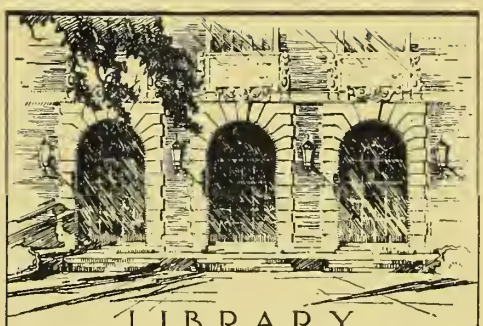


ORGANIC SEMINAR ABSTRACTS

1965-66

Semester II

Department of Chemistry and Chemical Engineering

University of Illinois

SEMINAR TOPICS

II Semester 1965-1966

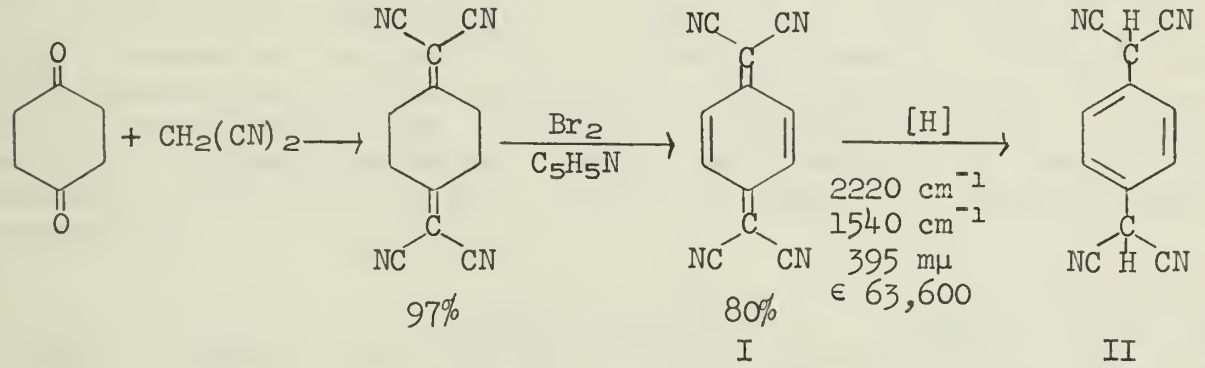
7,7,8,8-TETRACYANOQUINODIMETHAN AND ITS ANION-RADICAL SALTS

Reported by Robert E. Cunningham, Jr. February 17, 1966

7,7,8,8-Tetracyanoquinodimethan (TCNQ)[1,2] readily accepts one electron to form stable anion-radical derivatives which show remarkable magnetic and electrical solid-state properties. The chemistry of TCNQ and physical properties of its anion-radical derivatives are the topic of this seminar.

CHEMISTRY OF TCNQ

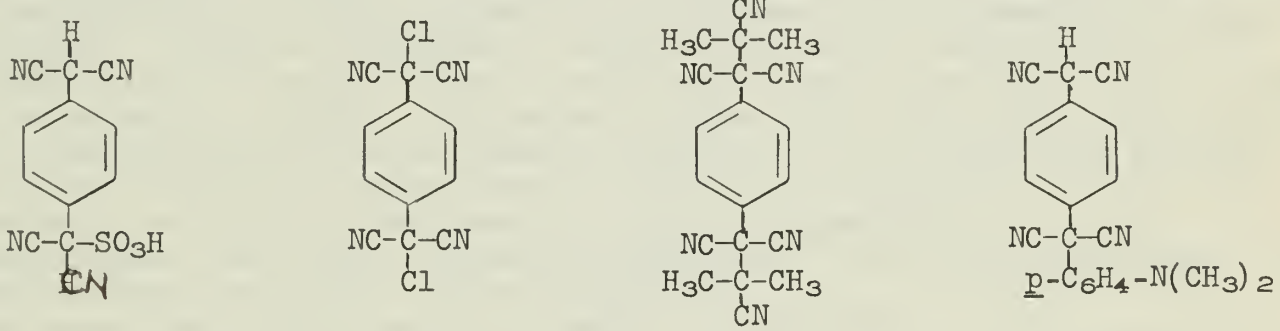
Tetracyanoquinodimethan (I), crystallizing as orange red monoclinic crystals, m.p. 296°, has been prepared as outlined below.[1,2] The structure has been confirmed



by x-ray analysis.[3]

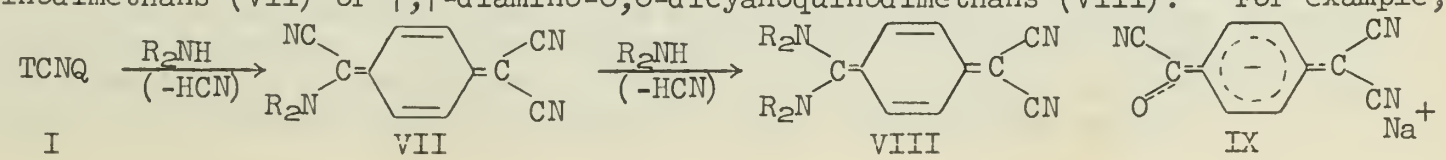
Tetracyanoquinodimethan is reduced to p-phenylenedimalononitrile (II) by thiophenol, mercaptoacetic acid, or hydrogen iodide.[2] Polarographic reduction of TCNQ in acetonitrile containing 0.1M lithium perchlorate with a dropping mercury electrode vs. a saturated calomel electrode yields two reduction waves with half-wave potentials of +0.127 and -0.291 V.[2] (For comparison, TCNE undergoes reduction at +0.152 and -0.568 V under similar conditions.[4])

The quinodimethan undergoes 1,6-addition reactions.[2,5] Treatment of TCNQ with sulfur dioxide in aqueous acetonitrile results in the adduct III, usually isolated as its tetramethylammonium salt in 92% yield. With trace amounts of triethylamine or tetramethylammonium chloride, chlorine adds to TCNQ to give the 1,6 adduct IV. This reaction may proceed by the initial attack of Cl^- as proposed by Dickinson[6]

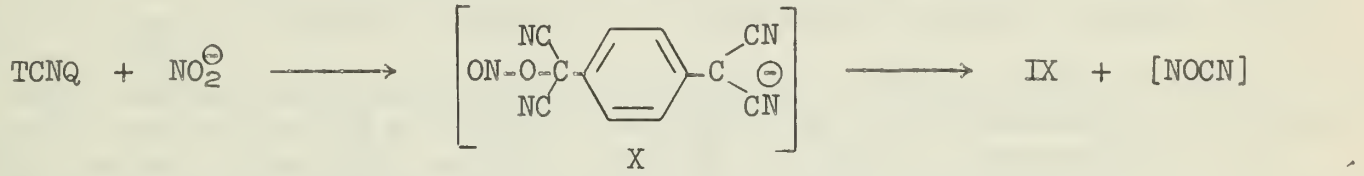


in his study of the action of chlorine on tricyanoethylene. The adduct V is obtained when α,α'-azo-bis-(isobutyronitrile) is thermally decomposed in the presence of TCNQ. Finally, N,N-dimethylaniline adds to TCNQ to give compound VI, whose structure has been assigned on the basis of elemental and spectroscopic analyses and the failure to yield a quinodimethan upon treatment with oxidizing agents.

