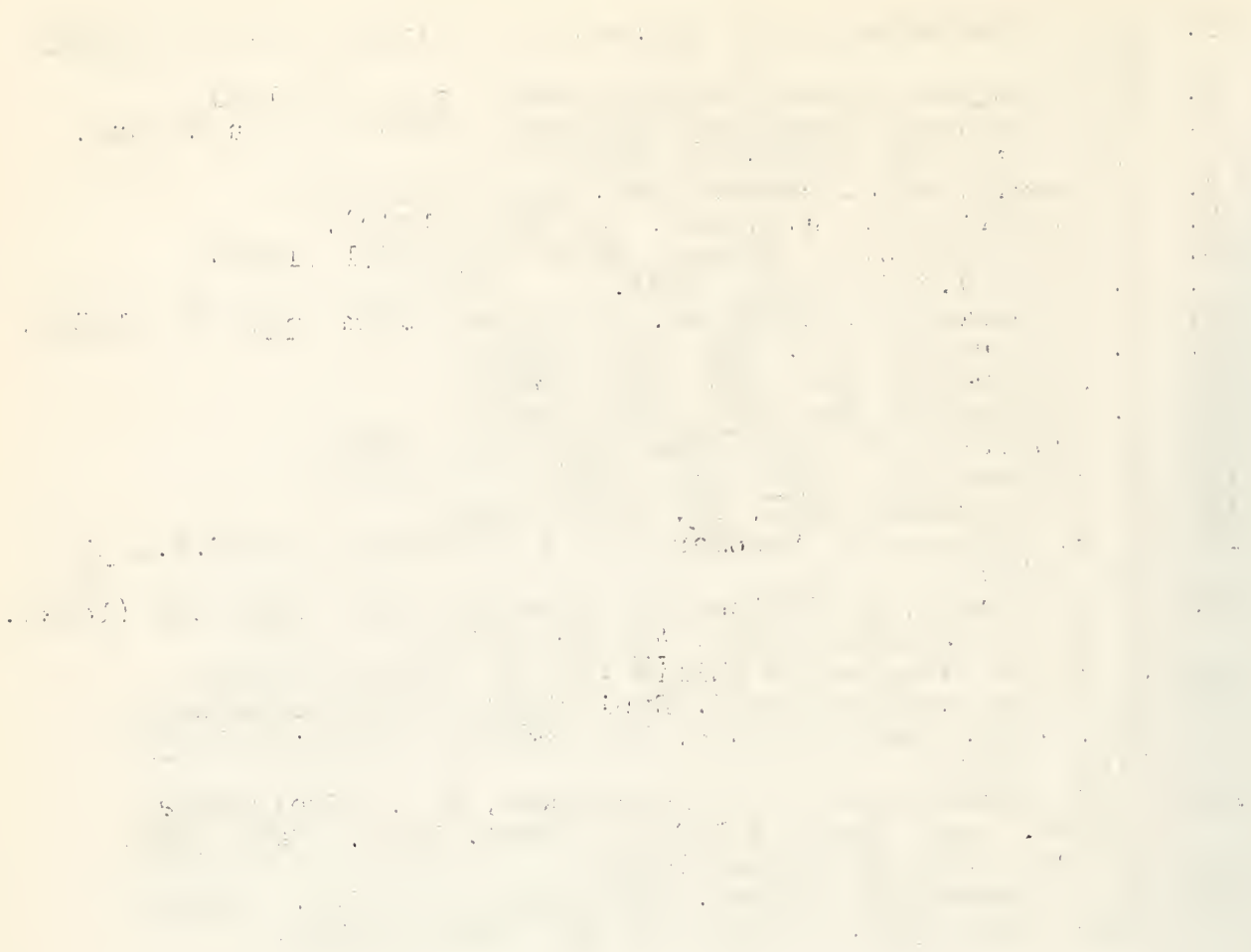


The dianilino derivative of trichloro acrolein is easily formed, but a Skraup-type ring closure was less successful. Even so, a fair yield of 2-hydroxy-3-chloroquinoline resulted.



BIBLIOGRAPHY

1. A. G. Catchpole, E. D. Hughes, C. K. Ingold, J.C.S., 1948, 10.
2. E. D. Hughes, Trans. Farraday Soc., 37, 627 (1941).
3. G. W. Wheland, Theory of Resonance, John Wiley and Sons, Inc., New York (1944): p. 272.
4. A. Roedig, H. J. Becker, Ann. 597, 214 (1955).
5. R. W. Taft, Jr., J.A.C.S., 70, 3364 (1949).
6. D. E. Jones, C. A. Vernon, Nature 176, 791 (1955).
7. V. Gold, J.C.S., 1951, 1431.
8. H. J. Becker, A. E. Beute, Rec. Trav. Chim. 54, 523 (1935).
9. W. Autenreith, Ann. 259, 335 (1890).
10. W. Autenreith, Ann. 254, 222 (1889).
11. W. Autenreith, Ber. 29, 1646 (1896).
12. H. Scheibler, J. Voss, Ber., 53, 379 (1920).
13. P. Fritsch, Ann. 297, 312 (1897).
14. W. Autentreith, Ber., 29, 1653 (1896).
15. C. F. Koelsch, H. Hochmann, C. D. LeClaire, J.A.C.S., 65, 59 (1943).
16. A. W. Bishop, L. Claisen, W. Sinclair, Ann. 281, 361 (1894). H. Rupe, M. Iselin. Ber. 49, 29 (1916).
17. M. Julia. Annales de Chimie (12) 5, 595-640 (1950).
18. N. K. Kotchetkov, M. I. Rybinskaya, A. N. Nesmeyanov. Dok. Akad. Nauk, S.S.S.R. 79, 798-802 (1951); C.A. 46, 6102 (1952).
19. A. N. Nesmeyanov, N. K. Kotchetkov, M. I. Rybinskaya, Izvest. Akad. Nauk, S.S.S.R., Odtel. Khim. Nauk 1954, 418-26; C.A. 49, 9634a (1955).
20. N. K. Kochetkov. Izvest. Akad. Nauk, S.S.S.R., Odtel. Khim. Nauk 1954, 47-55; C.A. 49, 6090i (1955).

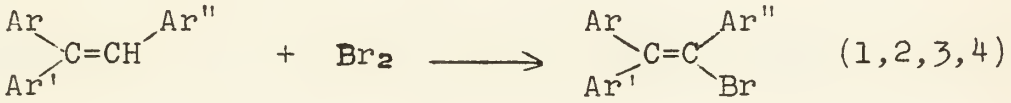


NON-POLYMER-FORMING REACTIONS OF VINYL HALIDES

Reported by H. Scott Killam April 6, 1956

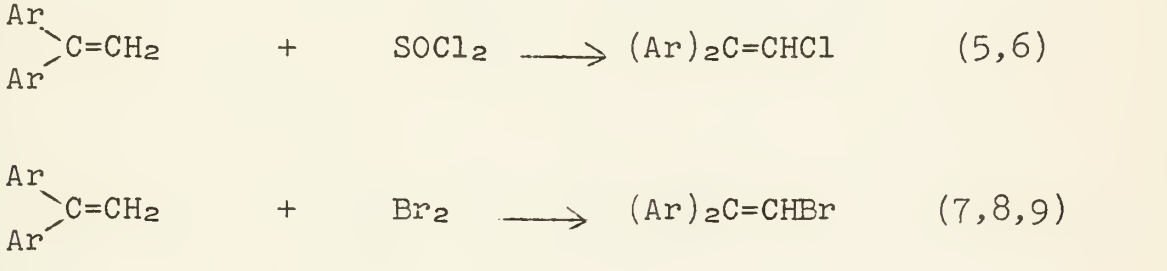
The use of vinyl halides in polymer chemistry is profusely illustrated in the current literature. Of importance also are those reactions of vinyl halides which do not involve the double bond directly. It is the purpose of this discussion to indicate the manner in which these halides may be prepared and utilized in synthetic work.

Preparation:

1. 

(1,2,3,4)

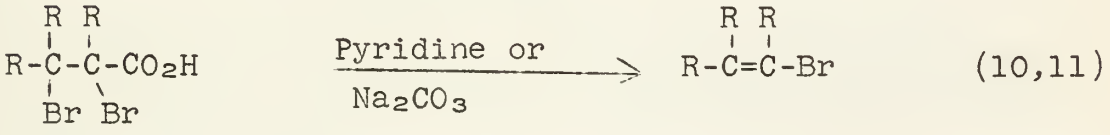
Ar=Ar'=$(CH_3)_2N$-, CH_3O-, $(CH_3)_3CO$-, I, Cl, Br, OH, $C_6H_5CH_2O$-
Ar"=Br, H-, CH_3-,

2. 

(5,6)

(7,8,9)

(18,19)

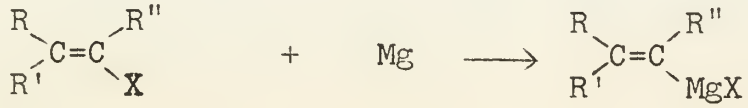
3. 

(10,11)

R=Alkyl

Reactions:

1. Grignard Formation. Until recently, employment of vinyl halides for the preparation of Grignard reagents has been limited to the use of the more highly substituted halides shown by formula I where R, R', and R" are aryl or R" is hydrogen.



I

A survey of the literature indicates that the frequency of application of vinyl Grignard reagents to synthetic problems is determined by the ease of preparation of the reagent. Until 1954, the more highly substituted vinyl Grignard reagents had been obtained with facility (21,22) while reports concerning the formation of vinyl magnesium bromide or chloride had not been adequately substantiated (23). This situation has been altered somewhat by the recent work of Normant (12). By utilizing solvents differing from those usually associated with the preparation of Grignard reagents he was able to apply to synthetic procedures even the simplest vinyl organo magnesium compounds.

2.

$$CF_2{=}CHCl + CH_3OH \longrightarrow CH_3OCF_2CH_2Cl \qquad (13)$$

3.

$$RCH{=}CHCl + Me\text{-}\overset{\overset{Me}{|}}{\underset{\underset{Me}{|}}{C}}\text{-}Cl \longrightarrow CHCl_2\underset{\underset{R}{|}}{C}HC(CH_3)_3 \qquad (14)$$

$$CH_2{=}CHCl + Me\text{-}\overset{\overset{Me}{|}}{\underset{\underset{Me}{|}}{C}}H \longrightarrow CHCl_2CHC(CH_3)_3 \qquad (15,16)$$

4.

$$\begin{matrix} Ar \\ \diagdown \\ \quad C{=}CHCl \\ \diagup \\ Ar \end{matrix} + KNH_2 \longrightarrow \begin{matrix} Ar & & Ar \\ \diagdown & & \diagup \\ & C{\equiv}C & \end{matrix} \qquad (17,18,19)$$

5.

$$ArMgX + \begin{matrix} R \\ \diagdown \\ \quad C{=}CHCl \\ \diagup \\ R \end{matrix} \xrightarrow{COCl_2} ArCH{=}CR_2 \qquad (20)$$

BIBLIOGRAPHY

1. W. Tadros and A. Latif, J. Chem. Soc., 3823(1952).
2. W. Tadros, Y. Akhnookh and G. Aziz, ibid., 186 (1953).
3. A. Schonberg, J. M. Robson, W. Tadros and H. A. Zahim, ibid., 1327 (1940).
4. W. Tadros and G. Aziz, ibid., 2553 (1951).
5. S. Patai and F. Bergmann, J. Am. Chem. Soc., 72, 1034 (1950).
6. F. Bergmann and J. Szmuszkowicz, ibid., 72, 1035 (1950); ibid., 69, 1777 (1947).
7. P. Lipp, Ber., 56, 567 (1923).
8. P. Pfeiffer and R. Wisinger, Ann., 461, 132 (1928).
9. E. Bergmann, L. Engel and H. Meyer, Ber., 65, 446 (1932).
10. J. Farrell and G. Bachman, J. Am. Chem. Soc., 57, 1281 (1935).
11. A. Kirrmann, Bull. soc. chim. France, 41, 316 (1927).
12. H. Normant, Compt. rend., 239, 1510, 1811 (1954); ibid., 240, 314,440, 631 (1955).
13. P. Tarrant and H. C. Brown, J. Am. Chem. Soc., 73, 1781 (1951).

14. K. Detling, C. Crawford, D. Yabroff and W. Peterson, Brit. Patent, 591,632, Aug. 25, 1947; Chem. Abs. 42, 919 (1948).
15. L. Schmerling, J. Am. Chem. Soc., 68, 1650 (1946): ibid., 67, 1438 (1945).
16. M. S. Malenovskii, J. Gen. Chem., 17, 2235 (1947).
17. G. Coleman, W. Holst and R. Maxewell, J. Am. Chem. Soc., 58, 2310 (1936).
18. G. Coleman and R. Maxewell, ibid., 56, 132 (1934).
19. W. Buttenberg, Ann., 279, 324 (1894).
20. M. S. Kharasch, J. Am. Chem. Soc., 65, 504 (1943).
21. W. Krestinsky, Ber., 55B, 2770 (1922).
22. C. F. Koelsch, J. Am. Chem. Soc., 54, 2045 (1932).
23. M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances", Prentice-Hall, Inc., New York, 1954, p. 36.

ALKALINE FERRICYANIDE OXIDATIONS

Reported by C. W. Schimelpfenig April 20, 1956

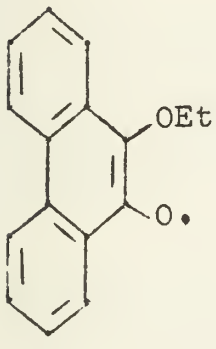
There have been a few recent reports dealing with the oxidation of simple molecules by alkaline ferricyanide. The fact that these recent reports invalidate structures assumed for years prompts this review of oxidations using potassium ferricyanide in alkaline media.

Waters[1] considers ferricyanide to be a reagent in which one electron is removed from its substrate, producing ferrocyanide. The "substrate minus 1 e" then reacts by decomposition and/or rearrangement to give the oxidized product. An example is the oxidation of β-naphthol to give β-dinaphthol and α-(β-naphthoxy)-β-naphthol as main products. These products indicate the mesomeric nature of the radical. This type of reaction, oxidation produced by electron-abstracting agents, includes those of ceric and ferric ions in acidic media and of ammoniacal silver nitrate. It is reminiscent of some biological oxidation systems, notably those linked with the cytochrome system.

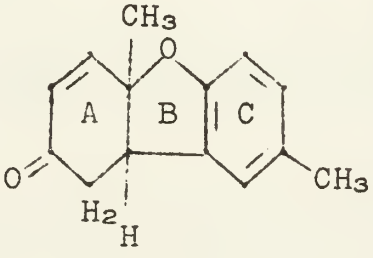
1. Kieffer[2] oxidized the phenol, morphine. However, it was only following the work of Goldschmidt and Pummerer that Small postulated the structure of pseudomorphine.

Goldschmidt[3] treated phenanthrene hydroquinone monoethyl ether and obtained "ethoxyphenanthroxyl" (I) whose molecular weight was intermediate between this monomer and the dimer.

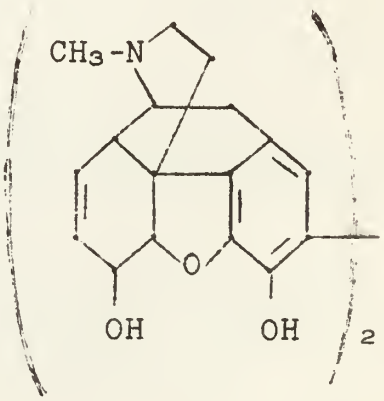
Pummerer[4] reported his oxidation of p-cresol to a "dimer minus 2H". On the basis of acid hydrolysis, hydrogenation, and other chemical studies, he suggested that the dimeric product was (II). Later work by Westerfield and Lowe[5] showed that the diphenol from acid hydrolysis was 2,3'-bi-p-cresol and they proved the structure of ring C.



I



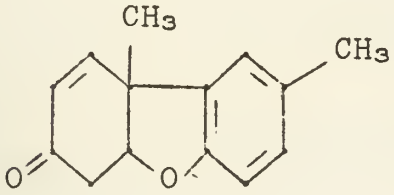
II



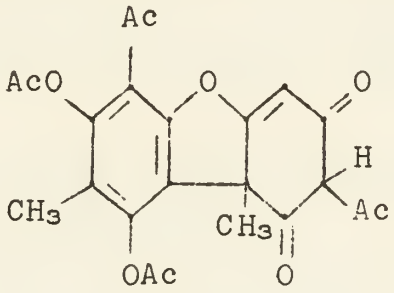
III

These data, together with his own observations, have led Small[6] to postulate that pseudomorphine is the 2,2' derivative (III).

Although the ideas of Pummerer led to the structure of pseudomorphine, his structure requires modification. Last year Barton[7] reported that the dimeric p-cresol had structure (IV) based on his degradation to ring A. This led him to the first total synthesis of usnic acid (diacetate, V).



IV



V

Another reaction involving a phenolic starting material is the synthesis of selected indoles, adrenochromes, from noradrenaline, adrenaline, and N-alkylated noradrenalines.[8,9]

2. Chronologically, the next application of ferricyanide oxidations is that to carbohydrates and glycols. The oxidation has been applied to a number of sugars; however, no products have been isolated and the reaction is still an empirical quantitative method.[10]

In the case of a glycol, the product of osmium tetroxide oxidation of anthracene was oxidized further to napthalene-2,3-dicarboxylic acid.[11]

3. Acid hydrazides and hydrazine have been oxidized.[12]

$$RCONHNH_2 \longrightarrow RCHO + N_2 + H_2O$$
$$RCONHNH_2 \longrightarrow RCONHNHCOR + N_2 + H_2O$$

(R = ø, 64% ØCHO)

If R is aromatic or heterocyclic, the aldehyde is the product. If R is alkyl or aromatic with a m-directing group in the o- or p-position, then the sym-diacylhydrazid is obtained.

4. A reaction which has been extensively used is the oxidation of N-substituted pyridinium compounds to the corresponding α-pyridones. It has been postulated[13] that the reaction proceeds by dehydrogenating the pseudo-base.

The structure of reduced diphosphopyridine nucleotide was proved[14] by determining that reduction of DPN with 1,1-dideuteroethanol followed by chemical oxidation, hydrolysis, methylation, and alkaline ferricyanide oxidation

produced the 2-pyridone and the 6-pyridone which contained equal amounts of deuterium.

5. Alkaline ferricyanide has been applied to a few amines. dl-Oxysparteine was obtained (35%) from dl-sparteine[15] and oxo-β-isosparteine was obtained (25%) from β-isosparteine.[16] Perrine[17], trying to prepare tropinone from tropine, obtained nortropine (87%). He found that whenever an N-methyl tertiary amine, where N is attached to a secondary or tertiary C atom, is treated with alkaline ferricyanide, demethylation occurs.

6. Toluene, xylene, and some of their derivatives were oxidized by Noyes[18] to the corresponding benzoic and phthalic acids by boiling with alkaline ferricyanide.

7. Furan derivatives have been oxidized[19] to the corresponding furoic or dehydromucic acids, also in boiling oxidizing media.

8. Thiophenol is quantitatively oxidized to diphenyl-disulfide.[20] Cysteine has been determined potentiometrically with neutral ferricyanide indicating the mercaptan-disulfide, ferricyanide-ferrocyanide equilibrium is reversible.[21]

A synthetic rubber polymerization catalyst includes neutral ferricyanide and a mercaptan such as n-dodecyl-mercaptan.[22] The proposed mechanism involves generation of a thioalkyl free radical which serves both as initiator and as chain transfer agent.

$$RSH + Fe(CN)_6^{3-} \longrightarrow RS\cdot + H^{\oplus} + Fe(CN)_6^{4-}$$

9. Among reactions which have not been fully investigated is the conversion of hydroxylamines to N-substituted oximes. Grammaticakis[23] reported the oxidation of N,N-di-(1-phenyl-propyl)-hydroxylamine to the corresponding N-substituted ketoxime.

10. Another synthetic method not fully explored is exemplified by the synthesis of 2-methylbenzothiazole from thioacetanilide.[24]

In retrospect, ferricyanide has been used in systems obviously favored for oxidation in this manner, that is, extraction of an electron from an electron-rich site. The reagent has also been utilized with some success where its capability was not originally apparent. It is likely that the potentiality of alkaline ferricyanide as an oxidizing agent has not been exhausted.

BIBLIOGRAPHY

1. W. A. Waters in Gilman, Organic Chemistry, vol. IV, p. 1214; Abstracts of 1955 IUPAC Meeting, 112.
2. L. Kieffer, Ann. Chem. Pharm., 103, 271 (1857).
3. S. Goldschmidt and W. Schnidt, Ber., 55, 3197 (1922).
4. R. Pummerer, D. Melamed and H. Puttfarcken, Ber., 58, 1808 (1925) and previous papers in the series.
5. W. W. Westerfield and C. Lowe, J. Biol. Chem., 145, 463 (1942).
6. L. F. Small and S. G. Turnbull, J. Am. Chem. Soc., 59, 1541 (1937).
7. D. H. R. Barton, A. M. Deflorin and O. E. Edwards, Chemistry and Industry, 1955, 1039; J. Chem. Soc., 1956, 530.
8. J. D. Bu'Lock and J. Harkey-Mason, J. Chem. Soc., 1951, 712, 2248.
9. P. Chaix and C. Pallaget, Biochim. et Biophys. Acta, 10, 462 (1953).
10. H. C. Becker, Thesis, Univ. of Illinois (1940) and references therein.
11. J. W. Cook and R. Schoental, Nature, 161, 237 (1948).
12. S. J. Angyal in Adams, Organic Reactions, vol. VIII, p. 233, and references therein.
13. H. L. Bradlow and C. A. Vanderwerf, J. Org. Chem., 16, 73 (1951).
14. M. E. Pullman, A. San Pietro and S. P. Colowick, J. Biol. Chem., 206, 129 (1954).
15. C. G. Clemo, W. M. Morgan and R. Raper, J. Chem. Soc., 1936, 1025.
16. B. P. Moore and L. Marion, Can. J. Chem., 31, 187 (1953).
17. T. D. Perrine, J. Org. Chem., 16, 1303 (1951).
18. W. A. Noyes and W. B.Wiley, Am. Chem. J., 11, 161 (1889), and previous papers in the series.
19. E. V. Brown, Iowa State College J. Sci., 11, 227 (1937).
20. V. O. Lukashevich and M. M. Sergeyeva, J. Gen. Chem., USSR, 19, 1493 (1949).
21. G. Gorin, Abstracts of ACS meeting, April 1956, p. 1C.
22. W. Kern, Makromol. Chem., 1, 199 (1948).
23. P. Grammaticakis, Compt. rend., 224, 1066 (1947).
24. P. Jacobson, Ber., 19, 1067 (1886).

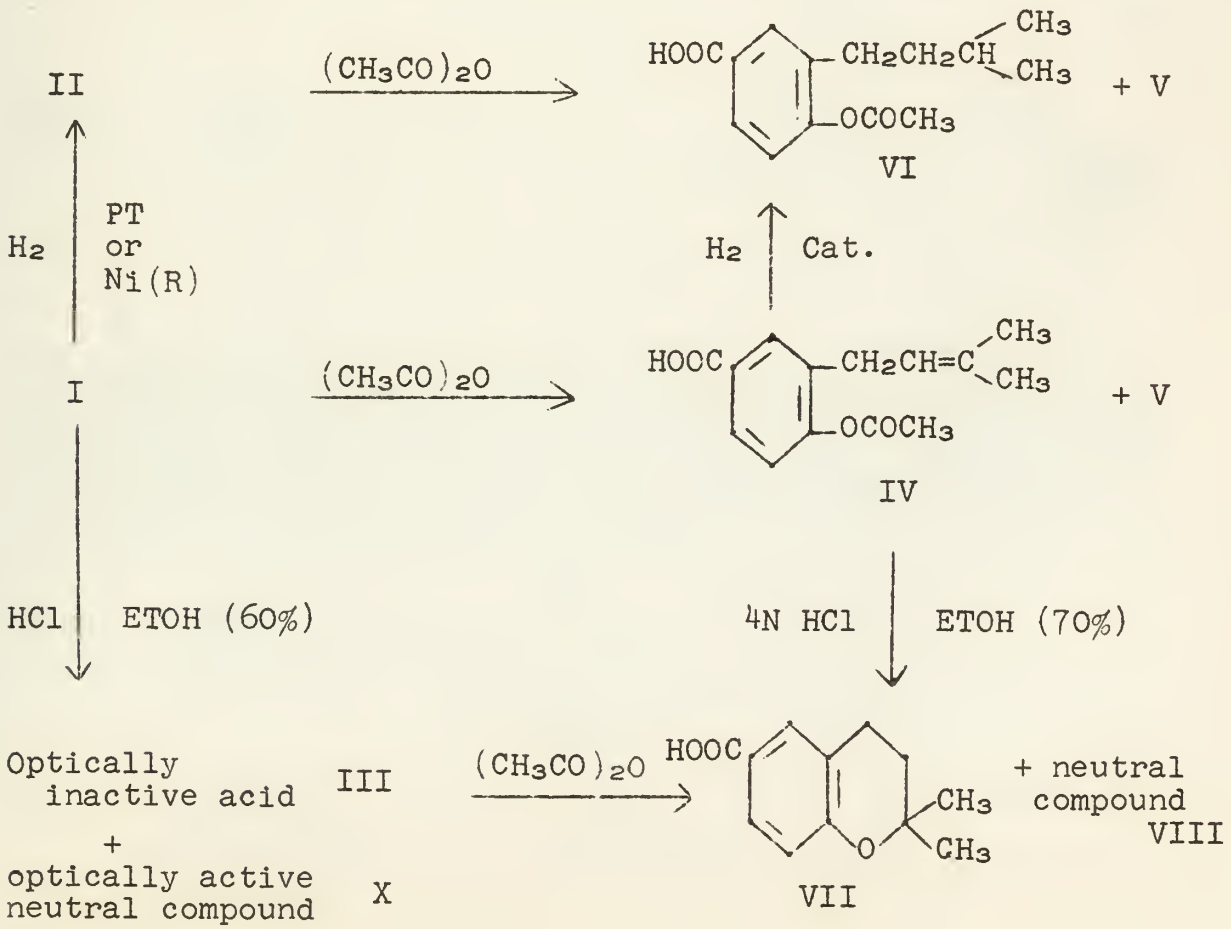
THE STRUCTURE OF NOVOBIOCIN

Reported by Kaye L. Motz April 20, 1956

Novobiocin has been isolated from fermentation broths by both solvent extraction and by acid precipitation. Two crystalline forms have been isolated, one with a melting point of 152-156° and the other melting at 174-178°. Both forms are optically active ($[\alpha]_D^{24}$ -63° 1% in EtOH). Rast determinations indicate a molecular weight of about 610, while X-ray crystallographic studies show 618 as the molecular weight.[1,5] Cryoscopic determinations show a molecular weight of 695 ± 25.[3] Since several bases form neutral and acid salts with novobiocin, the presence of a dibasic acid might well be suspected, and indeed, the ultraviolet spectrum indicates this to be true.[1,5] Potentiometric titration substantiates this and establishes pK_a' values of 4.3 and 9.1 in water and gives 636 as a value for the equivalent weight. It has also been established by Kuhn-Roth determination that there are two C-methyl groups and one O-methyl group in the molecule.[1]

Recent microanalysis[2] shows the composition of novobiocin (I) to be $C_{31}H_{36}N_2O_{11}$. On treatment of I with hydrogen in the presence of platinum or Raney nickel the dihydro-derivative II is formed. The optical activity and pK_a' values of II are close to those found for I. The infrared spectrum shows little change in the conjugated system or in the carbonyl region.

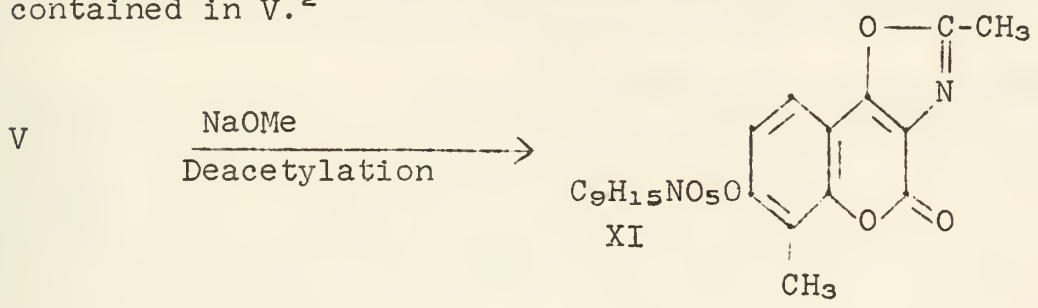
The following degradation was used to identify one part of the molecule.[1]

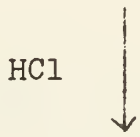


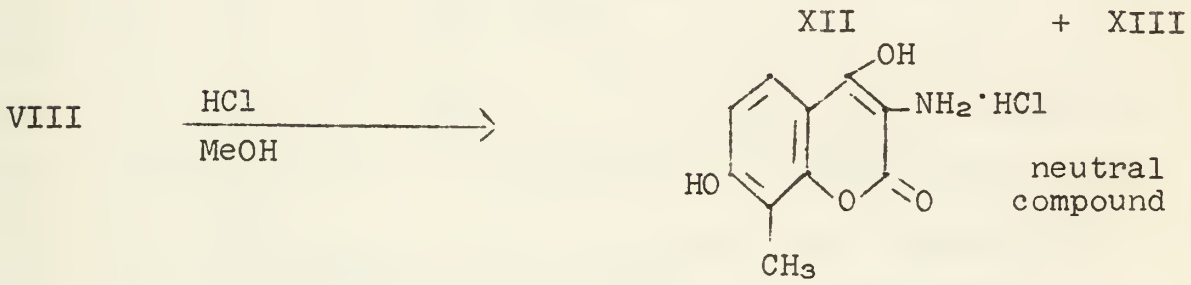
The first compound definitely identified was (VII) 2,2-dimethyl-6-carboxy chroman. This was identified by its p-bromophenacyl ester with the aid of infrared and ultraviolet spectra.

Since the acetic anhydride treatment always gives the same fragment of the molecule and no nitrogen is present in this portion it seems quite likely that an amide linkage has been broken in the process. The hydrogen chloride treatment may well have broken a glycosidic linkage since this treatment gives an optically active substance and an inactive acid. It is apparent that the identified portion of the molecule is linked to the rest of the molecule through its carboxyl group.

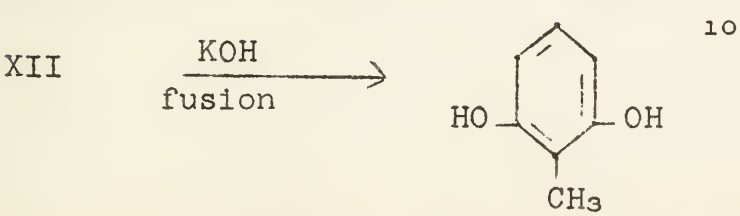
The unidentified part of the molecule must then all be contained in V.[2]

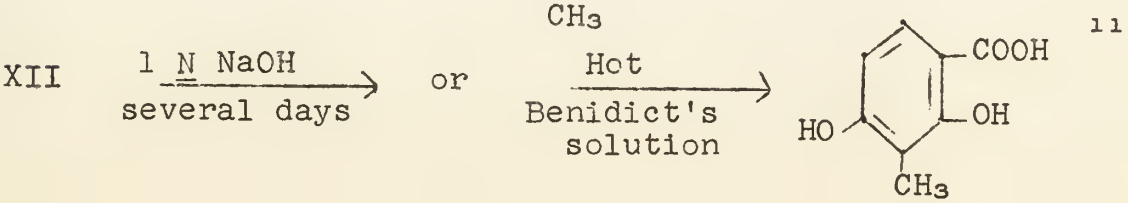






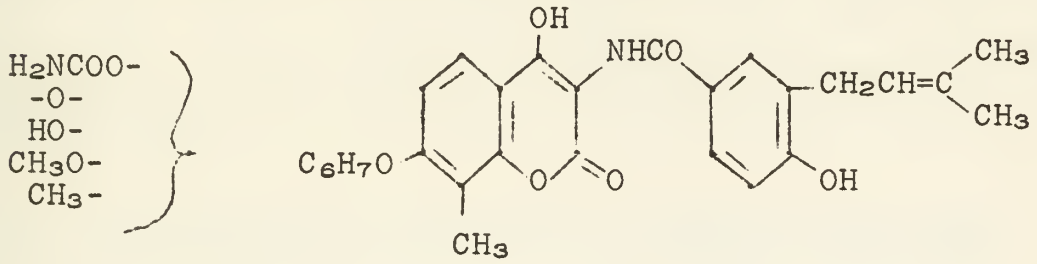
The lactone ring of the substituted coumarin was identified by direct comparison with known compounds. The spectrum of the compound differed from model compounds only in a manner which would be predicted by the presence of the substituents on the benzene ring. The benzene ring substitution was determined as follows.





The compound X ($C_{11}H_{21}NO_6$) appears to be an ethyl glycoside of a methoxy sugar and XIII the corresponding methyl glycoside.[2] The presence of infrared bands at 1702 + 1625 indicate a urethan grouping. The infrared spectrum and the liberation of NH_4Cl on methanolic HCl treatment indicates the presence of a cyclic carbonate ester. Barium hydroxide treatment gives the theoretical amount of barium carbonate which indicates the presence of nitrogen as a carbamate. The methoxyl group found to be present and the bridge oxygen account for all of the functionality of XIII.

Using the information presented above the following partial structure for novobiocin has been proposed.[2]



REFERENCES

1. H. Hoeksema, J. Johnson, J. Hinman, J. Am. Chem. Soc., 77, 6710 (1955).
2. J. Hinman, H. Hoeksema, E. Caron, W. Jackson, J. Am. Chem. Soc., 78, 1072 (1956).
3. E. Kaczka, F. Wolf, F. Rathe, K. Folkers, J. Am. Chem. Soc., 77, 6404 (1955).
4. C. G. Smith, A. Dietz, W. T. Sokolski and G. M. Savage Antibiotics and Chemotherapy, 6, 135 (1956).
5. H. Hoeksema et.al., Antibiotics and Chemotherapy 6, 143 (1956).
6. J. R. Wilkins, C. Lewis, A. R. Barbiers, Antibiotics and Chemotherapy 6, 149 (1956).
7. R. M. Taylor et.al., Antibiotics and Chemotherapy 6, 157 (1956).
8. R. M. Taylor et.al., Antibiotics and Chemotherapy 6, 162 (1956).
9. W. J. Martin et.al., Proc. Staff Meet. Mayo Clinic 30, 540 (1955).
10. E. T. Jones and A. Robertson, J. Chem. Soc., 1690 (1932).
11. R. C. Shah and M. C. Laiwalla, J. Chem. Soc., 1828 (1938).

OZONATION STUDIES OF AROMATIC HYDROCARBONS AND HETEROCYCLES

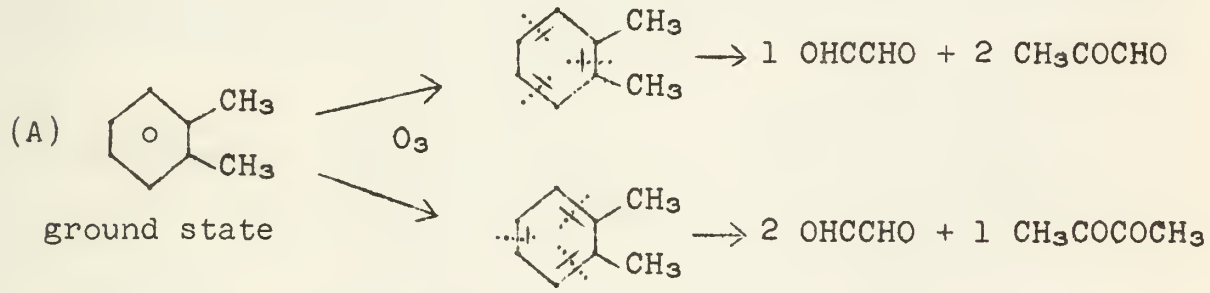
Reported by M. S. Konecky April 27, 1956

Since Kekule proposed his hexagonal alternating single and double bonded structure for benzene in 1865, chemists have been interested in the elucidation of the internal bond structure of aromatic compounds. Although many structures for benzene and naphthalene were postulated, none of the classical representations satisfactorily explained the chemical reactivity and physical characteristics of these type compounds.[1]

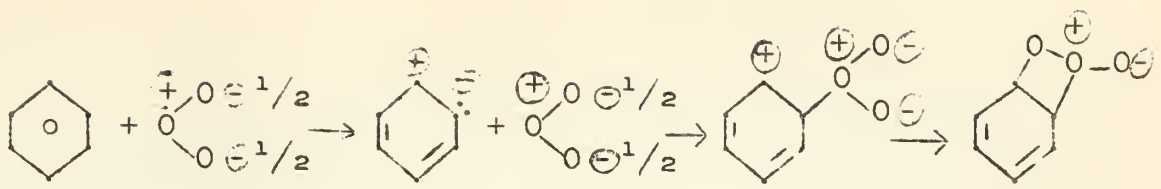
Today, the ground state, aromatic molecule is considered a resonance hybrid of various contributing classical structural forms, and, due to resonance stabilization, exhibits properties which are distinct from those expected for any of the contributing forms. Thus, application of the theory of resonance to aromatic structure leads to a distinction between the free molecule in the ground state and the reacting molecule in some excited state.