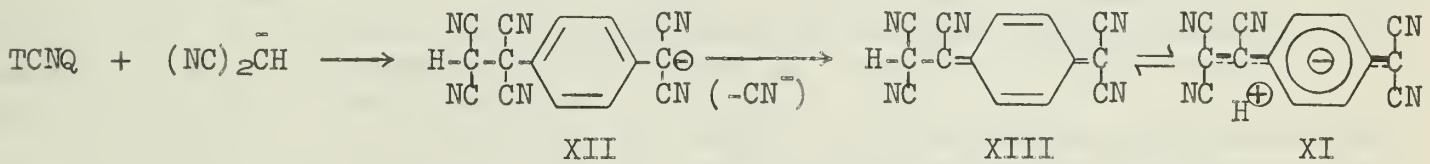
TCNQ reacts with primary and secondary amines to give 7-amino-7,8,8-tricyanoquinodimethans (VII) or 7,7-diamino-8,8-dicyanoquinodimethans (VIII).[7] For example,



one equivalent of pyrrolidine gives 7-pyrrolidino-7,8,8-tricyanoquinodimethan, whose structure was assigned on the basis of infrared and ultraviolet spectra[8] and elemental analysis. Treatment of either TCNQ or 7-pyrrolidino-7,8,8-tricyanoquinodimethan with an excess of pyrrolidine yields the same product--7,7-dipyrrolidino-8,8-dicyanoquinodimethan. A cyano group is also replaced by nitrite ion in the reaction of TCNQ with sodium nitrite in aqueous acetone to give IX.[7] The formation of IX may proceed through the unstable intermediate X, which then decomposes to IX.



An interesting nucleophilic replacement of a cyano group has been observed when TCNQ is warmed with malononitrile in dimethylformamide solution.[9] The product, the p-tricyanovinylphenyldicyanomethide ion (XI) (isolated as the tetramethylammonium salt), can be rationalized by adding the malononitrile anion to TCNQ to form the anion XII. Elimination of CN^- from XII can give XIII, the conjugate acid of XI. Similar reactions of TCNQ with other active methylene compounds have also been observed.[9]

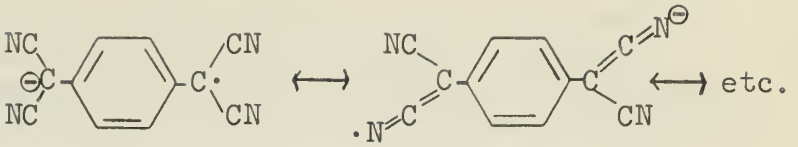


Tetracyanoquinodimethan is a strong pi-acid and consequently forms stable, solid complexes (generally 1:1) with aromatic amines, hydrocarbons, and polyhydric phenols.[10] The pi-acid character of TCNQ results partly from the high electron affinity of the polyene system conferred by the powerful electron withdrawing effect of the four cyano groups and partly from the planarity and high symmetry of the TCNQ system. If polarographic half-wave potentials for the one-electron reduction are used as criteria for pi-acid strength, TCNE is the slightly stronger pi-acid. This basis for comparison has the advantage of eliminating the apparent inconsistencies which arise when an attempt is made to establish the relative pi-acidities of TCNQ and TCNE by examining association constants for complex formation. Neprăs and Zahradnik,[11] using a plot of the energies of the 1st charge-transfer bands of various donors and acceptors vs. the energies of the highest occupied pi-molecular orbitals, obtained data which also indicate that TCNE is a somewhat stronger pi-acid. Charge-transfer complexes (1:1) of TCNQ with poly(N-vinylcarbazole),[12] poly(2-vinylpyridine),[13] and poly(4-vinylpyridine)[13] have also been obtained as well as 1:1 complexes with copper 8-quinolinolate, nickel 2-pyrolealdehydeimine, and copper 2-pyrolealdehydeimine.[10] The latter are unusual in that they have metal chelates as donor components.

When treated with certain metals or metal iodides, TCNQ undergoes a ready one-electron reduction to form simple anion-radical salts.[1,10] In fact, Boyd[14] has calculated the electron affinity of TCNQ to be 86 kcal./mole from the heats of formation of its aqueous ion-radical salt solutions and an estimation of the hydration energy of the ion-radical in conjunction with a Born-Haber cycle. In the case of a free metal, direct oxidation-reduction occurs. For example, the two methods are illustrated for the case of the cuprous salt of $TCNQ^{\cdot-}$. Preparations are usually carried out in acetonitrile or acetone with an excess of metal iodide so that the iodine by-product can be scavenged as I_3^-. The lithium salt of $TCNQ^{\cdot-}$ is slightly soluble in water or ethanol at room temperature (1% by weight) in contrast to other metal-TCNQ anion-radical salts which are essentially insoluble in water and organic solvents. This property makes $Li^+TCNQ^{\cdot-}$ a convenient intermediate for the preparation of a wide variety of $TCNQ^{\cdot-}$ derivatives containing metallic, organometallic, and onium cations by metatheses of the corresponding iodides.

$$CuI + TCNQ \longrightarrow Cu^{+}TCNQ^{\cdot -} + \tfrac{1}{2}I_2$$

$$Cu^{0} + TCNQ \longrightarrow Cu^{+}TCNQ^{\cdot -}$$



XIV

Treatment of simple TCNQ anion-radical salts with strong mineral acids forms TCNQ and p-phenylenedimalononitrile (II) in nearly quantitative yields. The reaction probably occurs by disproportionation of an intermediate radical produced by protonation of $TCNQ^{\cdot -}$.