This seminar is concerned with the use of ozone in elucidation of the reacting structure of aromatic compounds.

I - Benzene and Derivatives: The ozonolysis products obtained from o-xylene by Levine and Cole[2] first demonstrated the applicability of ozonation to aromatic structure studies. Haayman and Wibaut's[3] semi-quantitative isolation of the products from the ozonolysis of o-xylene chemically verified the resonance concept of the equivalence of the carbon-carbon bonds in the benzene nucleus. The products, glyoxal, methylglyoxal, and dimethylglyoxal were isolated in a molar ratio of 3:2:1, respectively, as shown in reaction scheme (A):

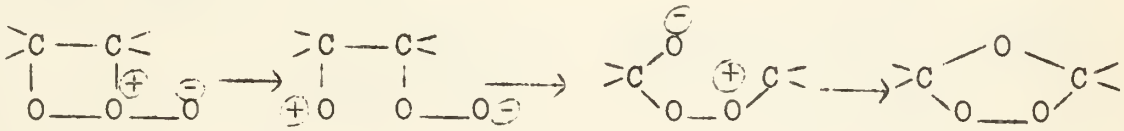


Boer[4,5] designed an improved ozonator which enabled accurate rate studies to be made during the ozonation of benzene and derivatives. These rate studies[6,7] showed that this ozonation is a bimolecular reaction, is catalyzed by $AlCl_3$, and involves the absorption of 3 moles of ozone per mole of hydrocarbon. Furthermore, nuclear substituted halogen and carbonyl decrease the rate of ozonation, while alkyl substitution increases the rate. Since these effects parallel effects observed in electrophilic substitution, a related reaction mechanism for ozonation was postulated, as follows:

(B) 

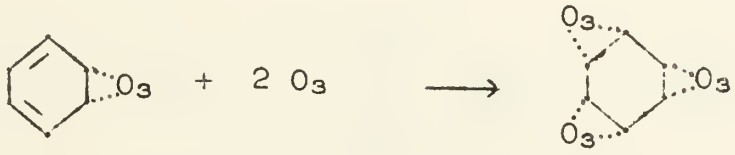
molozonide

The unstable molozonide is rapidly transformed into a stable iso-ozonide via the mechanism for aliphatic ozonides proposed by Criegee:

(C) 

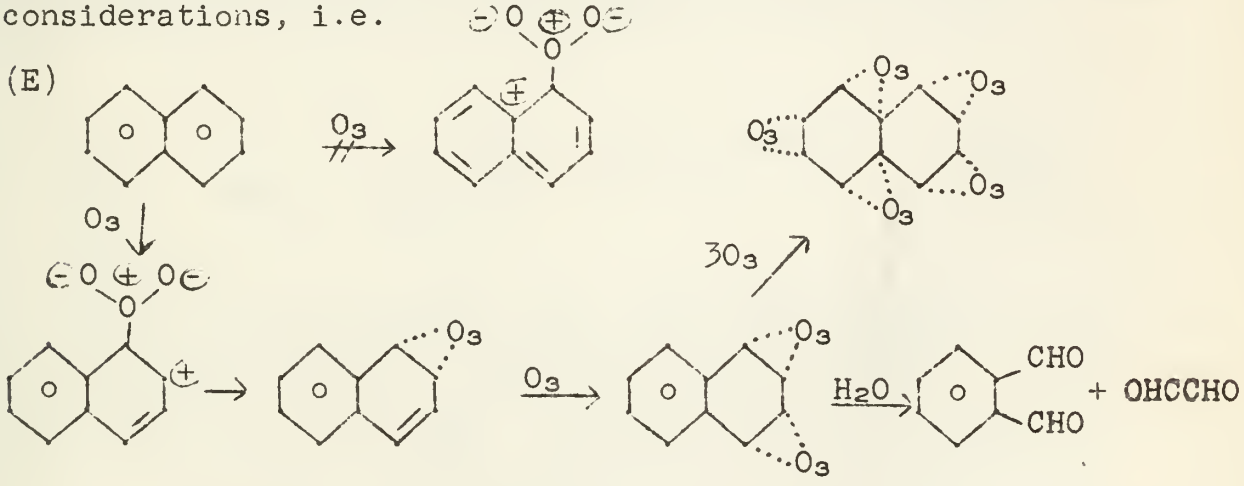
Molozonide Iso-ozonide

The stable mono-ozonide now contains two aliphatic double bonds and rapidly adds two additional moles of ozone to form the triozonide, i.e.

(D) 

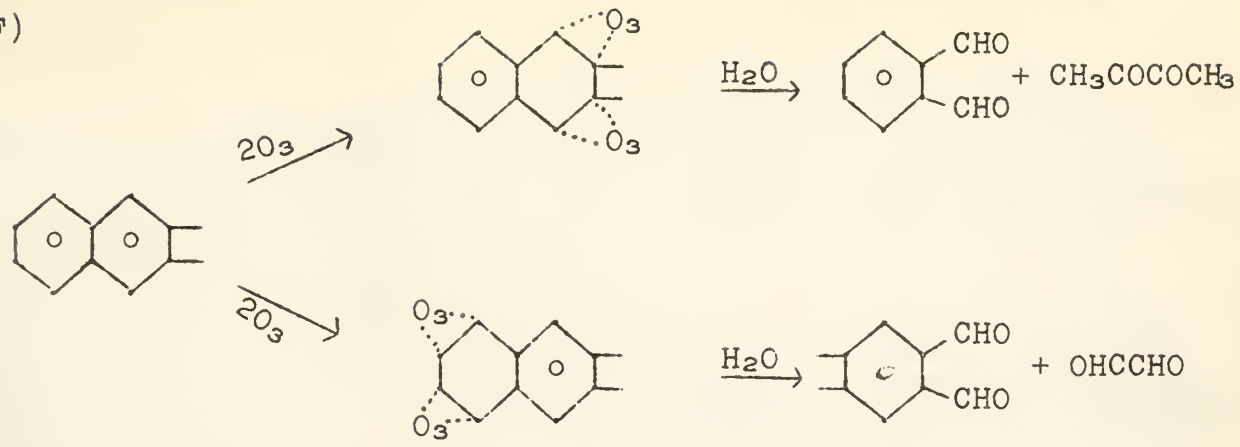
The rate determining step is the mono-ozonide formation.

II - Naphthalene and Derivatives:[8] Here, ozone preferentially reacts with an α-carbon atom since the energy required to localize a pair of electrons to an α-carbon is less than to a β-carbon.[9,10] Subsequently, only the α-β bond is polarized since any other polarization would destroy the aromaticity of both benzenoid nucleii--an improbable alternative from energy considerations, i.e.

(E) 

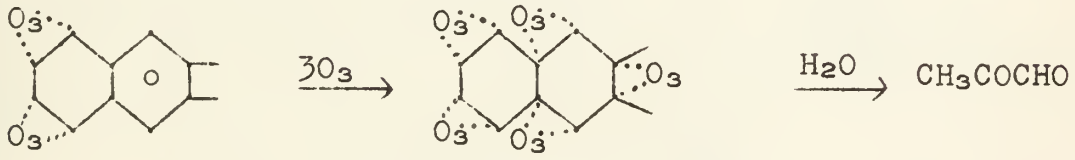
The decomposition products in the case of 2,3-dimethyl-naphthalene indicate a main reaction in which the methylated ring is attacked and a side reaction with attack on the non-methylated ring, i.e.

(F)



The small amount of methylglyoxal isolated was accounted for by the decomposition of the small amount of pentozonide originating from the side reaction:[11]

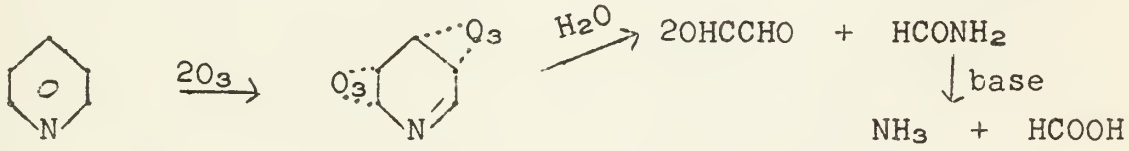
(G)



The predominant ozone attack of the methylated ring agrees with the benzene rate data which showed that methyl substitution increases the reactivity of the aromatic nucleus toward ozone.

III - Pyridine and Derivatives: The azomethine linkage in pyridine is not attacked by ozone; however, treatment of the ozonolysis mixture with base liberates NH_3. A reaction scheme[12] was proposed in which the -C=N- linkage is split during hydrolysis, giving rise to an amide, i.e.

(H)

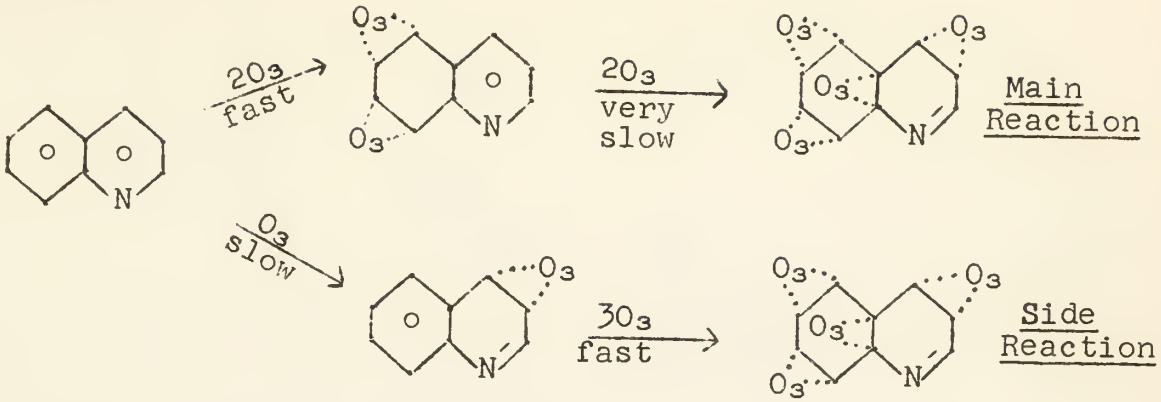


This reaction is also bimolecular. The quantitatively determined 2:1 ratio of ozone-absorbed to ammonia-produced verified the formation of a diozonide. The rates with 3-picoline, 2,6-dimethylpyridine, and 2,4,6-trimethylpyridine were faster and increased in the order named. A higher activation energy for pyridine in this reaction is indicated since the temperature coefficient is 3.8 as compared to 3.0 for benzene and 2.7 for toluene. Because of the electrophilic nature of this mechanism, these data support the concept of the diminished reactivity of the pyridine nucleus to electrophilic reactions as compared to the benzene nucleus.

IV - Quinoline and Isoquinoline: Reaction scheme (J) was proposed for the course of the ozonation of quinoline and its

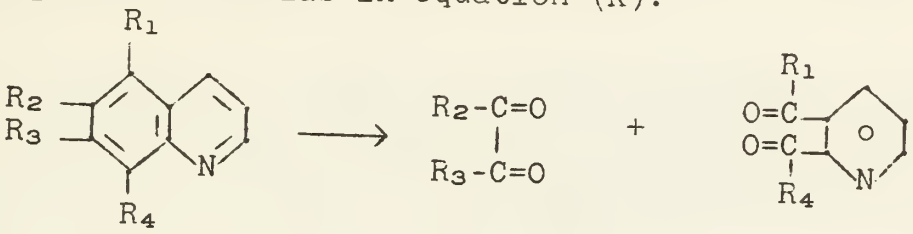
homologs.[13]

(J)



The isolated decomposition products, derived from the diozonide in the main reaction, are indicated for the quinolines studied by the general formulas in equation (K).

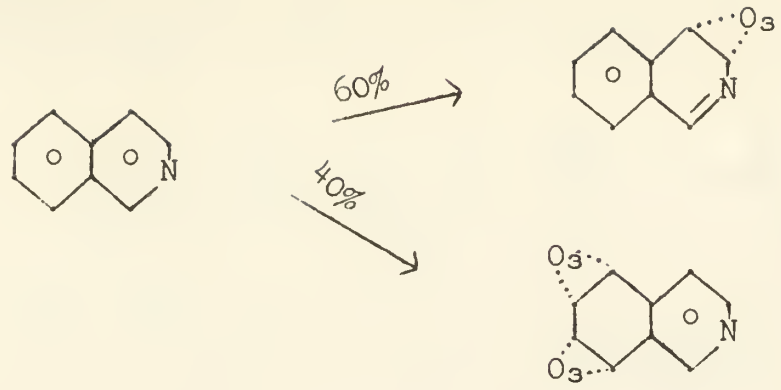
(K)



where, R_1, R_2, R_3, R_4 = H or CH_3

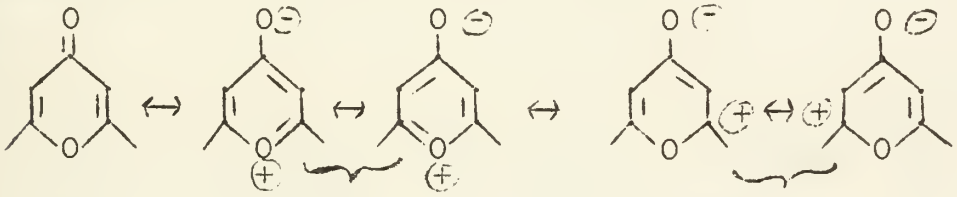
A small amount of ammonia, which can only be produced by decomposition of ozonides in which the pyridine nucleus has reacted with ozone, also is isolated. Quantitative evaluation of the ammonia produced and the total ozone absorbed verified the tetra-ozonide as the source of the ammonia. Rate studies indicated the rapid formation of the diozonide and slow formation of the tetra-ozonide of the main reaction. Initial addition of ozone at the 5-6 or 7-8 bond in the benzene nucleus or at the 3-4 bond in the pyridine nucleus is postulated on the basis of the charge distribution in the quinoline nucleus and the energy barrier to subsequent polarization of the bonding so as to destroy the aromaticity of both rings, as was shown in the case of naphthalene. The fast reaction of the mono-ozonide to form the tetra-ozonide in the side reaction was unexpected, but ozonation of benzal aniline revealed that the anil structure present in the mono-ozonide can be rapidly attacked by ozone with accompanying breakdown of the aromatic nucleus.

The reaction rate with isoquinoline decreases greatly after ~1.4 moles of ozone has been absorbed per mole of isoquinoline. An unexpectedly large amount of NH_3 is obtained on decomposition. A mono-ozonide was shown to be the source of the ammonia. After absorption of 1.4 moles of ozone, the reaction product consists of 60% of the pyridinic mono-ozonide and 40% of the benzenoid diozonide, as in (L).

(L) 

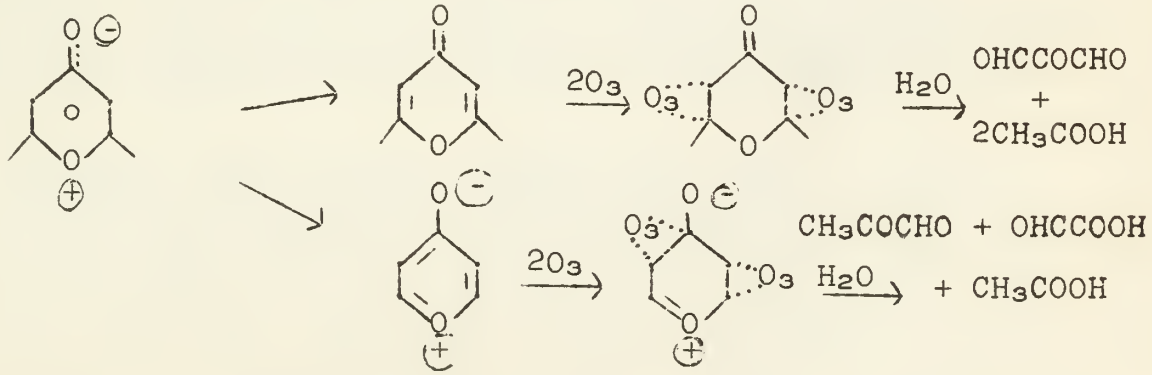
Thus, the pyridine nucleus reacts about 1-1/2 times as fast as the benzene nucleus. The isoquinoline mono-ozonide reacts slowly with additional ozone since there is no anil structure present.

V - γ -Pyrones:[14] Atypical carbonyl reactivity, oxonium salt formation, and unusually high dipole moment are properties of γ-pyrones which disagree with the classical representation, illustrated in (M) for 2,6-dimethyl- γ -pyrone. The actual structure is considered to be a resonance hybrid of contributing forms, some of which are shown below:



(M) (N) (O)

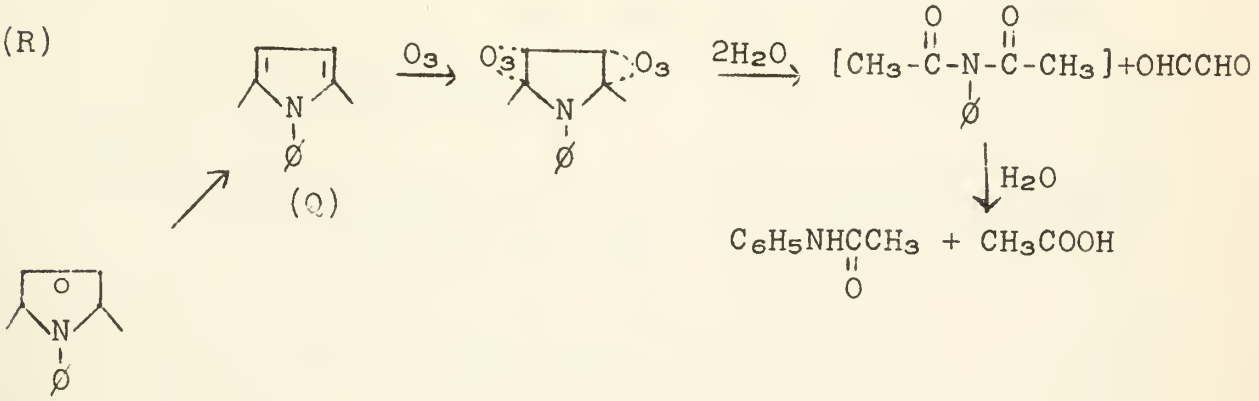
All the pyrones investigated[15] absorbed 2 moles of ozone per mole of pyrone at a rate faster than for benzene or toluene but slower than for a compound possessing 2 isolated double bonds such as in the classical structure (M). The decomposition products isolated (P) indicated reaction with ozone according to the canonical forms shown; no distinction can be made between (N) and (O) by the ozonation technique.