Under the conditions used for the polarography of TCNQ, $Li^{+}TCNQ^{\cdot -}$ yields a reversible anodic wave ($E_{\frac{1}{2}}$ = +0.127 V, corresponding to the one-electron oxidation to TCNQ) and an irreversible cathodic wave ($E_{\frac{1}{2}}$ = -0.291 V, corresponding to the thermodynamically irreversible one-electron reduction to $TCNQ^{=}$).[1,10]

$$TCNQ^{\cdot -} \underset{-e^{-}}{\overset{+e}{\rightleftharpoons}} TCNQ$$

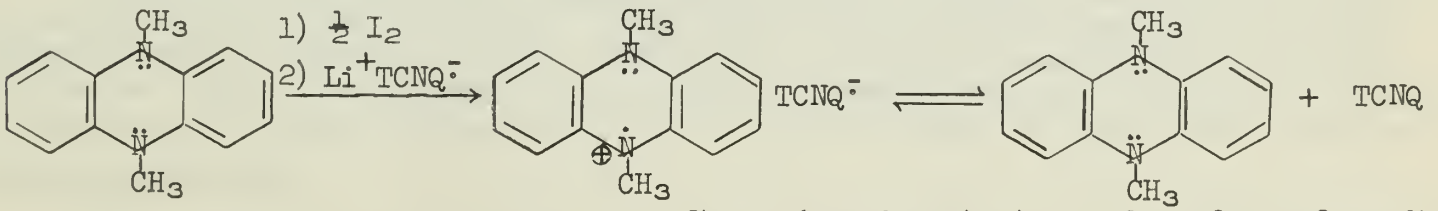
$$TCNQ^{\cdot -} \xrightarrow{+e} TCNQ^{=}$$

Alkyl-substituted tetracyanoquinodimethans have been prepared from the corresponding cyclohexa-1,4-diones.[15] The polarographic reductions of these compounds (methylTCNQ = +0.12 V, n-propylTCNQ = +0.10 V, and 2,5-dimethylTCNQ = +0.02 V) indicate that the introduction of alkyl groups in the TCNQ molecule progressively lowers the reduction potential for anion-radical formation. This decrease is in accord with a normal inductive effect.

The effect of a bulky group on the properties of the tetracyanoquinodimethan system is evident from the reduction potential of 2-benzhydryl-7,7,8,8-tetracyanoquinodimethan.[16] The compound, which was synthesized by treatment of TCNQ with diphenyldiazomethane in acetone or acetonitrile, shows two reversible, one-electron waves at -0.28 and -0.59 V vs. the saturated calomel electrode in the same solvent system mentioned above. The bulky benzhydryl group prevents planarity of the TCNQ system and hence destabilizes the anion-radical as evidenced by the above reduction potentials and unsuccessful attempts to make the copper (I) salt by reduction of benzhydrylTCNQ with copper. Only the copper (I) salt of $TCNQ^{\cdot -}$ was isolated. Supposedly, the benzhydryl group was eliminated as a radical, but the author did not report any products which could arise from such a radical. The lack of planarity of the 2-benzhydrylTCNQ is also reflected in its UV absorption ($\lambda_{max}^{acetonitrile}$ = 362[ϵ25,600], 258[ϵ6,650], and 221 mμ[ϵ17,700]. (Cf. TCNQ, λ_{max} 395 mμ[63,600].)

The ultraviolet absorption of the $TCNQ^{\cdot -}$ ion (XIV) in acetonitrile solution shows major maxima at 420 (ϵ24,300) and 842 mμ (ϵ43,300), the intensity ratio of the 420 and 842 mμ bands being approximately 0.5 for simple salts.[10] This ratio provides a convenient means for characterization of $TCNQ^{\cdot -}$ derivatives.

Unusual anion-radical salts (simple) of TCNQ have been prepared.[17,18] The salt of the radical-cation of 1,6-diaminopyrene (DAP) and TCNQ was obtained by treatment of TCNQ with DAP or by metathesis of $Li^{+}TCNQ^{\cdot -}$ with $DAP^{\cdot +}Br^{-}$.[17] Ultraviolet spectral analysis showed the adduct of TCNQ and DAP to consist of approximately 93% DAP^{+} and $TCNQ^{\cdot -}$. N,N'-Dimethyldihydrophenazinylium cation-radical TCNQ anion-radical salt (XV)[18] was produced as outlined below. The UV spectrum showed considerable



XV (λ_{max} 842[ϵ26,000], 394[ϵ43,300], 258mμ[ϵ58,000])

absorption due to neutral TCNQ. Attenuation of absorption by the cation-radical indicated an equilibrium between ion-radical and uncharged species. Relative values of the extinctions indicated an equilibrium of approximately 30-40% neutral products. This compound may be more properly regarded as a pi-complex rather than an ion-radical salt in the solid state.

In addition to the simple salts above TCNQ forms another series of stable anion-radical derivatives which contain molar proportions of neutral TCNQ associated with $TCNQ^{\cdot-}$ and a cation.[1,10] They may be represented as $M^{+}(TCNQ^{\cdot-})(TCNQ)$. Complex salts have been prepared in which M^{+} may be alkyl or aryl-substituted ammonium (including N-heterocycles), phosphonium, arsonium, stibonium, sulfonium, or oxonium ions.[1,10,18] There are four major synthetic routes to the complexes. These methods are illustrated below for the triethylammonium derivative.

$$(1)\quad Et_3NH^{+}TCNQ^{\cdot-} + TCNQ \xrightarrow[CH_3CN]{} \underset{XVI}{Et_3NH^{+}(TCNQ^{\cdot-})(TCNQ)} \quad 50\%$$

$$(2)\quad 3Et_3NH^{+}I^{-} + 2TCNQ \xrightarrow[CH_3CN]{} XVI \quad 50\%$$

$$(3)\quad 2Et_3N + H_2TCNQ + 3TCNQ \xrightarrow[CH_3CN]{} XVI \quad 90\%$$

$$(4)\quad Et_3N + 2TCNQ \xrightarrow[CH_3CN]{} XVI \quad 77\%$$

In method (4) the source of the proton is not known, but it may be derived from the amine as is the electron for $TCNQ^{\cdot-}$. (Buckley *et. al.* have reported that amines, including triethylamine are dehydrogenated by chloranil at room temperature to give vinylamine derivatives along with the expected reduction product.[19]) Two possibilities for the method of formation of XVI have been proposed.[10] The authors,