(P) 

Other γ-pyrones gave comparable results.

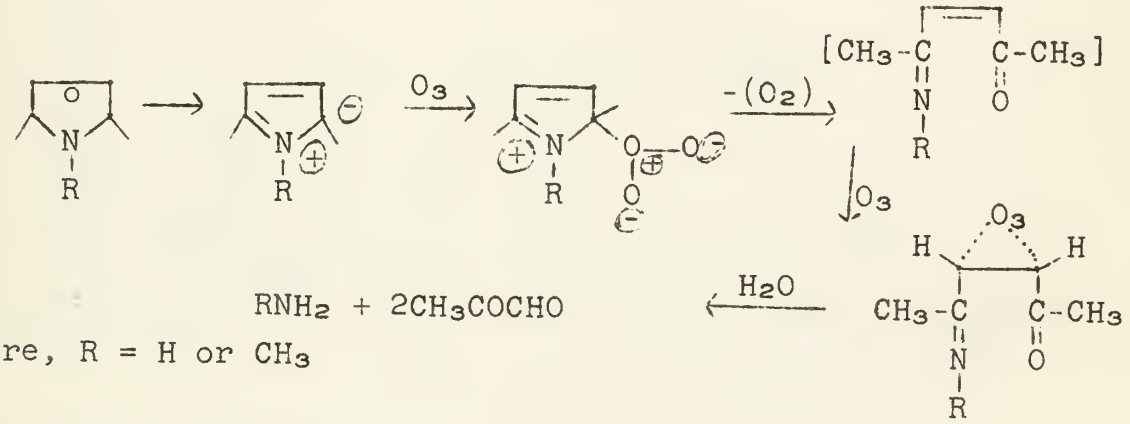
VI - Pyrroles:[14] Ozonolysis of pyrrole, 2,4-dimethylpyrrole, N-phenylpyrrole, and N-phenyl-2,5-dimethylpyrrole yields products which are explained by reaction of the pyrrole as if it were the classical imine structure (Q) in reaction scheme (R):[16]

(R)



However, 2,5-dimethylpyrrole and 1,2,5-trimethylpyrrole give ozonolysis products which are not explained by the imine structure. Reaction according to the imine structure can explain the small amount of glyoxal produced, but cannot explain the large amount of methylglyoxal isolated. A proposed mechanism, based upon a polar form of the pyrrole nucleus and utilizing the electrophilic initial step, rationalizes the methylglyoxal formation.

(S)



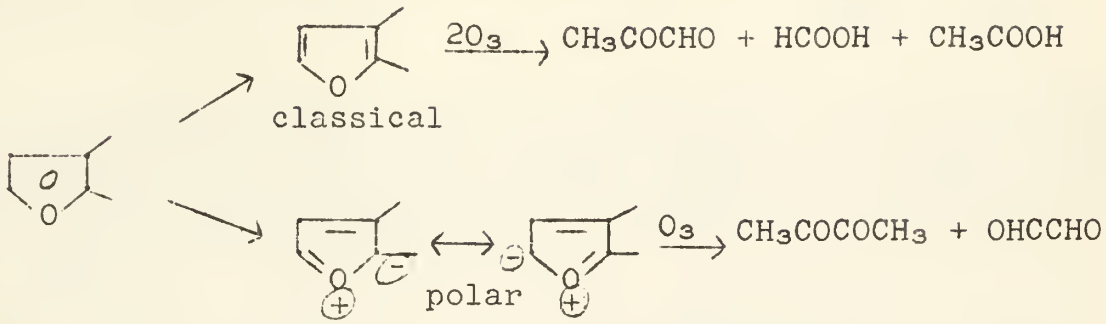
where, R = H or CH_3

Simultaneous reaction via the imine structure is also postulated. The rate of ozonation is too fast for measurement. The ratio of ozone absorbed to NH_3 or CH_3NH_2 produced is 2:1 which is in agreement with reaction via the imine and polar structures.

VII - Furans:[14] Furan reacts rapidly with ozone to form an ozonide which on decomposition produces glyoxal, a product which agrees with reaction via the classical structure. Methylglyoxal is a product of the ozonolysis of 2-methylfuran and 2,5-dimethylfuran. This product cannot be explained by the classical structure, but can be explained by reaction via a polar structure. The mechanism is best illustrated with 2,3-dimethylfuran which gives glyoxal, methylglyoxal, and dimethylglyoxal as ozonolysis products. These products and the absorption of 1.5 to 1.6 moles of ozone per mole of furan agree with the postulated simultaneous reaction via the classical and

polar structures, as in scheme (T).

(T)



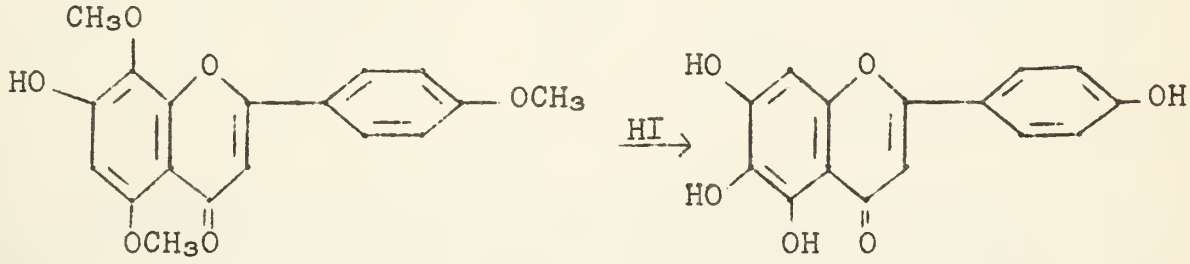
BIBLIOGRAPHY

1. Gilman, Organic Chemistry, vol I, chapter 3 (Fieser), J. Wiley and Sons, N.Y., 1942.
2. Levine and Cole, J. Am. Chem. Soc., 54, 338 (1932).
3. Haayman and Wibaut, Rec. Trav. Chim., 60, 842 (1941).
4. Boer, ibid., 67, 217 (1948).
5. Boer, ibid., 70, 1020 (1951); Boer and Sixma, ibid., 70, 997 (1951).
6. Sixma, Boer, and Wibaut, ibid., 70, 1005 (1951); Wibaut and Sixma, ibid., 71, 761 (1952).
7. E. R. Lovejoy, Organic Seminar, Univ. of Illinois, May 11, 1951.
8. Kampschmidt and Wibaut, Rec. Trav. Chim., 73, 431 (1954); Wibaut and Van Dijk, ibid., 65, 413 (1946).
9. Sixma, ibid., 68, 915 (1949).
10. Suyver and Wibaut, ibid., 64, 65 (1945).
11. Kooyman, ibid., 66, 201 (1947).
12. Sixma, ibid., 71, 1124 (1952).
13. Boer, Sixma, and Wibaut, ibid., 70, 509 (1951).
14. Wibaut, J. Chim. Phys., 53, 143 (1956).
15. Wibaut and Herzberg, Proc. Kon. Nederl. Akad. Wentensch., 56, 333 (1953).
16. Wibaut and Gulje, ibid., 54, 330 (1951).

ISOMERIZATION IN THE FLAVANOIDS

Reported by Jerome Gourse May 4, 1956

In the synthesis of flavones, demethylation is an essential step and hydriodic acid is a favored reagent. No complications were reported until 1930 when Wessely and Moser[1] observed that 5,8,4'-trimethoxy-7-hydroxyflavone yielded 5,6,7,4'-tetrahydroxyflavone on demethylation.

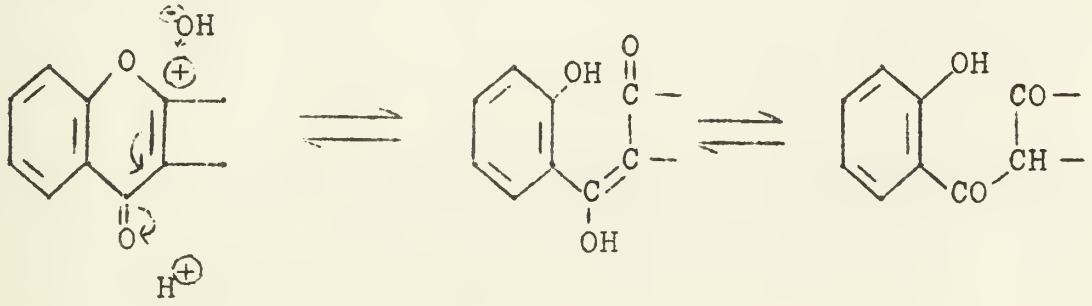


Wessely and Kallab[1] confirmed this isomerization by using the tetramethyl ether. This was also found to be true in the case of the 8-methoxy-5,7-dihydroxy[2] and the 5,7,8-trimethoxy compounds. Sastri and Seshadri[3] proved that the resultant 5,6,7-trihydroxy compounds do not undergo this isomerization and are therefore the stable forms.

A similar observation was made by Baker[4] in the demethylation of the 5,8-dihydroxy series of flavones yielding the corresponding 5,6-dihydroxy flavones.

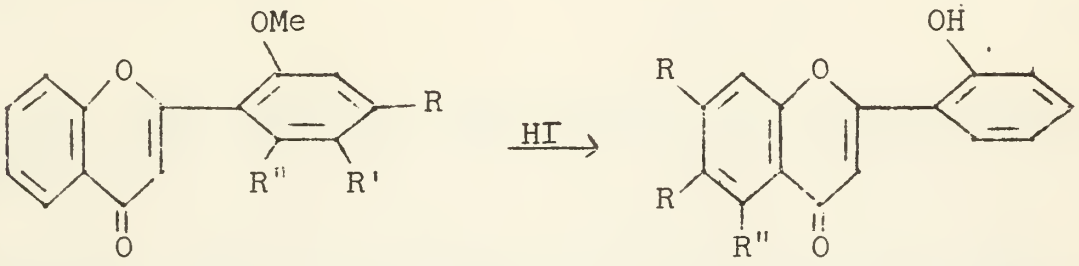
In the above cases, there is no substitution in the 3-position. None of the flavanols (3-hydroxy compounds) with the 5,7,8 arrangement of hydroxy groups have been known to isomerize except under drastic demethylation conditions. Studying appropriate isoflavones, it has been shown[5] that a phenyl group in the 3-position also inhibits this change. A methyl group does not seem to prevent this isomerization[6].

Mukerjee, Seshadri and Varadarajan[7] have proposed the following mechanism for this reaction:

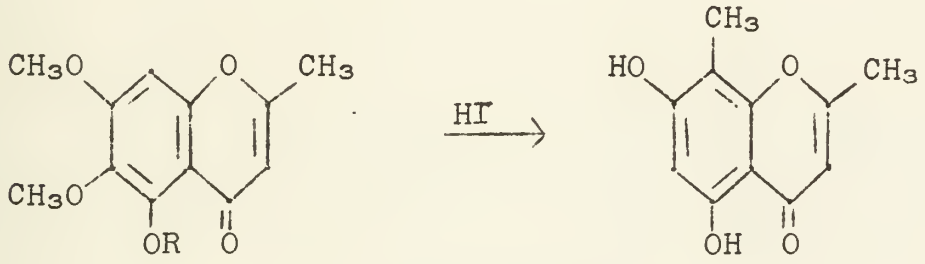


The presence of hydroxyl or phenyl groups in the 3-position seems to inhibit ring opening. This is attributed to their ability to reduce the electrophilic character of the 2-position.

Gallagher[8] has shown a similar rearrangement involving the 2'-hydroxy compounds.

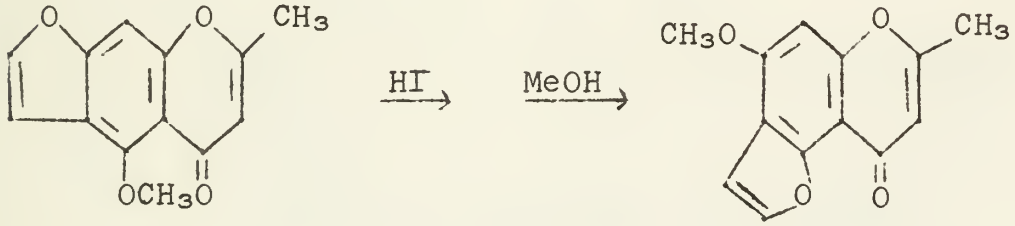


A similar isomerization is found in 8- and 6-methyl-chromones, flavones, and flavanols. In these cases the 6-methyl compound is isomerized to the 8-methyl compounds.[7,10]



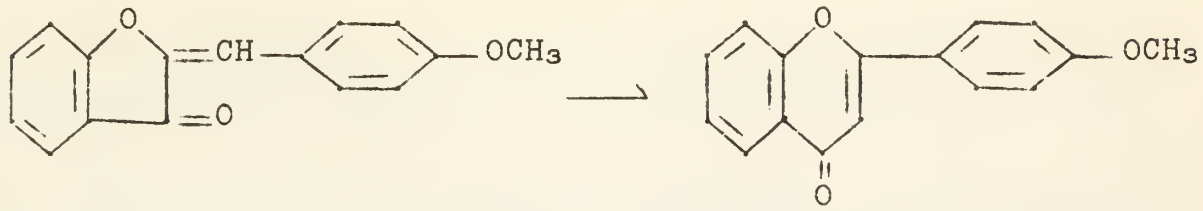
In this case also, the presence of a phenyl group in the 3-position, inhibits the isomerization.

In the furanochrome series, an isomerization has been found that involves the rearrangement of the furan ring.[9]



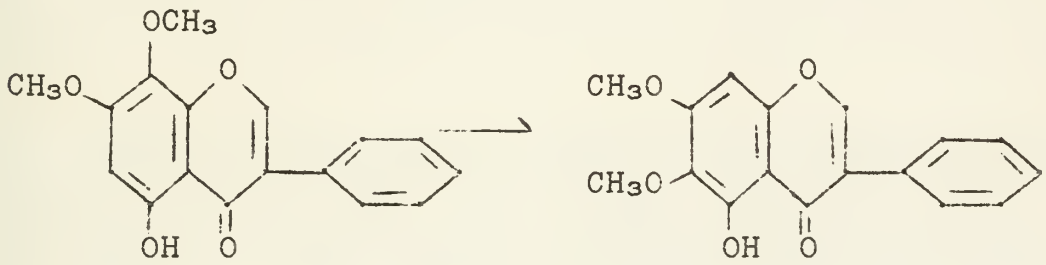
These isomerizations have been of great assistance in synthesizing the compounds resulting from the rearrangements. In view of the relative ease of preparation of the 5,7,8-trimethoxy compounds, their conversion to the 5,6,7-trihydroxy compounds offers a distinct advantage over direct synthesis of the latter.

Another type of rearrangement has been utilized in the synthesis of flavanones and flavanols. In certain cases 2-benzylidene coumaran-3-ones (aurones) can be treated with alcoholic potassium cyanide to give flavanones.[12]



These same compounds, when treated with alkaline hydrogen peroxide, yield a mixture of flavanols as well as the aurome epoxides.[13]

Not only has isomerization been brought about in acid solution but also in basic solution. It has been reported[14] that when 5-hydroxy-7,8-dimethoxy-isoflavone is boiled with 2% absolute alcoholic potassium hydroxide for 15 minutes, the isomeric 5-hydroxy-6,7-dimethoxy isoflavone is produced in 60% yield.



BIBLIOGRAPHY

1. S. K. Mukerjee and T. R. Seshadri, Chem. and Ind., 271 March (1955).
2. R. C. Shah, C. R. Mehta and T. S. Wheeler, J.Chem.Soc., 1555 (1938).
3. V. D. N. Sastri and T. R. Seshadri, Proc.Ind.Acad.Sci., 24A, 243 (1946).
4. W. Baker, J.Chem.Soc., 1922 (1939).
5. S. K. Mukerjee et.al., Proc.Ind.Acad.Sci., 35A, 46 (1952).
6. S. K. Mukerjee, T. R. Seshadri and S. Varadarajam, ibid., 35A, 82 (1952).
7. S. K. Mukerjee, T. R. Seshadri and S. Varadarajam, ibid., 37A, 127 (1953).
8. K. M. Gallagher, A. L. Hughes, M. D'Donnell, E. M. Philbin and T. S. Wheeler, J.Chem.Soc., 3770 (1953).
9. J. R. Clarke, G. Glaser and A. Robertson, J.Chem.Soc., 2260 (1948).
10. W. B. Whalley, Chem. and Ind., 1230 (1954).
11. K. V. Rao, T. R. Seshadri and N. Viswanadham, Proc.Ind. Acad. Sci., 29A, 72 (1949).
12. D. M. Fitzgerald, E. M. Philbin and T. S. Wheeler, Chem. and Ind., 130 (1952).
13. W. E. Fitzmaurice, W. I. O'Sullivan, E. M. Philbin and T. S. Wheeler, Chem. and Ind., 652 (1955).
14. V. B. Mahesh and T. R. Seshadri, J. Sci. Ind. Res., 14B, 671 (1955).

VITAMIN B_{12}

Reported by L. R. Haefele May 11, 1956

The isolation of vitamin B_{12} from liver extracts by Smith[1,2] and Folkers[3] in 1948 marked the beginning of a series of investigations leading to the complete elucidation of the structure of one of the most complex molecules known.

The vitamin is an odorless, tasteless, red, crystalline compound with the rather formidable empirical formula $C_{63}H_{90}N_{14}O_{14}PCo$. It is active in microgram quantities against pernicious anemia and is a growth factor for several micro-organisms.

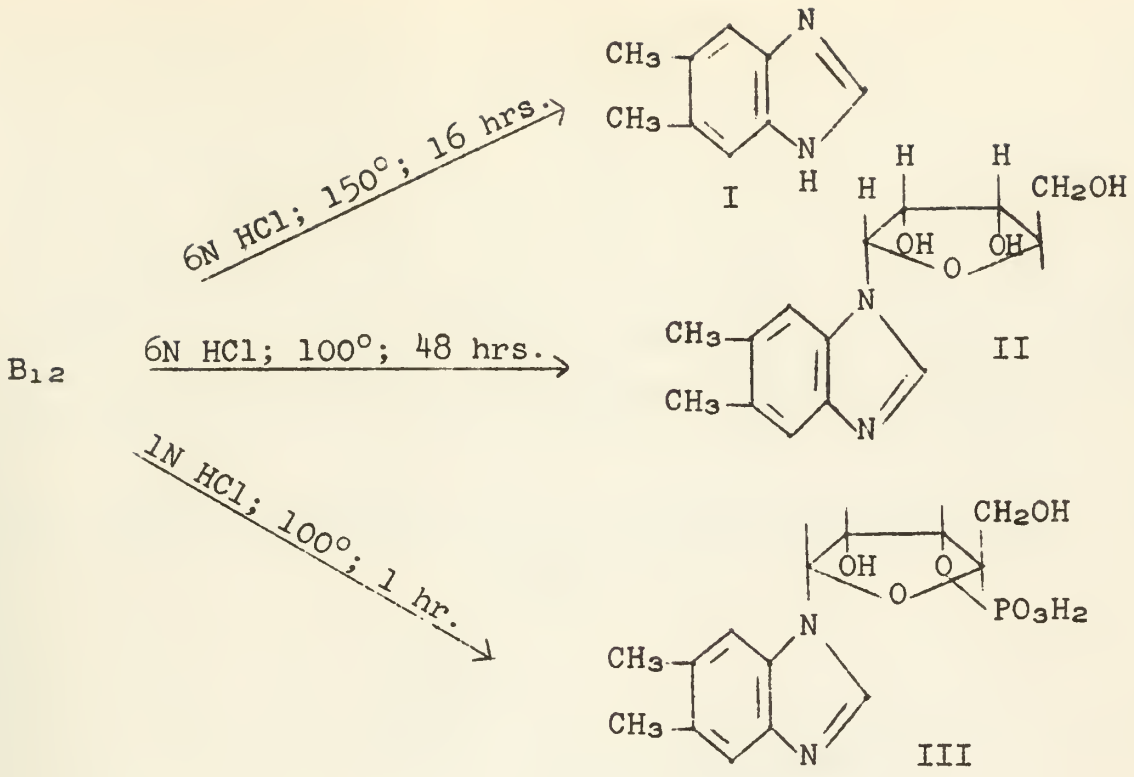
From the beginning, there were indications that the structure of B_{12} differs greatly from that of any other substance known. Thus the discovery that the molecule contains cobalt[4,5] was somewhat surprising, since, although cobalt was recognized as an essential trace element in nutrition, no biochemical role had been assigned to it. Further, the cobalt atom was found to be complexed with a cyanide ion[6]; until this time, most cyano compounds had been considered to be highly toxic.

A great deal of information concerning the structure of the vitamin was obtained by a study of the products of acid hydrolysis, which gave rise to large amounts of ammonia (5-6 moles) and a red, acidic cobalt-containing gum, as well as a number of other products, depending upon the conditions employed.

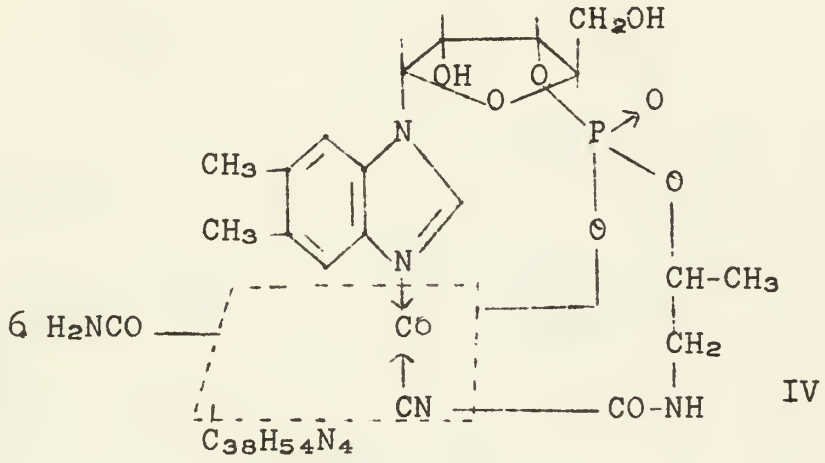
Heating with 20 per-cent hydrochloric acid followed by paper chromatography produced a compound which gave a purple color with ninhydrin[7]. After some confusion[7,8], this was shown to be D-1-amino-2-propanol[9].

Hydrolysis of vitamin B_{12} with 6N hydrochloric acid at 150° for sixteen hours gave rise to a basic compound with a characteristic ultraviolet spectrum, which suggested that it might be a substituted benziminazole[10-12]. By degradation and synthesis, it was shown to be 5,6-dimethylbenziminazole (I). Milder conditions (6N hydrochloric acid at 100° for 48 hours) led to the corresponding 1-α-D-ribofuranoside (II)[13], while 1N acid at 100° for one hour gave the 3'-phosphate derivative (III)[14,15], the alternative 2'-phosphate structure being eliminated by X-ray methods later on. The structures of II and III were confirmed by degradation and synthesis.

Acid hydrolysis under still milder conditions, using paper electrophoresis, led to the conclusion[16] that the vitamin contains at least four and probably six primary amide groups, and also that the propanolamine residue was present as a phosphate ester on the hydroxyl, and as an amide on the amino end.



Spectroscopic studies[17] showed that the benziminazole ring is co-ordinated directly to the cobalt atom. This led to the proposal[9] of the partial structure IV for the vitamin.



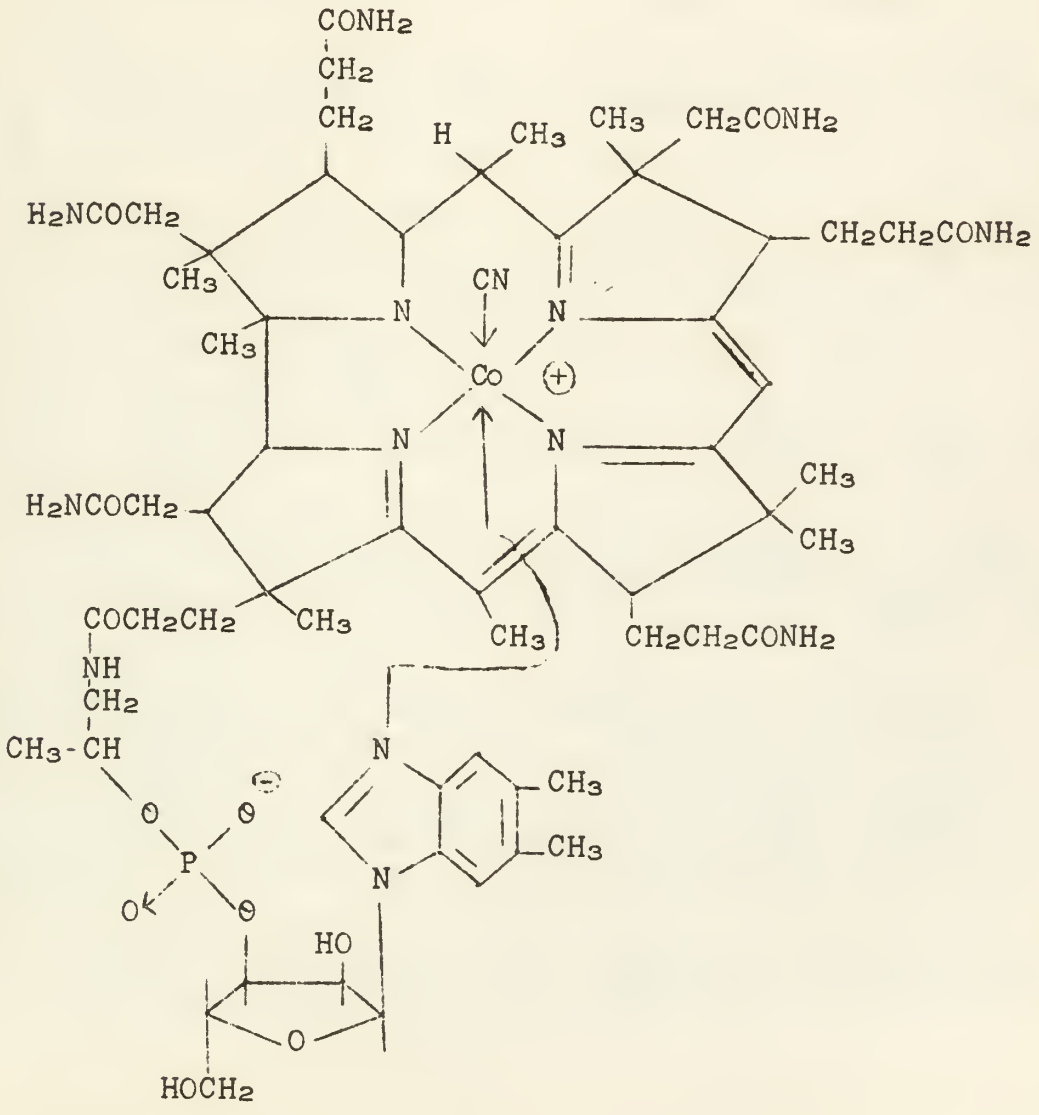
Until late. in 1954, little was known about the nature of the groups surrounding the cobalt atom. Some confusion resulted when Karrer[18] isolated succinic, methylsuccinic and dimethylmalonic acids from permanganate oxidation of the red gum obtained on acid hydrolysis of B_{12}. He suggested that there might be a terpene type of structure present in the molecule.

The first real break in this phase of the work came when Todd[19] was able to isolate a crystalline hexacarboxylic acid from a red gum obtained by hydrolysis with 30 per-cent sodium hydroxide at 150° for one hour.

Hodgkin and co-workers[20] had begun X-ray studies on the vitamin shortly after its discovery. They were able to confirm the structure of the nucleotide portion of the molecule and to place the phosphate definitely in the 3'-position of the ribose. Furthermore, the structure about the cobalt seemed to be similar to that of the porphyrins, but with one carbon missing. This was so unusual that they were hesitant to accept it. However, when this same pattern showed up on X-ray analysis of Todd's hexacarboxylic acid, it appeared certain that the atoms were, in fact, arranged in this way. Further refinements in the procedure finally led to the placement of all of the atoms in the molecule, giving the structure[21-23] shown below. The only part of the structure which was in the least doubtful was the placement of the conjugated double bond system.

Todd has assigned this on the basis of both the X-ray data and on the results of chlorination studies[22-24].

VITAMIN B_{12}



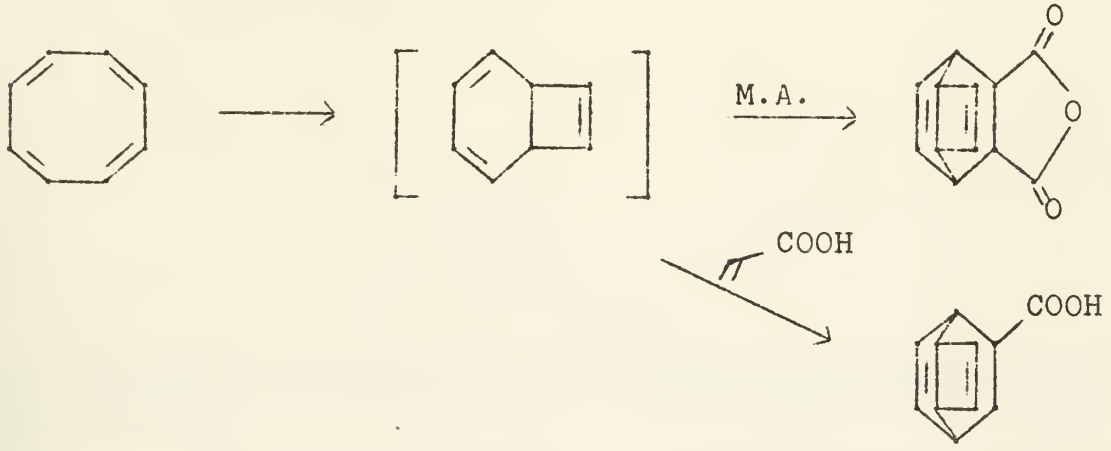
BIBLIOGRAPHY

1. E. L. Smith and L. F. J. Parker, Biochem. J., 43, viii (1948).
2. E. L. Smith, Nature, 161, 638 (1948).
3. E. L. Rickes, N. G. Brink, F. R. Koniuszy, T. R. Wood and K. Folkers, Science, 107, 936 (1948).
4. E. L. Smith, Nature, 162, 144 (1948).
5. E. L. Rickes, N. G. Brink, F. R. Koniuszy, T. R. Wood and K. Folkers, Science, 108, 134 (1948).
6. N. G. Brink, F. A. Kuehl and K. Folkers, Science, 112, 354 (1950).
7. B. Ellis, V. Petrow and G. F. Snook, J. Pharm. Pharmacol. 1, 60, 950 (1949).
8. G. Cooley, B. Ellis and V. Petrow, J. Pharm. Pharmacol., 2, 128 (1950).
9. D. E. Wolf, W. H. Jones, J. Valiant and K. Folkers, J. Am. Chem. Soc., 72, 2820 (1950).
10. E. R. Holiday and V. Petrow, J. Pharm. Pharmacol., 1, 734 (1949).
11. G. R. Beaven, E. R. Holiday, E. A. Johnson, B. Ellis, P. Mamalis, V. Petrow and B. Sturgeon, J. Pharm. Pharmacol., 1, 957 (1949).
12. N. G. Brink and K. Folkers, J. Am. Chem. Soc., 71, 2951 (1949).
13. N. G. Brink, F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill and K. Folkers, J. Am. Chem. Soc., 72, 1866 (1950).
14. J. G. Buchanin, A. W. Johnson, J. A. Mills and A. R. Todd, J. Chem. Soc., 2845 (1950).
15. E. A. Kaczka, D. Heyl, W. H. Jones and K. Folkers, J. Am. Chem. Soc., 74, 5549 (1952).
16. J. B. Armatage, J. R. Cannon, A. W. Johnson, L. F. J. Parker, E. L. Smith, W. H. Stafford and A. R. Todd, J. Chem. Soc., 3849 (1953).
17. G. R. Beaven, E. R. Holiday, A. W. Johnson, B. Ellis, V. Petrow and G. Cooley, J. Pharm. Pharmacol., 2, 733 (1950).
18. H. Schmid, A. Ebnöther and P. Karrer, Helv., 36, 65 (1953).
19. J. R. Cannon, A. W. Johnson and A. R. Todd, Nature, 174, 1168 (1954).
20. C. Brink, D. C. Hodgkin, J. Lindsey, J. Pickworth, J. H. Robertson and J. G. White, Nature, 174, 1169 (1954).
21. D. C. Hodgkin, J. Pickworth, J. H. Robertson, K. N. Trueblood, R. J. Prosen and J. G. White, Nature, 176, 325 (1955).
22. D. C. Hodgkin, A. W. Johnson and A. R. Todd, "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds", Special Publication no. 3, The Chemical Society, London, (1955).
23. A. W. Johnson and A. R. Todd, Endeavor, 15, 29 (1956).
24. R. Bonnet, J. R. Cannon, A. W. Johnson, I. Sutherland and A. R. Todd, Nature, 176, 328 (1955).

REACTIONS OF CYCLOOCTATETRAENE AND ITS DERIVATIVES

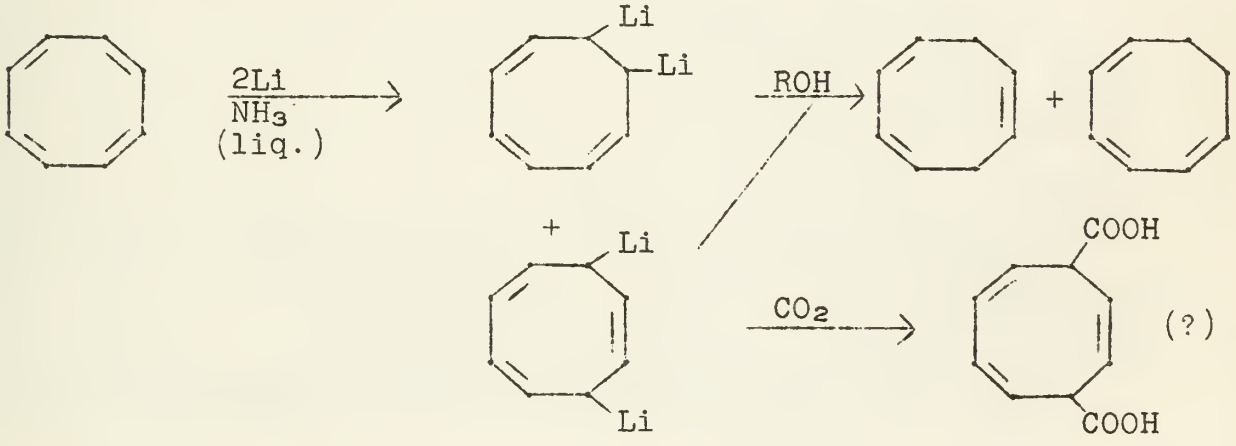
Reported by W. A. Remers May 11, 1956

Reactions of Cyclooctatetraene: In Diels-Alder reactions, cyclooctatetraene reacts as a diene in the form of its valence tautomer, bicyclo (4.2.0) octa-2,4,7-triene, with maleic anhydride or acrylic acid.[1,12]



Catalytic hydrogenation gives cyclooctane. No difference in the reactivity of individual double bonds is observed.[1]

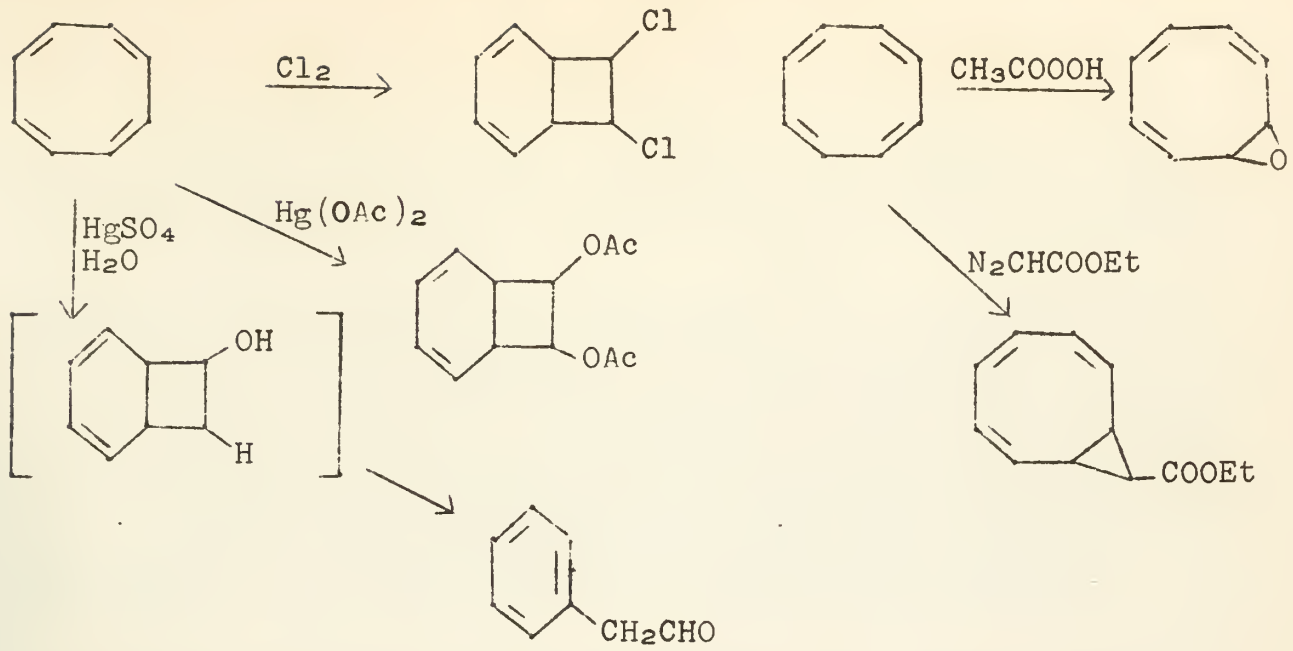
With lithium in liquid ammonia, 1,2- and 1,4-dilithium salts are formed. The lithium atoms may be displaced by protons to yield a mixture of cyclooctatrienes or may be displaced by carbon dioxide to form a dicarboxylic acid.[1,2]



A similar mixture of cyclooctatrienes is obtained with sodium in liquid ammonia.[3]

Phenyllithium adds to give phenylcyclooctatetraene and the mixture of cyclooctatrienes. An equivalent of lithium hydride must be transferred from the initial adduct to a molecule of cyclooctatetraene for this reaction to occur. Some phenylcyclooctatriene is also formed.[4]

Addition reactions initiated by electrophilic attack proceed with bridging and addition to the cyclobutene type double bond. Chlorination,[1,5] hydration,[1] and reaction with mercuric acetate[1,6] are examples.