$$(1)\quad Et_3N + TCNQ \longrightarrow CH_3CH{=}\overset{\oplus}{N}Et_2 + HTCNQ^{-} \xrightarrow[2Et_3N]{TCNQ} CH_2{=}NEt_2 + 2[Et_3NH^{+}TCNQ^{\cdot-}] \xrightarrow{2TCNQ} 2[Et_3NH^{+}(TCNQ^{\cdot-})(TCNQ)]$$

$$(2)\quad Et_3N + TCNQ \longrightarrow Et_3N^{\oplus\cdot} + TCNQ^{\cdot-} \xrightarrow{Et_3N} Et_3NH^{+}TCNQ^{\cdot-} + CH_3\dot{C}HNEt \xrightarrow{Et_3N^{+\cdot},TCNQ^{\cdot-}} XVI \xleftarrow{2TCNQ} [2\,Et_3NH^{+}TCNQ^{\cdot-}] + CH_2{=}CHNEt_2$$

however, did not isolate the vinylamine derivative which is required by either rationale. Another possible source of the electron and proton is the acetonitrile, but the expected coupling product, succinonitrile was not found. A thorough investigation of the mechanism of method (4) would be in order, or at least, a concentrated effort to find the missing vinylamine derivative.

The complex salts show electronic absorption in solution which is essentially a summation of the bands characteristic of TCNQ and $TCNQ^{\cdot-}$.[10] For example, the UV of XVI in acetonitrile has maxima at 395 (ϵ85,500) and 842 mμ (ϵ43,400). The ratio of the 395 and 842 mμ bands is approximately two when no complicating cation absorption is present. A rare complex, $Cs^{+}{}_2(TCNQ^{\cdot-})_2(TCNQ)$ has a 395/842 band intensity ratio of about 1.2-1.5.

Similarly, polarograms of complex salts display two waves which are additive curves of neutral TCNQ and $TCNQ^{\cdot-}$.[10] The first is a composite wave with an anodic component from oxidation of $TCNQ^{\cdot-}$ to TCNQ and a cathodic component from reduction of TCNQ to $TCNQ^{\cdot-}$. For a completely dissociated complex the wave heights of the two components are directly proportional to the ratio of $TCNQ^{\cdot-}$ to TCNQ in the complex.

PHYSICAL PROPERTIES

The simple and complex anion-radical salts of TCNQ show electrical conductivities, some of which are the lowest reported for organic compounds.[10,20,21] Measurements of conductivities have been made on single crystals (when available)

or on compactions. Most of the compounds are classed as semiconductors because of exponential variation of their electrical resistivities with temperature. The conductivity of semiconductors is often referred to by the reciprocally related term resistivity, ρ, defined by $\rho = (RxA)/L$, where R is the resistance (ohm), A is the area (cm^2), and L the length (cm) of the sample being examined. The majority of organic compounds are insulators ($\rho = 10^{10}$-10^{14} ohm-cm) and show the exponential temperature dependence characteristic of semiconductors--

$$\rho = \rho_o \exp(E/kT) \qquad \text{Equation (1)},$$

where ρ is the resistivity, ρ_o a constant, and E the activation energy for conduction. For metallic conductors $\rho \tilde{=} 10^{-6}$ ohm-cm and varies linearly with temperature.

The pi-complexes of TCNQ with aromatic hydrocarbons, amines, and polyhydric phenols generally show resistivities in the range of 10^6-10^{12} ohm-cm.[10] Isolated examples may show lower resistivities. For example, the N,N,N',N'-tetramethyl-p-phenylenediamine/TCNQ complex, whose crystal structure has recently been determined,[22] has a resistivity of about 10^6 ohm-cm at room temperature, whereas the complex of TCNQ and p-phenylenediamine has a resistivity of 10^3 ohm-cm.[10] The pi-complexes are either totally diamagnetic in the solid state or exhibit only weak paramagnetism (shown by ESR absorption).[10]

The other types of TCNQ derivatives have more interesting properties. The simple TCNQ anion-radical salts generally show high resistivities (10^4-10^8 ohm-cm) and relatively high activation energies for conduction (0.2-0.3eV).[20] (The potassium $TCNQ^{\cdot-}$ salt has a resistivity of 5.3×10^3 ohm-cm and an activation energy of 0.36eV.[20]) Single crystal measurements on a few salts have shown that resistivities along different crystal directions (for monoclinic and triclinic crystals) are isotropic. For example, single crystal measurements on morpholinium TCNQ have yielded a resistivity of 10^8 ohm-cm (E = 0.32eV).[21] Conduction in the simple salts takes place by an activated process, but it is not certain whether the carrier production or the carrier motion is activated.[21]

Complex TCNQ anion-radical salts show intermediate (10^0-10^5 ohm-cm) to low resistivities (10^0-10^{-2}ohm-cm) depending on the cation involved.[20,21] Activation energies range between 0.30 and 0.03eV. These complexes are unusual in that their single-crystal resistivities are highly anisotropic, depending upon the crystal axis used for measurement. For example, triphenylmethylphosphonium $(TCNQ^{\cdot-})(TCNQ)$ has resistivities of 5×10^1, 5×10^2, and 5×10^4 ohm-cm along the crystal axes (E = 0.30eV).[21] Quinolinium $(TCNQ^{\cdot-})(TCNQ)$ has a room temperature value of 10^{-2} ohm-cm along the direction of lowest resistivity (E = 0.01eV). The resistivity of this compound is higher when a powder (compaction) is used--2.5×10^{-1} ohm-cm.[20,21] (For comparison, the resistivity of graphite is about 10^{-3} ohm-cm.) It has been suggested[20,21] that, in the salts of lowest resistivity, the electrons are degenerate as in a metal since these compounds exhibit temperature independent paramagnetism, are highly conductive, and virtually lack an activation energy for conduction. Measurements of the temperature dependence of compacted samples have indicated that their conductivity is an activated process between room and liquid nitrogen temperatures with activation energies between 0.02 and 0.10ev.[21] The major part of the activation energy for compactions of this group is caused by interparticle boundaries.