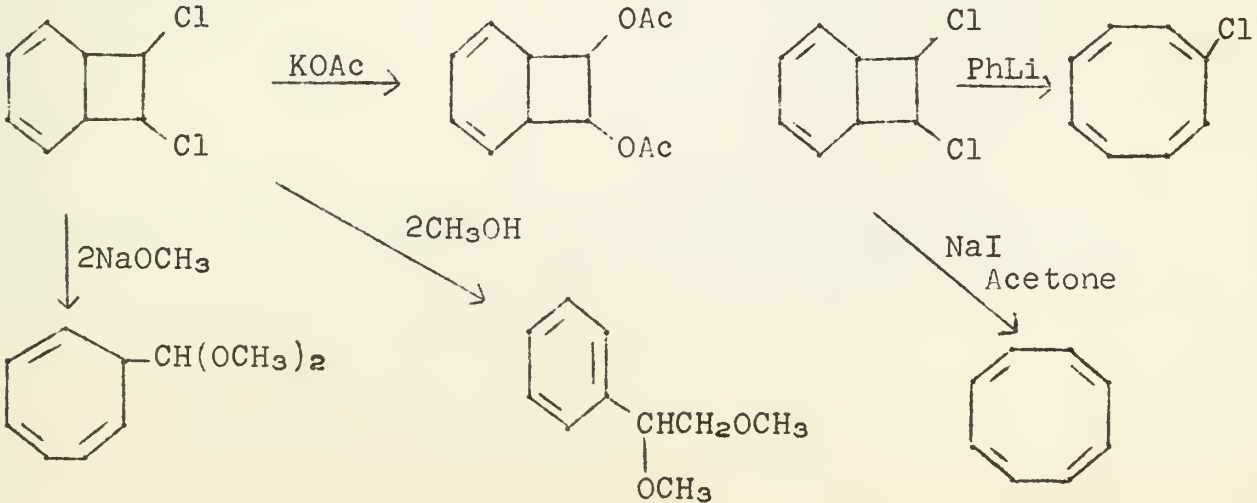


Reactions with peracids[1,7] or ethyl diazoacetate[8] form three membered ring derivatives with retention of the eight membered ring.

With strong oxidizing agents, monosubstituted or para-di-substituted benzene derivatives are formed.[1] Aqueous permanganate yields benzaldehyde and benzoic acid. Alkaline hypochlorite yields terephthaldialdehyde, benzaldehyde, and benzoic acid. Chromic acid yields terephthaldialdehyde and terephthalic acid.

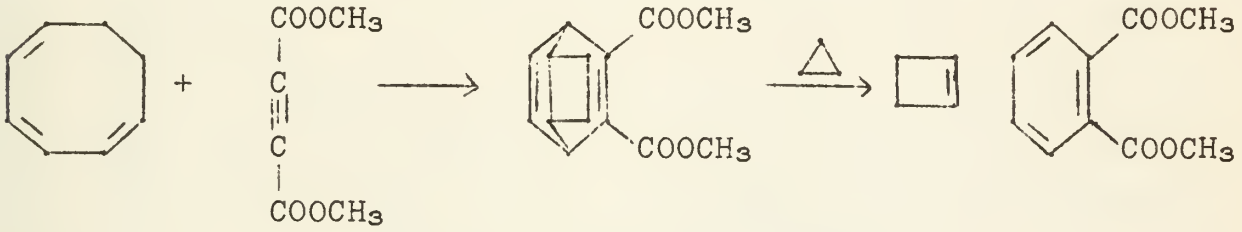
Chlorocyclooctatetraene, when heated in an inert atmosphere, rearranges to cis-β-chlorostyrene[5,9] which is thermodynamically more stable. Bromocyclooctatetraene reacts with lithium to give cyclooctatetraenyl lithium, which reacts with carbon dioxide to form cyclooctetraenecarboxylic acid.[10]

Reactions of Bicyclo (4.2.0) octadiene structures: Nucleophilic substitution leads to several different types of structures. With 7,8-dichlorobicyclo (4.2.0) octa-2,4-diene, the two chlorine atoms may be replaced by acetate without change in the ring system.[1,11] Methanolysis, however, leads to ring opening and formation of α,β-dimethoxyethylbenzene.[1] Reaction of the dichloro compound with sodium methoxide gives 2,4,6-cycloheptatriene-1-carboxaldehyde dimethyl acetal.[6]

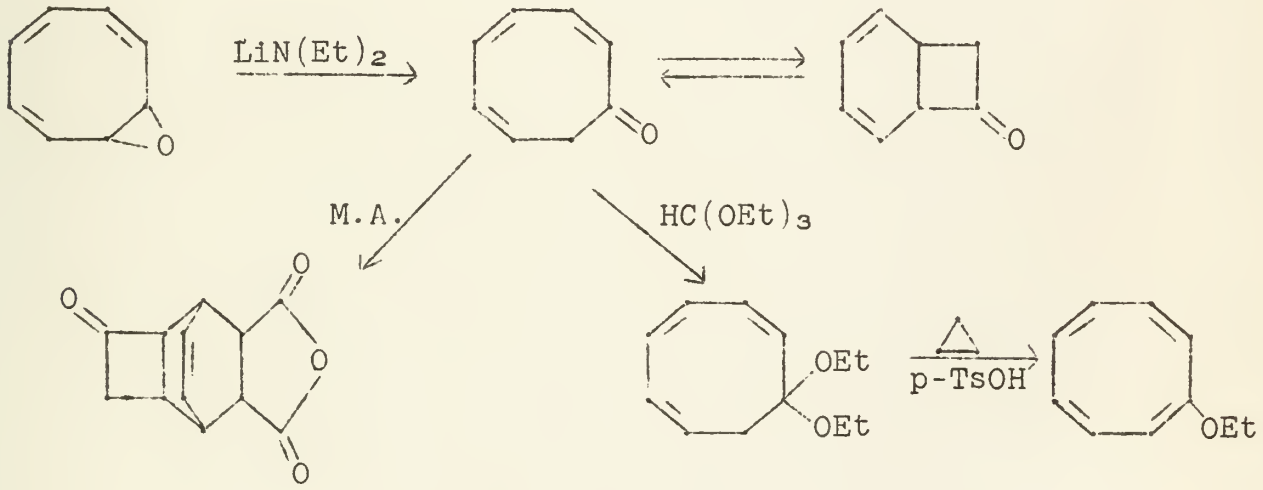


Elimination reactions initiated by nucleophilic attack regenerate cyclooctatetraene structures by a reversal of the bridging step. The dichloro compound gives chlorocyclooctatetraene when it reacts with phenyllithium,[5] and cyclooctatetraene when it reacts with sodium iodide in acetone.[9]

Reactions of Cyclooctatriene Structures: By heating briefly to 80- 100° a mobile equilibrium is established between 1,3,5-cyclooctatriene (85%) and its valence tautomer, bicyclo (4.2.0) octa-2,4-diene.[12] The presence of the bicyclic isomer may be demonstrated by hydrogenation to bicyclo (4.2.0) octane or ozonization and peroxidation to cis-1,2-cyclobutanecarboxylic acid. Dimethylacetylenedicarboxylate adds to 1,3,5-cyclooctatriene to give an adduct possessing the cyclobutane structure. Pyrolysis of the adduct gives cyclobutene and o-dimethyl phthalate.



1,3,5-cyclooctatriene-7-one, formed by the lithium diethylamide catalyzed rearrangement of cyclooctatetraene oxide,[7,13] is also in equilibrium with a valence tautomer, bicyclo (4.2.0) octa-2,4-diene-7-one. About 5% of the bicyclic isomer is present.



The reaction of 1,3,5-cyclooctatriene-7-one with maleic anhydride gives an adduct with the cyclobutanone structure. With ethyl orthoformate, 1,3,5-cyclooctatriene-7-one forms a ketal which splits out ethanol to form ethoxycyclooctatetraene when heated with p-toluenesulfonic acid.[13]

REFERENCES

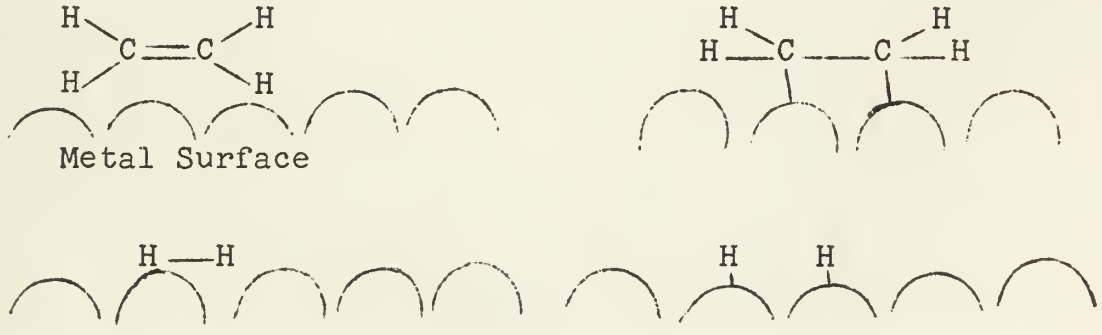
1. Reppe, W., Schlicting, O., Klager, K., and Toepel, T., Ann., 560, 1 (1948).
2. Cope, A. C., Stevens, C. L., and Hochstein, F. A., J. Am. Chem. Soc., 72, 2510 (1950).
3. Craig, L. E., Elfson, R. M., and Ressa, T. J., J. Am. Chem. Soc., 75, 480 (1953).
4. Cope, A. C. and Kinter, M. R., J. Am. Chem. Soc., 72, 630 (1950).
5. Cope, A. C. and Burg, M., J. Am. Chem. Soc., 74, 169 (1952).
6. Cope, A. C., Nelson, N. A., and Smith, D. S., J. Am. Chem. Soc., 76, 1100 (1954).
7. Cope, A. C. and Tiffany, M. D., J. Am. Chem. Soc., 4158 (1951).
8. Akiyoshi, S., and Matsuda, T., J. Am. Chem. Soc., 77, 2476 (1955).
9. Benson, R. E. and Cairns, T. L., J. Am. Chem. Soc., 72, 5355 (1950).
10. Cope, A. C., Burg, M., and Fenton, S. W., J. Am. Chem. Soc., 74, 173 (1952).
11. Cope, A. C. and Herrick, E. C., J. Am. Chem. Soc., 72, 983 (1950).
12. Cope, A. C., Haven, A. C., Jr., Ramp, L. F., and Trumbull, E. R., J. Am. Chem. Soc., 74, 4876 (1952).
13. Cope, A. C., Schaeren, S. F., and Trumbull, E. R., J. Am. Chem. Soc., 76, 1096 (1954).

SOME ASPECTS OF THE MECHANISMS OF CATALYTIC HYDROGENATION

Reported by C. K. Sauers May 18, 1956

Heterogeneous catalysis, of which hydrogenation is only one example, contains such dissimilar transformations as the Fischer-Tropsch synthesis, the Oxo process, catalytic dehydrogenation, petroleum "cracking", the ortho-para hydrogen conversion, and the Haber process for ammonia.[1] Principles derived from a study of the course of any one of these reactions have been generally applied to studies of them all and correlations between them have been particularly useful in attempts to understand their mechanisms. It should not be thought, however, that the mechanisms are identical; in the field of hydrogenation alone there are almost as many detailed mechanisms as there are reactions which have been thoroughly studied.[2] For this reason, this abstract is concerned with the elucidation of some general principles which will then be applied to a few specific examples of the reduction of unsaturated molecules.

Perhaps the most intriguing fact about hydrogenation is the activity and selectivity of certain metals in promoting the reaction. A large amount of research has been devoted to the study of metals involved in hydrogenation reactions and the results have led to a substantial increase in our understanding of the processes involved.[3] The overall process in the hydrogenation of an olefin involves the breaking of a carbon-carbon bond and of a hydrogen-hydrogen bond with the resultant formation of two new carbon-hydrogen bonds. The cleavage steps usually occur homolytically,[3] but the energies required to unpair the electrons in a carbon-carbon or hydrogen-hydrogen bond are so large and the resulting radicals are so unstable that some unique role in supplying this energy and in stabilizing the radical products must be performed by the catalyst. It is known that metals of the transition group are capable of adsorbing large amounts of hydrogen, deuterium and unsaturated molecules by a process known as chemisorption,[4] and illustrated below for ethylene and hydrogen:[5,6]



This process can continue to occur in this simple manner until a monolayer of adsorbed molecules completely covers these metals. Thus the first step in a hydrogenation reaction is the formation of radicals on the surface of the metal in such a manner that these radicals are stable relative to free radicals.

Another characteristic which is demanded of these species is that they be held weakly enough so that reaction may take place and the products desorbed. This is necessary because new molecules must occupy the surface sites in order for the reaction to continue.

The ability of certain transition metals to function in these processes of adsorption and desorption can be largely explained in terms of the electronic structural theory of metals advanced by Pauling.[7] This theory proposes that the bonding orbitals of the transition metals are hybrids of d, s, and p atomic orbitals and that metallic and atomic orbitals of mainly d character remain which gives these metals some of their characteristic properties. Dowden[8] and Dilke, Maxted, and Eley[9] suggested that the high activity of catalysts depends upon chemisorption involving the atomic d orbital. It was shown that a change in the magnetic susceptibility of palladium occurs upon adsorption of dimethyl sulfide.[9] Beeck then supplied very convincing evidence for such bonding of hydrogen and ethylene to various metal surfaces. He showed that as the "percent d character"[7] of the metallic bonds was increased, the heats of adsorption of both hydrogen and ethylene were decreased and that the catalytic metals had both low heats of adsorption and high amounts of "d character".[10] This correlation leads to an expected order of metal activity,

$$Rh > Pd > Pt > Ni > Fe > W \equiv Cr \equiv Ta,$$

which is in general agreement with the rates of hydrogenation of ethylene over these metals.

Another correlation which is based on the geometric arrangement of atoms in metal crystals can be made. This relationship is not quite so basic because the geometry of metals depends in turn on electronic factors. However a consideration of geometry will enable us to understand why only certain transition metals are particularly active catalysts when all of them have the requisite "d character".[11] If an olefin is chemisorbed on a metal surface, it has a carbon-carbon bond distance close to 1.54 Å and the bond angles will try to approximate 109° 28'. Since differences exist in the metal to metal atom distances, various chemisorbed molecules will have varying degrees of strain. On the 111 plance of nickel, the atoms are 2.47 Å apart and an olefin may be bonded so that the C-C-Ni angle is 105° 28'. On the 110 plane some nickel atoms are spaced 3.50 Å apart giving rise to a chemisorbed ethylene C-C-Ni angle of 122° 57' which represents considerably more strain. Hydrogenation proceeds faster on the 110 face because for high activity adsorption must be both rapid and <u>weak</u>. Figure I shows the results of applying this reasoning to a series of transition metals.[12]

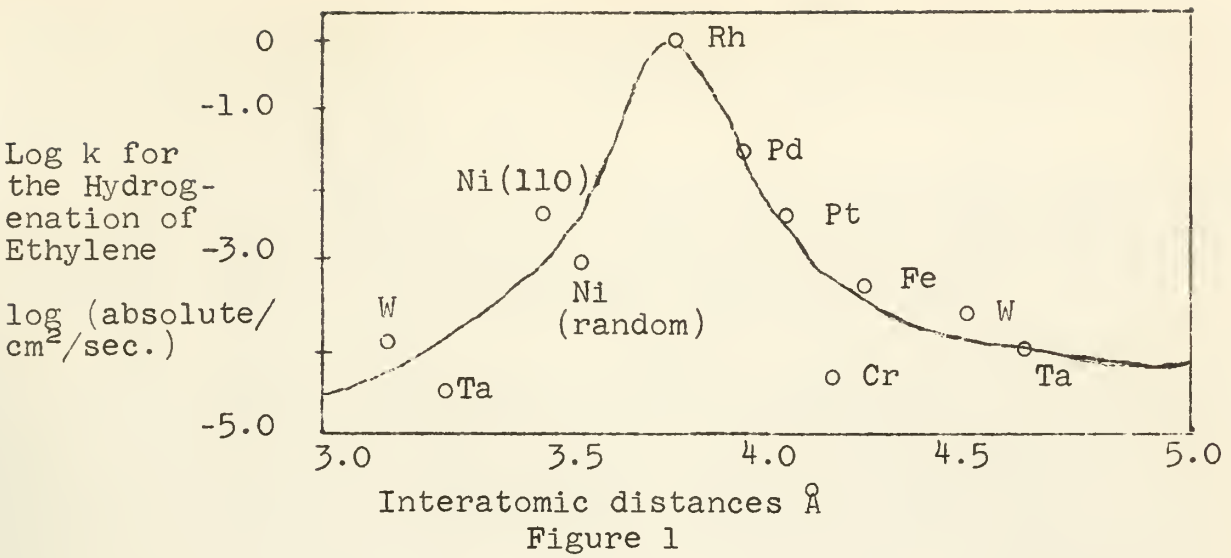


Figure 1

The catalytic hydrogenation of ethylene over nickel has been extensively studied,yet there is still no general agreement concerning the details of its mechanism.[2] The initial rate kinetics in the gas phase are usually reported to be

$$-\frac{dP}{dT} = k [H_2] [C_2H_4]^{0}$$, though the ethylene exponent is sometimes slightly negative.[2,14] This indicates that ethylene is adsorbed preferentially on the catalyst surface. That addition does not occur in one step has been demonstrated by much experimental evidence. It was shown by Twigg that the infrared spectrum of ethanes obtained by hydrogenation with a non-equilibrated mixture of H_2 and D_2 is identical to that obtained from an equilibrated mixture containing H_2, D_2 and HD.[15] If the reaction is interrupted in the beginning stages, ethanes found have less than the stoichemetric amount of deuterium.[16]

Thus the existence of half hydrogenated states has been postulated.[2,17] These are of the nature CH_3CH_2--Ni. The process for their formation is the most widely disputed detail in the mechanism of ethylene hydrogenation, and many proposals, all in some way supported by experimental evidence, have been advanced.[13] Once they are formed, they supply a ready explanation for the fact that in the deuteration of ethylene, ethylenes and ethanes have been detected containing from 0 to 4 or 6 deuterium atoms. These half-hydrogenated states are important in all the hydrogenations studied though their method of formation may be different in each case.

In spite of these wide differences, some general principles have evolved concerning olefin hydrogenations. The rates of these reactions obey the following expression where E is the energy of the desorption process, A is the Arrhenius frequency factor, R is the ideal gas constant, and T is the absolute temperature.[3]

$$\text{Specific rate} = A\, e^{-E/RT}$$

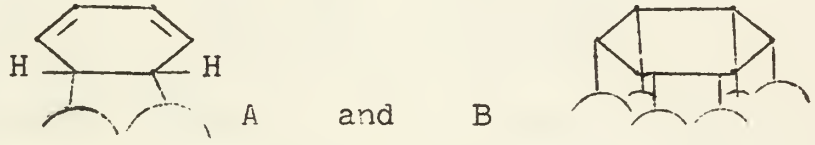
Increasing the olefin substitution decreases E but at the same time decreases the effectiveness of collisions and thus decreases A. These effects tend to cancel each other and lead to the interesting result that the rates for addition to simple olefins vary little with substitution.[2]

Acetylene hydrogenation presents an interesting case because the expected half hydrogenated state can "rearrange" to a vinyl radical. That this occurs is substantiated by the evidence of polymers formed in many acetylene hydrogenations.[18]

The hydrogenation of cyclopropane occurs in a somewhat different manner from simple olefin hydrogenation.[19] In this case hydrogen atoms are preferentially adsorbed on the catalyst and thus may react either one or two at a time with the approaching gaseous cyclopropane. In cases where the reaction involves addition of one atom of hydrogen the resulting half-hydrogenated state can readily give rise to products containing 0 to 8 deuterium atoms. Since hydrogen or deuterium is preferentially adsorbed, the expected course rate law,

$$-\frac{dP}{dT} = k\,[\,C_3H_6\,]\,[\,D_2\,]^{\circ}$$ is observed experimentally over platinum from -18 to 200°.

In the catalytic hydrogenation of benzene and of aromatics in general, the picture is again slightly different.[20,21] A consideration of two possible structures for a chemisorbed benzene molecule,



A and B

leads to the conclusion that B should be far more stable than A, and the fact that no cyclohexene or cyclohexadiene is detected at intermediate stages in the reaction, substantiates this. Some attempts have been made to correlate metal surface structure with catalytic activity in cyclohexane dehydrogenation and benzene hydrogenation, but in the latter case these attempts lead to conflicting reports in the literature.[22]

The study of more complicated molecules, which in general seem to have simpler mechanisms, has led to further knowledge concerning the stereochemistry of the reaction. There are many examples of stereospecific hydrogenations, but only a few are chosen for consideration here. Siegel has shown that hydrogenation of methyl substituted cyclohexanones where methyl's preference for the equatorial position controls the stereochemistry in the starting material leads to addition from the side where the non-bonded interactions between C_3 and C_5 of the ring and the catalyst are at a minimum.[23] If other effects are equal, this principle is general for cyclohexanones. Cholestanone gives α-cholestanol, while coprostanone leads to β-coprostanol upon hydrogenation.[24]

Further evidence for stereospecificity is given in the 3-α- and β-cholesterol series. The α-derivative undergoes hydrogenation from the top of the molecule giving the α-coprostanol while 3-β-cholesterol gives β-cholestanol.[25]

This evidence for high stereospecificity does not supply proof that the mechanisms for these reactions are simple additions. In at least one complex molecule, hydrogenation reactions employing deuterium have shown that the mechanism is still complicated. To explain the fact that cholesteryl acetate upon hydrogenation with deuterium in acetic acid-d over platinum produces cholestanyl acetate with 2.55 D/mole, Fukishima has postulated a migration of the point of attachment of the chemisorbed molecule via a half hydrogenated state.[26] This is done by addition of a deuterium and loss of a hydrogen and leads to the observed incorporation of the more than theoretical amount of deuterium. Oxidation of various positions to carbonyl groups and subsequent exchange has substantiated his hypothesis.

Though much work has been done on the mechanisms of hydrogenation, the picture is still far from clear and even more work remains to be done before a complete understanding of these reactions at metal surfaces can be obtained.

BIBLIOGRAPHY

1. P. H. Emmett, (Editor), "Catalysis", Reinhold Publishing Corporation, Vols. I,II, and III, New York, (1954-1955).
2. G. C. Bond, Quart. Rev., 8, 279 (1954).
3. B. M. W. Trapnell, ibid., 8, 404 (1954).
4. J. E. Lennard-Jones, Trans. Faraday Soc., 28, 333 (1932).
5. E. B. Maxted, J. Chem. Soc., 1990 (1949).
6. J. Sheridan, J. Chem. Soc., 373 (1944).
7. L. Pauling, Phys. Review, 54, 899 (1938); Proc. Roy. Soc., A, 196, 343 (1949).
8. D. A. Dowden, Research, 1, 239 (1948); J. Chem. Soc., 242 (1950).
9. M. H. Dilke, E. B. Maxted and D. D. Eley, Nature, 161, 804 (1948).
10. O. Beeck, Discuss. Faraday Soc., 8, 118 (1950).
11. J. H. Twigg and E. K. Rideal, Trans. Faraday Soc., 36, 533 (1940).
12. O. Beeck, Rev. Mod. Physics, 17, 61 (1945).
13. "Heterogeneous Catalysis", Discuss. Faraday Soc., 8, 3(1950).
14. N. Thon and H. A. Taylor, J. Am. Chem. Soc., 75, 2747 (1953). D. D. Eley, Quart. Rev., 3, 209 (1949); T. Keii, J. Chem. Phys., 22, 144 (1954).
15. J. H. Twigg, Discuss. Faraday Soc., 7, 152 (1950).
16. J. Turkevich, D. O. Schissler and P. Irsa, J. Phys. Chem., 55, 1078 (1951).
17. I. Horiuti and M. Polyani, Trans. Faraday Soc., 30, 1164 (1934).
18. P. Sebatier and J. B. Senderens, Compt. rend., 128, 1173 (1899).
19. G. C. Bond and J. Turkevich, Trans. Faraday Soc., 50, 1335 (1954).
20. A. A. Balandin, Z. physikal. Chem., 2 B, 289 (1929); ibid., 3 B, 167 (1929).

21. B. M. W. Trapnell, "Advances in Catalysis", Academic Press, vol. 3, New York, (1951).
22. J. H. Long, J. C. W. Frazer and E. Ott, J. Am. Chem. Soc., 56, 1101 (1934); P. H. Emmett and N. Skau, J. Am. Chem. Soc., 65, 1029 (1943); O. Beeck and A. W. Ritchie, Discuss. Faraday Soc., 8, 159 (1950).
23. S. Siegel, J. Am. Chem. Soc., 75, 1317 (1953).
24. L. Ruzicka, Helv. Chim. Acta., 19E, 90 (1936).
25. J. R. Lewis and C. W. Shoppee, Chem. and Ind., 897 (1953); E. B. Hershberg et.al., J. Am. Chem. Soc., 73, 1144 (1951).
26. D. K. Fukushima and T. F. Gallagher, J. Am. Chem. Soc., 77, 139 (1955).

ORGANIC PEROXIDES

Reported by J. C. Little May 18, 1956

Almost every type of organic compound has been subjected to peroxidation. The valuable intermediates provided by organic peroxides are receiving new and widespread attention. It is worthwhile, therefore, to review these compounds as a class.

1. Peracids[1]

I. Preparation

A. $RCO_2R' + H_2O_2 \underset{\text{Low Temp.}(H^+)}{\rightleftharpoons} RCO_3H$

R'= -H or -COR

B. $RCHO + O_2$ (or O_2-O_3) $\xrightarrow{h\nu}$ RCO_3H

C. $RCOCl + H_2O_2 \longrightarrow RCO_3H$

D. $R_2C{=}C{=}O + H_2O_2 \longrightarrow R_2CHCO_3H$

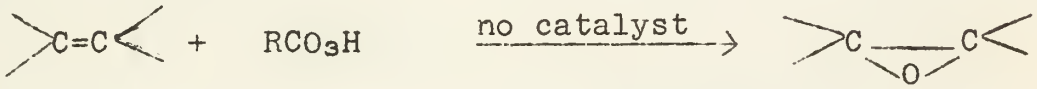
E. $RCO_2BO_2H_2 + H_2O_2 \longrightarrow RCO_3H$

F. $(RCO)_2O + NaBO_3 \longrightarrow RCO_3H$

II. Reactions

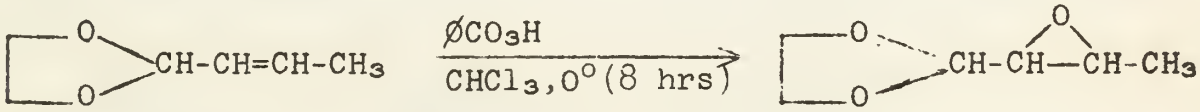
A. Oxidation of Unsaturated Compounds

1) Epoxide (Oxirane) Formation:



Perbenzoic, monoperphthalic and peracetic acids effect epoxide formation under mild conditions in a convenient solvent: yields are high and product isolation is not difficult. The peracid is usually made *in situ*; active oxygen is supplied by hydrogen peroxide or molecular oxygen (air) and the peracid is consumed as it is formed.

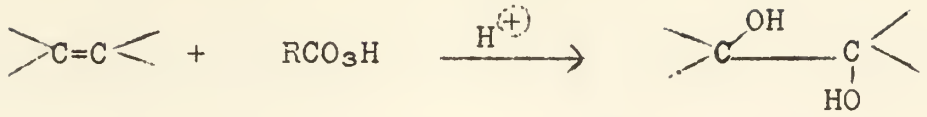
Example[2]:



Other examples: Ref. 3-9

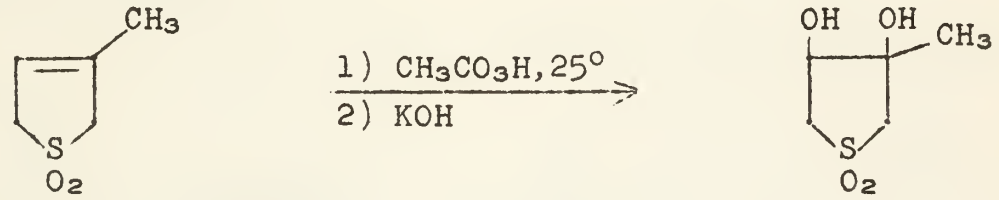
---

2) Preparation of α-glycols:



Peracetic acid is by far the most popular means of effecting this transformation. Again the procedure of producing the peracid *in situ* is usual. Performic acid has been found to be highly effective for isolated double bonds.[10] A comparative newcomer, peroxytrifluoroacetic acid, has been useful with negatively substituted olefins.[11,19,20]

Examples[12]:



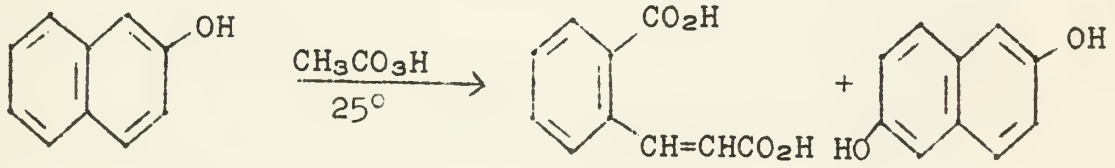
Other examples, Ref. 1, 13

---

3) Miscellaneous:

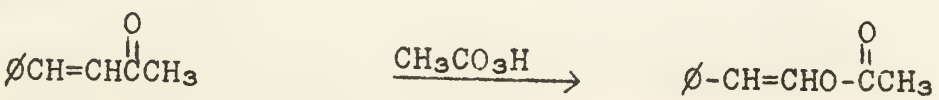
Peracids also attack active aromatic double bonds to give various oxidation products including quinones and ring-scission acids.

Example[14]:



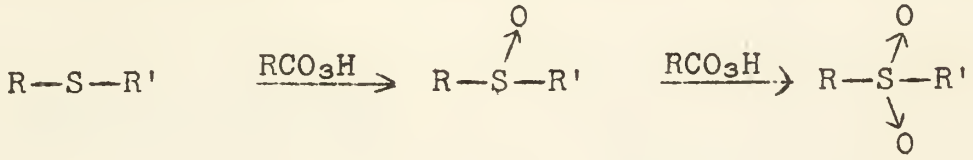
Peracid oxidation of α,β-unsaturated ketones gives vinyl esters. The epoxide is probably not an intermediate in this reaction.[15]

Example[15]:



B. Oxidation of Organic Sulfur Compounds

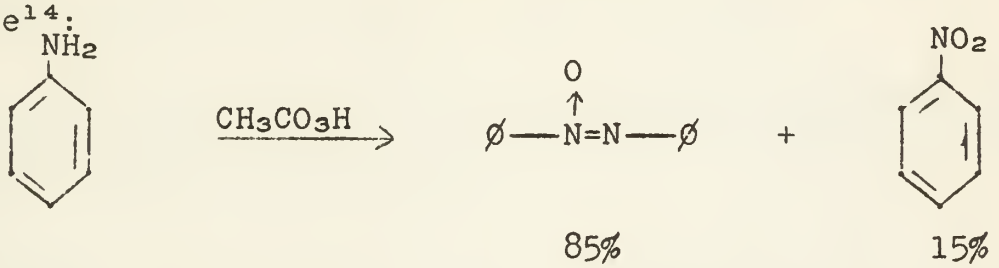
A very efficient and widely used application of organic peracids is the oxidation of organic sulfides and mercaptans to sulfoxides and sulfones.[1,16]



C. Oxidation of Amines and Azo Compounds

Amines are oxidized by peracids to nitroso, azo, azoxy and nitro compounds.[1]

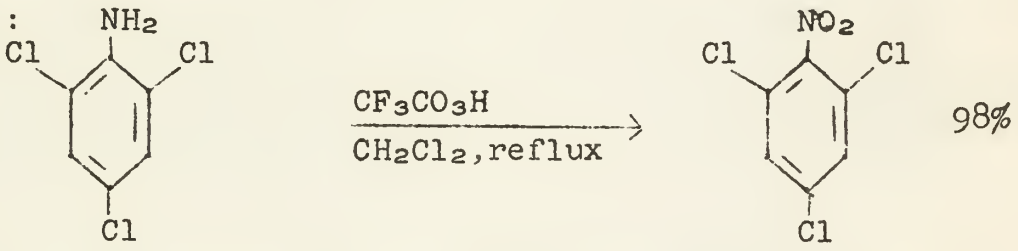
Example[14]:



85% 15%

The oxidation of azo compounds to azoxy compounds proceeds in high yields.[1,17,18] A specific reagent in the conversion of amines to nitro compounds is peroxytrifluoroacetic acid.[19,20,21] This reagent also converts nitrosamines to nitramines.[22]

Example[21]:



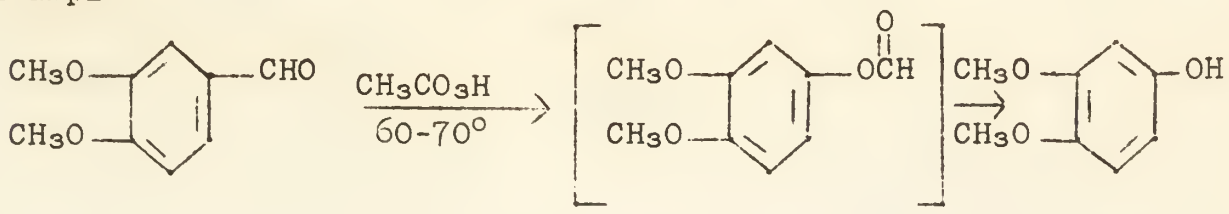
98%

The oxidation of amines to amine oxides proceeds smoothly with perbenzoic and monoperphthalic acids.[23,24] Certain N-alkyl-arylamines, however, give o-hydroxy compounds in modest yields.[25]

D. Oxidation of Aldehydes

Aldehydes are oxidized to the corresponding acids in good yields by peracids, with the exception that with phenolic aldehydes , the aldehyde group is replaced by a phenolic hydroxyl (Dakin Reaction).[26,27]

Example[28]:



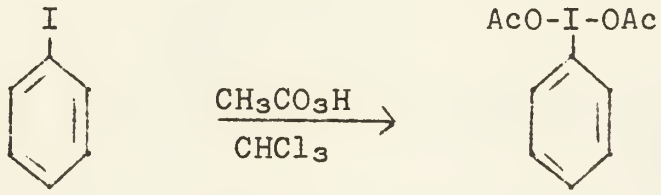
E. Oxidation of Ketones

Monoketones are in general not affected by peracids although the Baeyer-Villager rearrangement wherein the ketone is converted to an ester has been observed.[29] Quinones and α-diketones are oxidized to the corresponding diacids.[1] The peroxidation of enol acetates has been utilized to prepare α-hydroxy ketones from ketones in the steroid field.[30]

F. Oxidation of Organic Iodine Compounds

Peracetic acid oxidizes aryl iodides to iodoso acetates.[1] The latter compounds are useful as oxidizing agents for certain primary aromatic amines.[31] If perbenzoic acid is used the iodoxy compounds are obtained.[1]

Example[32]:



G. Use of Peracids in Structure Determination

Peracids have been invaluable in the location of double bonds, etc., in a molecule as well as in effecting desired degradations under mild conditions.[1]