With compounds of intermediate resistivities [for example, $Et_3NH^+(TCNQ^{\cdot-})(TCNQ)$] the paramagnetic component of the magnetic susceptibility (χ_p) follows equation (2).[20,26]

$$\chi_p = (2g\,\beta^2 N/kT)[3 + \exp(J/kT)]^{-1} \qquad \text{Equation (2)},$$

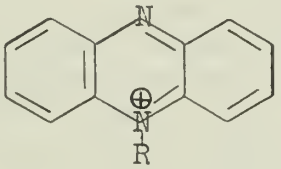
where g is the gyromagnetic ratio, β the Bohr magneton, and J the singlet-triplet separation. This corresponds to an assembly of N quasi-molecules, each having a triplet state lying at an energy J above a singlet ground state. As with the compounds of high resistivity, the conduction takes place by an activated process.

Menefee and Pao[23] have combined a LCAO-MO method with crystal field splitting to calculate the activation energy for triethylammonium ($TCNQ^{\cdot-}$)($TCNQ$), obtaining a value of 0.12eV (Exp. = 0.14eV[21]).

Preliminary crystallographic data on triethylammonium ($TCNQ^{\cdot-}$)($TCNQ$)[20] indicate that there are four molecular units per unit cell and that the TCNQ units appear to be arranged in infinite face-to-face stacks with the direction of highest conductivity (lowest resistivity) lying along these stacks and approximately normal to the plane of the TCNQ molecules. Similarly, a recent x-ray study of $Cs^{+}_{2}(TCNQ^{\cdot-})_{2}(TCNQ)$ has shown that the TCNQ units are stacked face-to-face in the crystal with two molecular units/unit cell. Cesium ions separate the rows of stacks. Structures such as these are consistent with the observed resistivity anisotropies. A similar structural arrangement may be present in the highly conductive salts.

Le Blanc[25] has recently proposed that the electronic polarizability of the cation is the principal reason for variation of resistivities in the TCNQ anion-radical salts. Salts with planar, aromatic heterocyclic cations have the lowest resistivities since these cations have higher polarizabilities and are more effective in reducing activation energies for conduction.

Steric factors which determine packing within the crystals are also important as can be seen by comparing the resistivities (single crystal) of N-methylphenazinium ($TCNQ^{\cdot-}$) and N-ethylphenazinium ($TCNQ^{\cdot-}$).[18] The N-methyl group in XVIIa (density =



$TCNQ^{\cdot-}$

XVIIa R=CH_3, $\rho=7\times10^{-3}$ohm-cm
XVIIb R=C_2H_5, $\rho=1\times10^{9}$ ohm-cm

1.44g./cm^3) allows very efficient packing of the $TCNQ^{\cdot-}$ units which presumably mediates the electrical conduction. The bulky N-ethyl group in XVIIb apparently disrupts the packing (density = 1.33g./cm^3), resulting in an appreciable barrier to electron movement.

Kepler[26] has studied the magnetic properties of a wide variety of TCNQ anion-radical salts. The more conductive salts show a temperature independent paramagnetic contribution to their magnetic susceptibilities. This is interpreted to mean that the odd electrons are degenerate as in a metal. For materials of intermediate conductivity, the extra electrons on the TCNQ molecules appear to be paired by an exchange interaction in quasimolecular states with a singlet ground state and a triplet state lying J eV above the ground state. The singlet-triplet gaps for the triphenylmethylarsonium and cesium complexes are temperature dependent. The compounds with low conductivities (high resistivities) and diamagnetic cations are diamagnetic at both low and high temperatures.

Electron spin resonance studies have been carried out on a number of the TCNQ complexes with intermediate conductivities.[27,28,29,30] These studies have established that spin correlation exists between the magnetic electrons in these salts, giving rise to a ground singlet state and a thermally accessible triplet state. Singlet-triplet separations that were obtained from the temperature dependence of ESR line intensities [given by Eq. (3)] are comparable to those obtained by the susceptibility measurements (above). (These values did not show a temperature dependence since the

$$I \propto 1/T[\exp(J/kT) + 3]^{-1} \qquad \text{Equation (3)}$$

relative ESR line intensities were used.)

Below -150°C the single-crystal ESR spectra of the triphenylmethylarsonium and phosphonium salts show two sharp peaks, the spacing of which is dependent on the crystal orientation relative to the external field.[27,28] These two peaks are due to an anisotropic splitting of the resonance into a doublet (zero-field, or dipolar splitting). (The ESR spectrum of the cesium salt[29] shows four outer lines which represent the fine structure from two physically equivalent but geometrically non-equivalent triplet entities which are related by the two fold screw axis of the $P2_1/c$ space group.[24]) As the temperature is raised above -150°, the zero-field

components broaden, coalesce, and finally narrow at room temperature to a single, sharp resonance. These effects have been attributed to exchange interactions between the triplet entities in the solid. The ESR spectra of the above salts and of morphilinium $TCNQ^{\cdot-}$ and $Et_3NH^+(TCNQ^{\cdot-})(TCNQ)$ as well have been represented by the spin Hamiltonian[27,28,29]--

$$\mathcal{H} = \beta H \cdot g \cdot S + DS_z^2 + E(S_x^2 - S_y^2), \qquad \text{Equation (4)}$$

where S_x, S_y, and S_z are spin components along the respective axes and D and E are the fine interaction tensors (or splittings). D and E may be experimentally determined from the doublet splittings along the respective axes.

In the case of the $\Phi_3As^+CH_3$ and $\Phi_3P^+CH_3$ salts half-field ($\Delta m = \pm 2$) transitions are observed.[28] The above phenomena and the relatively small observed values of D,E, and J[27,28,29] are consistent with a molecular solid obeying singlet-triplet statistics. The triplet entity involved is likely composed of at least two TCNQ units, and the electron pair giving rise to the triplet state may be distributed over all four TCNQ molecules in the unit cell (in the case of the phosphonium and arsomium salts). In other words, the structural formulae for the cesium and phosphonium salts may be more properly written as $(Cs^+)_2(TCNQ)_3^{=}$ and $(\Phi_3P^+CH_3)_2(TCNQ)_4^{=}$. Spin correlation may also be responsible for the diamagnetism of the salts of low conductivities. Spin pairing has also been indicated in the complex salts based on 3,4- and 7,8-benzoquinoline and complete degeneracy in the case of the N-methyl-2,3-benzoquinoline complex.[30]

In these ESR spectra, no hyperfine splittings are observed. Earlier considerations[27,28] led to the conclusion that, because of the apparent equivalence of J and the activation energy for exchange (ΔE), the temperature dependence of the exchange process arose simply from the temperature dependence of the triplet state population. This exchange also removed the hyperfine splitting. Since J and ΔE are not equal for the cesium salt, it is clear that this is not the only temperature-dependent mechanism. It is possible that the magnetic species may move as a triplet exciton, the collision or mutual scattering of these mobile excitons being responsible for the observed exchange effects and the loss of hyperfine structure.[29] The term triplet exciton is used to describe any S=1 electronic excitation that can propagate through a perfect crystal lattice irrespective of whether the motion is purely wavelike with no activation energy or diffusional with an activation energy. McConnell and Lynden-Bell[31] have used triplet excitons to interpret the above results.

McConnell et. al.[32] in a study of the ESR spectra of x-ray irradiated $\Phi_3P^+CH_3(TCNQ)_2^{-}$ have presented experimental results which further support the idea of mobile triplet excitons. The ESR spectra show a $S=\frac{1}{2}$ radical which is produced from the x-rays and whose signal undergoes a broadening comparable to that for the triplet fine structure.

Jones and Chesnut[33] have studied the effects of spin exchange on the ESR spectra of some ion-radical salts using three limiting approximations relating to the line width and line separation of the exchange-modified Bloch equations and have discussed some of the results in terms of triplet excitons.

In another paper Jones[34] has studied the spin lattice relaxation in the phosphonium, arsonium, and cesium salts as a function of temperature.

Halford and McConnel[35] have studied the effects of pressure on the fine splitting constants of the ESR spectrum of morpholinium $(TCNQ)^{\cdot-}$ and have tentatively reached the conclusion that there is no dominant intramolecular spin-spin contribution to the fine splitting in the salt. With this assumption and some preliminary x-ray data on the morpholinium salt, Maréchal and McConnell[36] have made a theoretical calculation of D and E, the agreement with experimental being excellent. McConnel et. al.[37] have studied the pressure dependence of the exchange-narrowed triplet-exciton magnetic resonance in the phosphonium and arsonium salts.

In a study of the magnetic susceptibility of $TCNQ^{\cdot-}$ salts, Kepler[26] observed a sharp discontinuity in that of $\Phi_3P^+CH_3(TCNQ)_2^{-}$ at 315°K. He tentatively attributed this to a phase transition in the crystal. This transition has been the subject of some more recent work by Iida et. al.[38,39] They observed sharp discontinuities

in both the intensities and line widths of the ESR spectra and the same in the resistivities over a range near 315°K.[38] Preliminary x-ray diffraction measurements showed that there was a slight, but clear difference in the crystal lattice before and after the transition temperature. The small value of the enthalpy change for the transformation has also supported the x-ray data.[39]

Aust, Samara, and Drickamer[40] have published a study of the effects of high pressure on the properties of TCNQ and a few of its ion-radical salts.

A few results have been reported concerning the ESR absorption of the TCNQ anion-radical in solution.[41,42] Fisher and McDowell,[41] by generating the radical by electrolysis at a Pt electrode, observed a well-resolved spectrum which was interpreted as arising from the expected hyperfine interactions of the unpaired electron with four equivalent nitrogen and hydrogen nuclei (45 lines). This is to be contrasted with an earlier attempt to study the ESR of electrolytically generated $TCNQ^{\cdot-}$.[43] Some C^{13} splittings were observed, and theoretical ones were calculated. However, later work[42] involving C^{13} enriched $TCNQ^{\cdot-}$ showed that the C^{13} splitting calculated from the simple Hückel LCAO or McLachlan theory and the σ-π parameters of Fraenkel et. al.[44] are not in very good agreement with experiment and that the previous assignments based on the above theories and the hyperfine splitting arising from C^{13} in natural abundance are in error.

In conclusion, although 7,7,8,8-tetracyanoquinodimethan does not undergo Diels-Alder reactions[2] as does its close relative tetracyanoethylene, the compound shows interesting chemistry, the most notable of which is the formation of simple and complex anion-radical salts. These salts show remarkable solid-state properties which have initiated a large amount of experimental and theoretical study. Further work on the mechanism of the synthesis of the complex anion-radical salts of amines would be in order. Perhaps even more conductive TCNQ salts may be synthesized which will eventually find use in the electronics industry.

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SOME PHOTOCHEMICAL ISOMERIZATIONS IN THE VITAMIN D SERIES

Reported by Wayne R. Messer February 21, 1966

INTRODUCTION

The original impetus to study in this area was the observation that irradiation of certain foods leads to an increase in their ability to prevent rickets.[1] Further work demonstrated the inactive precursors were steroids which were transformed into vitamin D upon irradiation.

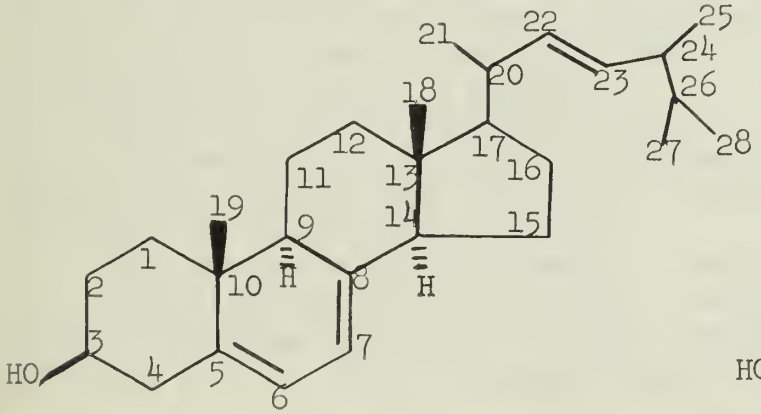
These transformations are of interest both because of the biolgical activity of the compounds formed and because of the number and complexity of related products. The products offer the first examples of the photochemical reactions of the 1,3-cyclohexadiene chromophore. The structures determined in this series are often cited as analogies for structures proposed or determined in other examples. Therefore, it is pertinent to examine the evidence upon which these structures are based.

It will be the purpose of this seminar to discuss the structure of one example of each photochemical isomerization observed, with the exception of cis-trans, for which a recent review is available.[2] The chemistry of these compounds has been reviewed[3,4,5] and will be outside the scope of this seminar.