2. Peroxide Derivatives of Acids[33]

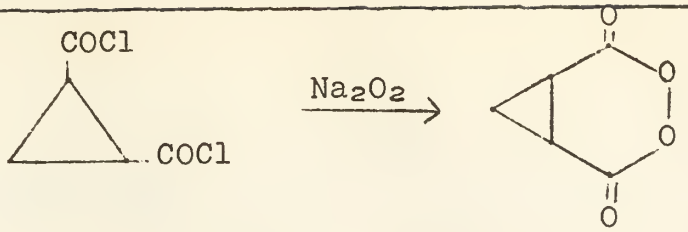
I. Preparation

A. $RCOCl + Na_2O_2 \longrightarrow R\text{-}C(=O)\text{-}OO\text{-}C(=O)\text{-}R'$ peranhydride

B. $ArCHO + (R\text{-}C(=O))_2O \xrightarrow{O_2} ArC(=O)\text{-}OO\text{-}C(=O)\text{-}R$ mixed peranhydride

C. $R\text{-}CH(COCl)\text{-}CH(R')\text{-}COCl + Na_2O_2 \longrightarrow$ Superoxide

Example[34]:



D. $RCOCl + R'O_2H \longrightarrow RC(=O)OOR'$

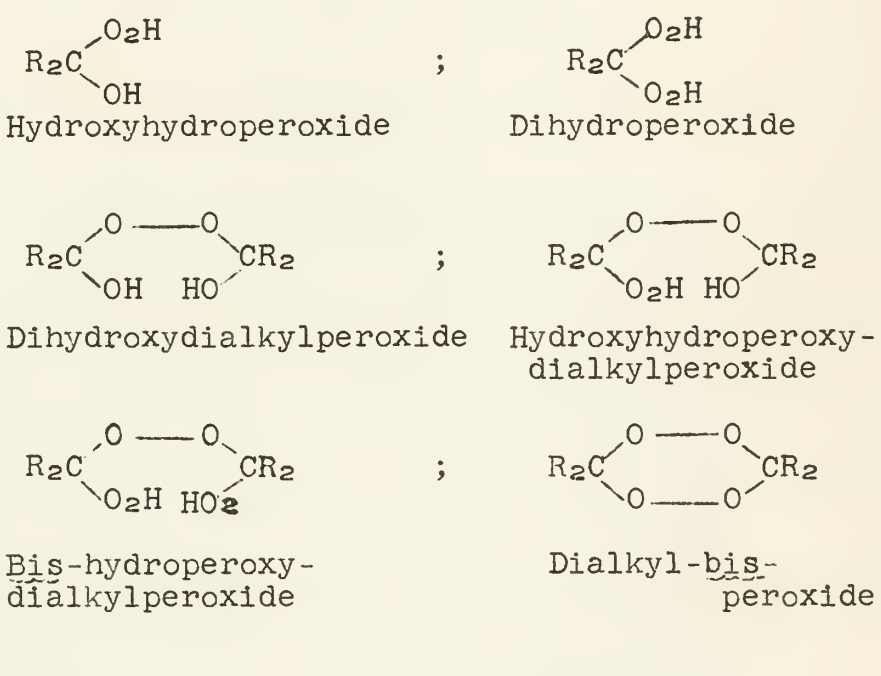
Hydroperoxide — Perester

---

3. Peroxide Derivatives of Aldehydes and Ketones[33,35]

I. Preparation

$R_2C{=}O \xrightarrow[\text{or } O_2]{H_2O_2}$



Hydroxyhydroperoxide ; Dihydroperoxide

Dihydroxydialkylperoxide ; Hydroxyhydroperoxy-dialkylperoxide

Bis-hydroperoxy-dialkylperoxide ; Dialkyl-bis-peroxide

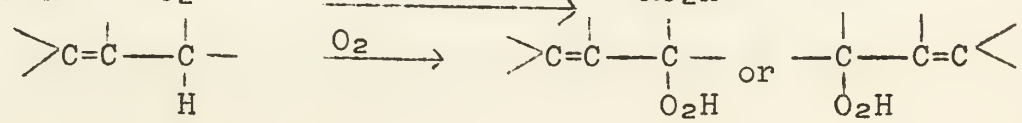
Nearly all of the above structure types have been reported from the peroxidation of cyclohexanone under various conditions.[33,35]

---

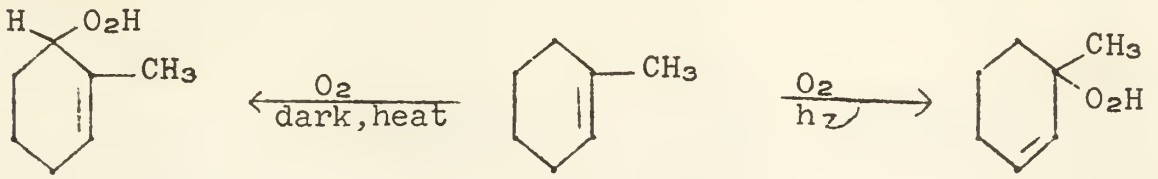
4. Peroxide Derivatives of Olefins and Other Hydrocarbons

I. Preparation or Formation[36,37,38]

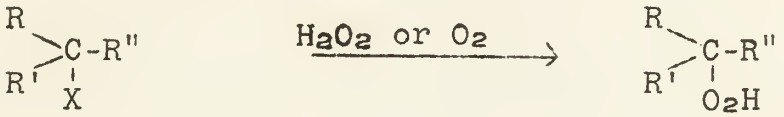
A. $R\text{-}H + O_2 \xrightarrow{h\nu \text{ or heat}} RO_2H$

B. 

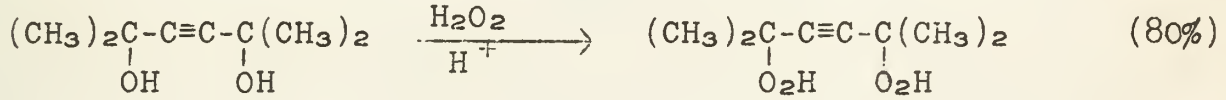
Example[39]:

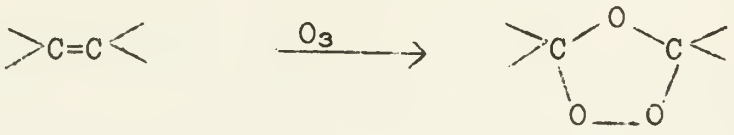


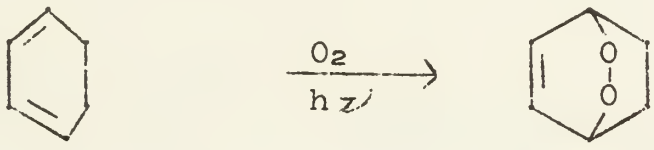
It is generally agreed that the autoxidation of olefins proceeds by initial attack on the allylic hydrogen.[41] When there is no allylic hydrogen, no autoxidation takes place in the case of aliphatic olefins. Aromatic olefins such as stilbene yield epoxides and glycol esters only after a peroxidation catalyst is added.

C. 

Example[40]:



D.[42] 

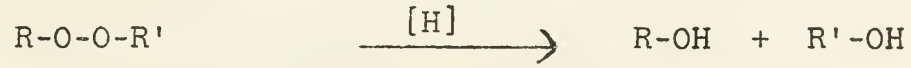
E. 

Transannular Peroxide

Molecular oxygen adds quite readily to conjugated dienes to form peroxide bridges. Polynuclear aromatic hydrocarbons and many steroid series have been investigated and shown to form stable transannular peroxides.[43-45]

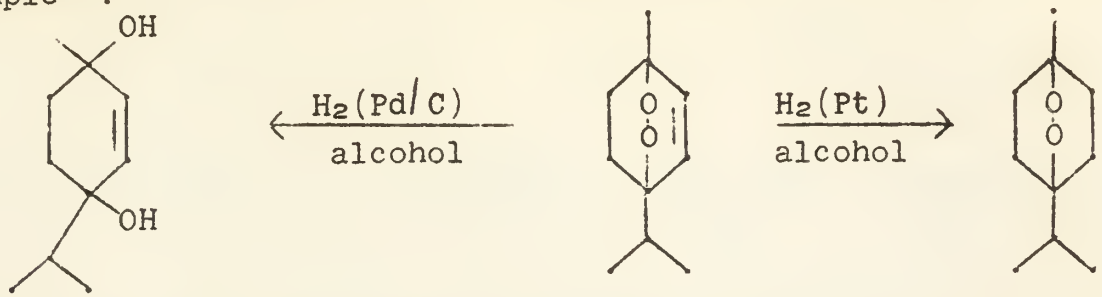
5. Other Reactions of Organic Peroxides[35]

A. Reduction

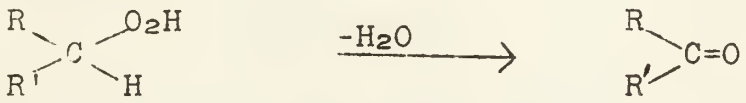


Various reduction methods have been used and often selective procedures can be found to yield cleavage or preservation of the -O-O- bond.[46,47]

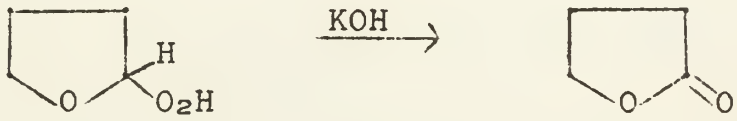
Example[46]:



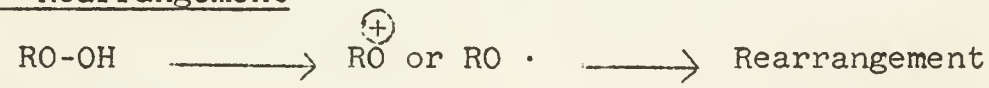
B. Dehydration



Example[48]:

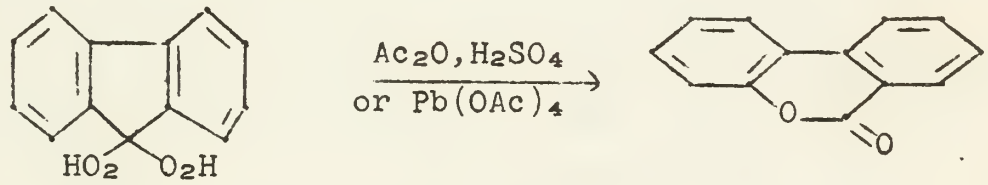


C. Rearrangement

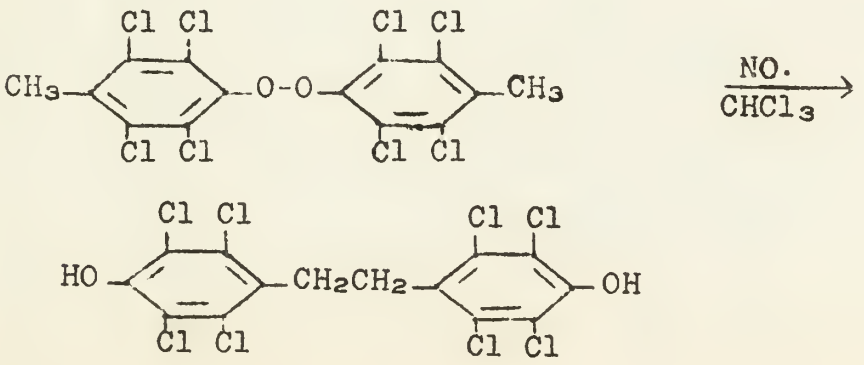


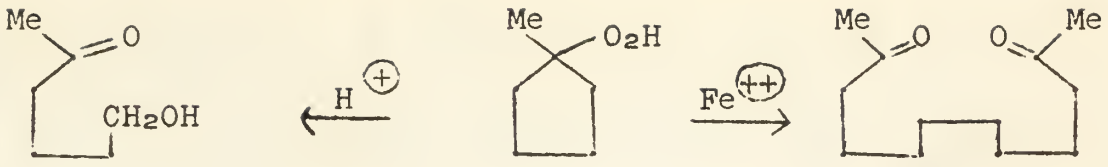
Examples:

1)[49-51]

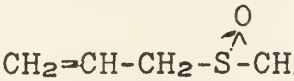


2)[52]



3)[53] 

4)[54] $C_9H_{19}CO_2H \xrightarrow{80\text{-}100^\circ} C_9H_{19}CO_2H + C_9H_{19}OH$ (50% and 6%)

5)[55] $CH_2=CH-CH_2-S-CH_2-CH=CH_2 + t\text{-}BuO_2H \xrightarrow[50^\circ]{CH_3OH}$  (Quantitative)

BIBLIOGRAPHY

1. D. Swern, Chemical Reviews, 45, 1 (1949).
2. J. P. Fourneau and S. Chantalou, Bull. soc. chim. France, 12, 845 (1945).
3. J. R. McNesby and C. A. Heller, Jr., Chemical Reviews, 54, 325 (1954).
4. F. D. Grieve, Absts. 128th A.C.S. Mtg., p. 16-O, Sept. 1955.
5. J. Boekesen, Rec. trav. chim., 47, 683 (1928).
6. P. A. Plattner, L. Ruzicka, H. Heusser and K. Meier, Helv. Chim. Acta, 29, 2023 (1946).
7. B. A. Arbuzow and B. M. Michailow, J. Prakt. Chem., 127, 1, 92 (1930).
8. W. D. Emmons and A. S. Pagano, J.A.C.S., 77, 89 (1955).
9. J. Gregor et.al., J. Chem. Soc., 1954, 2333.
10. D. Swern, G. N. Billen, T. W. Findley and J. T. Scanlon, J.A.C.S., 67, 1786 (1945).
11. W. D. Emmons, A. S. Pagano and J. P. Freeman, J.A.C.S., 76, 3472 (1954).
12. E. de R. Van Zuydewijn, Rec. trav. chim., 57, 445 (1938).
13. J. Boekesen, Rec. trav. chim., 54, 657 (1935).
14. F. P. Greenspan, Ind. Eng. Chem., 39, 847 (1947).
15. J. Boekesen and J. Jacobs, Rec. trav. chim., 55, 786 (1936).
16. H. Gilman and D. R. Swayampati, J.A.C.S., 77, 5944 (1955).
17. D. Bigiavi and B. de Benedetti, Gazz. chim. ital., 54, 363 (1927).
18. D. F. Morrow, U. of I. Organic Seminar Absts., Oct. 22, 1954.
19. L. M. Werbel, ibid., May 20, 1955.
20. G. F. Holland, MIT Organic Seminar Absts., October 27, 1954.
21. W. D. Emmons, J.A.C.S., 76, 3470 (1954).
22. W. D. Emmons, J.A.C.S., 76, 3468 (1954).
23. R. N. Chakravarti and R. Robinson, J. Chem. Soc., 1947, 78.
24. R. D. Smith, MIT Organic Seminar Absts., Sept. 23, 1953.
25. J. T. Edward, J. Chem. Soc., 1954, 1464.
26. S. A. Aspey, U. of I. Organic Seminar Absts., May 7, 1954.
27. R. B. Hodgdon, Jr. and W. Helmreich, Absts. 128th A.C.S. Mtg., p. 21-O, Sept. 1955.
28. A. von Wacek and A. von Bezard, Ber. 74B, 845 (1941).
29. E. J. Strojny, U. of I. Organic Seminar Absts., Nov. 13, 1953.

30. See for example: R. B. Moffitt and G. Slomp, Jr., J.A.C.S., 76, 3678 (1954); H. V. Anderson et.al., J.A.C.S., 76 743 (1954).
31. E. Tanda, U. of I. Organic Seminar Absts., Jan. 7, 1955.
32. J. Boekesen and G. C. C. C. Schneider, J. Prakt. Chem. 131, 285 (1931).
33. V. Karnojitzky, Chemie et Industrie, 74, 929 (1955).
34. F. Fichter and H. Spiegelberg, Helv. Chem. Acta, 12, 1152 (1929).
35. R. Criegee, "Peroxyde" in Methoden der Org. Chemie, Houben-Weyl, 4th Ed., Vol. 8, Thieme, Stuttgart, 1952.
36. J. W. Crump, U. of I. Organic Seminar Absts., Feb. 18, 1955.
37. A. G. Davies, et.al., J. Chem. Soc., 1956, 665 and preceding papers.
38. K. J. Iwanow and W. K. Ssawinowa, Dok. Akad. Nauk (SSSR), 54, 493 (1948) [C.A. 42, 6757d (1948)].
39. G. O. Schenk, Naturwiss., 35, 28 (1948).
40. N. H. Milas and O. L. Mageli, J.A.C.S., 74, 1471 (1952).
41. E. G. E. Hawkins and D. C. Quin, J. Appl. Chem., 6, 1 (1956).
42. M. S. Konecky, U. of I. Organic Seminar Absts., April 27, 1956; J. T. Kafron, Jr., MIT Organic Seminar Absts., Nov. 10, 1954.
43. W. Bergmann and M. J. McLean, Chem. Rev., 28, 367 (1941).
44. M. J. Gortakowski, U. of I. Organic Seminar Absts., Oct. 30, 1953.
45. E. H. Petrie, MIT Organic Seminar Absts., May 5, 1954.
46. H. Paget, J. Chem. Soc., 1938, 829.
47. C. Djerassi, A. T. Lemin, G. Rosenkranz and F. Sondheimer, J. Chem. Soc., 1954, 2346.
48. A. Robertson, Nature, 162, 153 (1948).
49. G. Wittig and G. Pieper, Ber. 73, 295 (1940).
50. R. Criegee, W. Schnorrenberg and J. Becke, Ann., 565, 7 (1949).
51. E. F. Cox, MIT Organic Seminar Absts., April 22, 1953.
52. R. Pummerer, G. Schmidutz and H. Leifert, Ber. 85, 535 (1954).
53. E. G. E. Hawkins, J. Chem. Soc., 1950, 2801; E. G. E. Hawkins and D. P. Young, ibid., 2804.
54. E. Späth, U. Pailer and M. Schmid, Ber. 74, 1552 (1941).
55. D. Bainard, J. Chem. Soc., 1956, 489.
56. D. Swern, L. P. Witnauer, C. R. Eddy and W. E. Parker, J.A.C.S., 77, 5537 (1955).
57. D. B. Denney, J.A.C.S., 78, 590 (1956).
58. J. T. Edward, J. Chem. Soc., 1956, 222.
59. L. A. Cohen and B. Witkop, J.A.C.S., 77, 6595 (1955).
60. J. Minn, T. F. Sanderson and L. A. Sublusky, J.A.C.S., 78, 630 (1956).
61. S. F. Strause and E. Dyer, J.A.C.S., 78, 136 (1956).
62. A. A. Miller and F. R. Mayo, J.A.C.S., 78, 1017 (1956).
63. G. A. Russell, J.A.C.S., 78, 1035 (1956).
64. J. Gregor, W. Laird, D. MacClean, G. T. Newbald and F. S. Spring, J. Chem. Soc., 1954, 2333.

UNIVERSITY OF ILLINOIS-URBANA
Q.547IL6S C001
ORGANIC SEMINAR ABSTRACTS URBANA
1955/56
3 0112 025513570