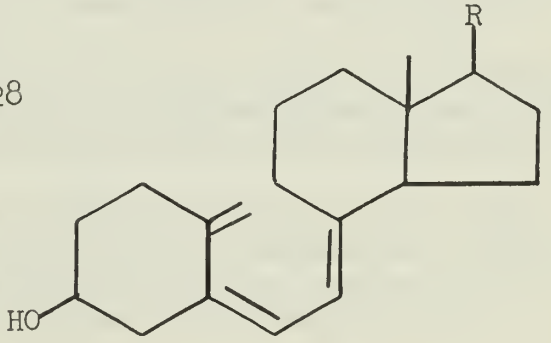
The steroid numbering system, shown in I, will be used. Wedges indicate substituents above the plane of the system and are referred to as β-substituents. Dotted lines are below and designated α. Wedges or dotted lines not carrying substituents imply the presence of a methyl group.

ERGOSTEROL-PRECALCIFEROL

The intermediacy of precalciferol in the photochemical conversion of ergosterol (I) to calciferol (=vitamin D) (II) was not known for many years due to the easy thermal conversion of precalciferol to calciferol. By carrying out the irradiation at 20° in ether, rather than approximately 50° in ethanol according to the usual procedure, precalciferol could be isolated as its 3,5-dinitrobenzoate ester.[6] It was found that starting with either calciferol or precalciferol the same equilibrium mixture of the two was obtained upon heating.[7] This equilibration was determined by the change in optical rotation upon heating either of the 3,5-dinitrobenzoates in benzene at 60° and isolation of the corresponding 3,5-dinitrobenzoates.



I



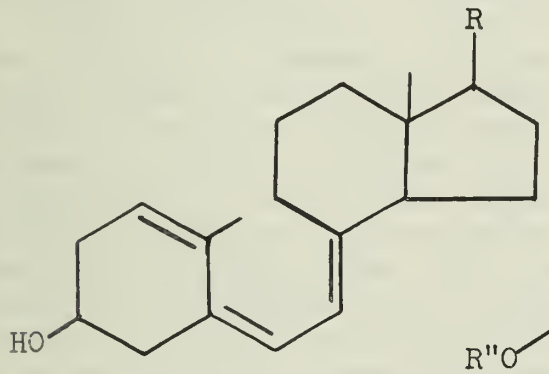
II

The ease of thermal interconversion led to the suggestion that precalciferol might be calciferol with the 10-19 double bond in the 10-1 position (III), a cis-trans isomer of calciferol, or an s-cis s-trans isomer. It also limited the reactions which could be used to determine the structure to those not requiring an elevated temperature. These included ozonolyses which were carried out at 0° followed by zinc in acetic acid, typical reducing conditions. The formaldehyde formed was determined as its dimedone derivative. In parallel experiments, the dinitrobenzoates

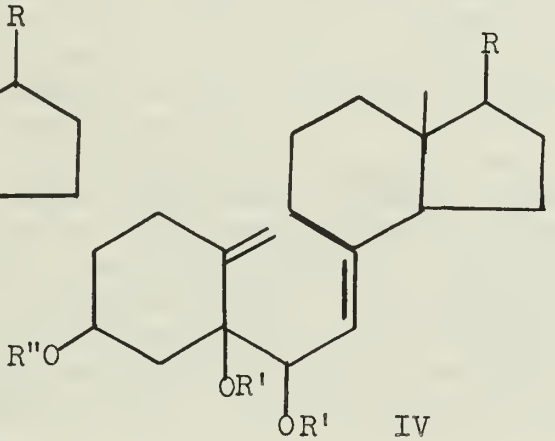
of equimolar amounts of ergosterol (I), precalciferol (VII), and calciferol (II) gave formaldehyde in the ratio of 1:2:10.4.[8] Similarly, without the double bond in the side chain, the ratio from II and VII was 1:10. Also, the infrared spectrum of precalciferol does not show a band near 900 cm^{-1} which is present in calciferol and attributable to the terminal methylene group. These results argue against the structures possessing terminal methylene groups.

Treatment of the dinitrobenzoate of calciferol with lead tetraacetate at room temperature produces the diacetate (IV R' = $COCH_3$, R" = 3,5-dinitrobenzoate), which can be saponified to the triol (IV R' = R" = H).[9] Treatment of the triol with lead tetraacetate gives the aldehyde (V). Similar treatment of precalciferol 3,5-dinitrobenzoate did not furnish any crystalline material, even upon treatment with semicarbazide.[8] Similarly, oxidation of calciferol with CrO_3 leads directly to the aldehyde (V)[10], isolated as the semicarbazone, while precalciferol furnishes no crystalline products.[8] These results eliminate structures possessing a 5-6 double bond and the same geometry around the 7-8 double bond.

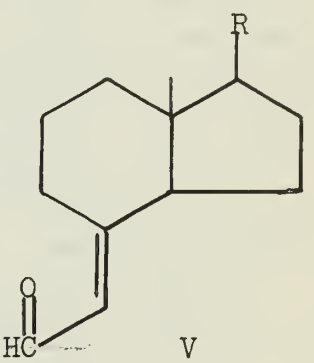
Thus, the structures originally suggested were rejected, although combinations



III



IV



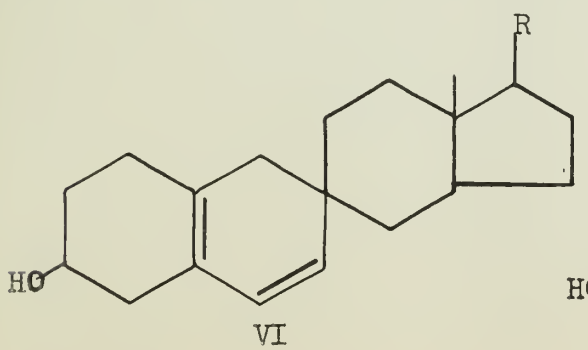
V

of the changes suggested could still give acceptable structures. The authors preferred to suggest the possibility of the spiro-steroid (VI) as the structure, based on known thermal analogies in larger rings.

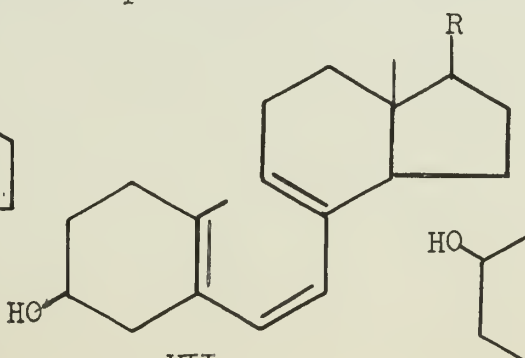
This structure was rejected when it was found that I_2 in nonpolar solvents rapidly converts precalciferol (VII) to tachysterol (VIII)[11], the structure of which had been previously determined. This isomerization reaction together with the other evidence cited shows that precalciferol is the cis isomer of tachysterol. Ultraviolet radiation was observed to effect the conversion of tachysterol to precalciferol as would be expected.

The conversion to tachysterol was followed by the shift in ultraviolet maximum and increase in absorption during the reaction. The tachysterol was isolated as its 3,5-dinitrotoluylate and identified by melting point, mixed melting point, optical rotation and x-ray powder diagrams.

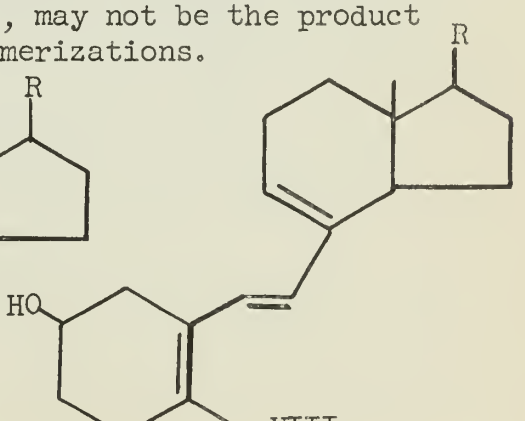
The conversion of ergosterol to precalciferol illustrates the usual behavior of 1,3-cyclohexadienes upon irradiation. A sigma bond is broken and a new pi bond is formed to give an open chain triene. The triene, however, may not be the product isolated because it can undergo further photochemical isomerizations.



VI



VII



VIII

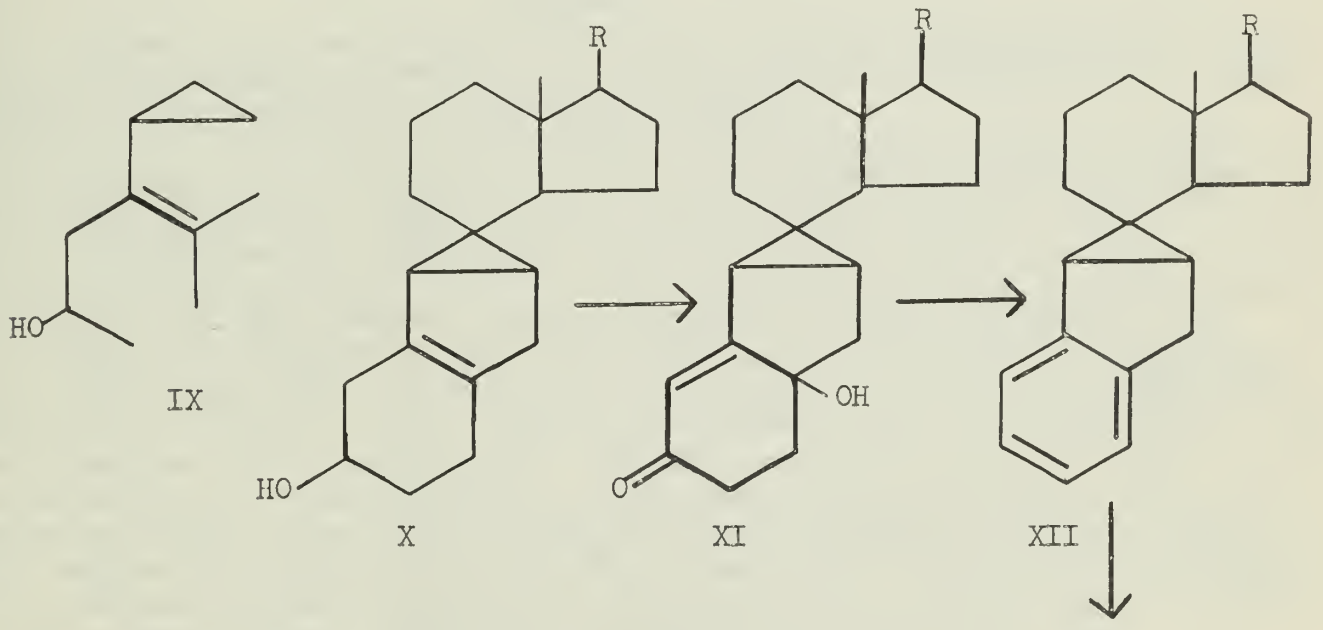
CALCIFEROL-SUPRASTEROL-II

Further irradiation of vitamin D, for example, leads to products possessing mainly end absorptions in the ultraviolet. Of these, only the structure of suprasterol-II has been determined.

Quantitative microhydrogenation in acetic acid showed three reactive groupings,[12] one being the double bond in the side chain. The NMR showed two vinyl protons. Osmium tetroxide gives a triol still possessing a band at 970 cm^{-1} in the infrared for the side chain double bond. This can be hydrogenated to give a 22-dihydro derivative possessing only end absorption in the ultraviolet (ϵ_{205} 140). The formation of a triol suggests there is only one tetrasubstituted double bond and not two. Similarly, the low end absorption in the ultraviolet suggests there is not a tetrasubstituted double bond remaining. Suprasterol-II therefore has five rings from its analysis.

A tetrahydosuprasterol-II can be prepared which has end absorption (ϵ_{205} 5200) in the ultraviolet. Comparison with 22-dihydrosuprasterol-II (λ_{max} 210 mu, ϵ 7100) implies conjugation of a cyclopropane ring with the double bond in the latter.

The relationship of the alcohol to the other groups was gained by considering its oxidation. Treatment of 22-dihydrosuprasterol-II with CrO_3-H_2SO_4 in acetone, Jones' reagent, gave an oily ketone having no maximum in the ultraviolet above 220mu. Chromatography upon alumina isomerizes the double bond into conjugation with the ketone as shown by the ultraviolet absorption (λ_{max} 268 mu, ϵ 19,200). For this isomerization to occur, the double bond must originally have been β,γ to the hydroxyl. Similar treatment of tetrahydrosuprasterol-II gives a conjugated ketone from an unconjugated one, this time with λ_{max} 242 mu (ϵ 14,600). The difference shows the cyclopropane ring is also conjugated after migration of the double bond. This latter ketone may be ozonized and then methylated to give a keto-ester with infrared absorption at 1736 cm^{-1} (ester) and 1704 cm^{-1} indicating a ketone in a six or larger membered ring. The structural relationship is summarized in IX.



IX X XI XII

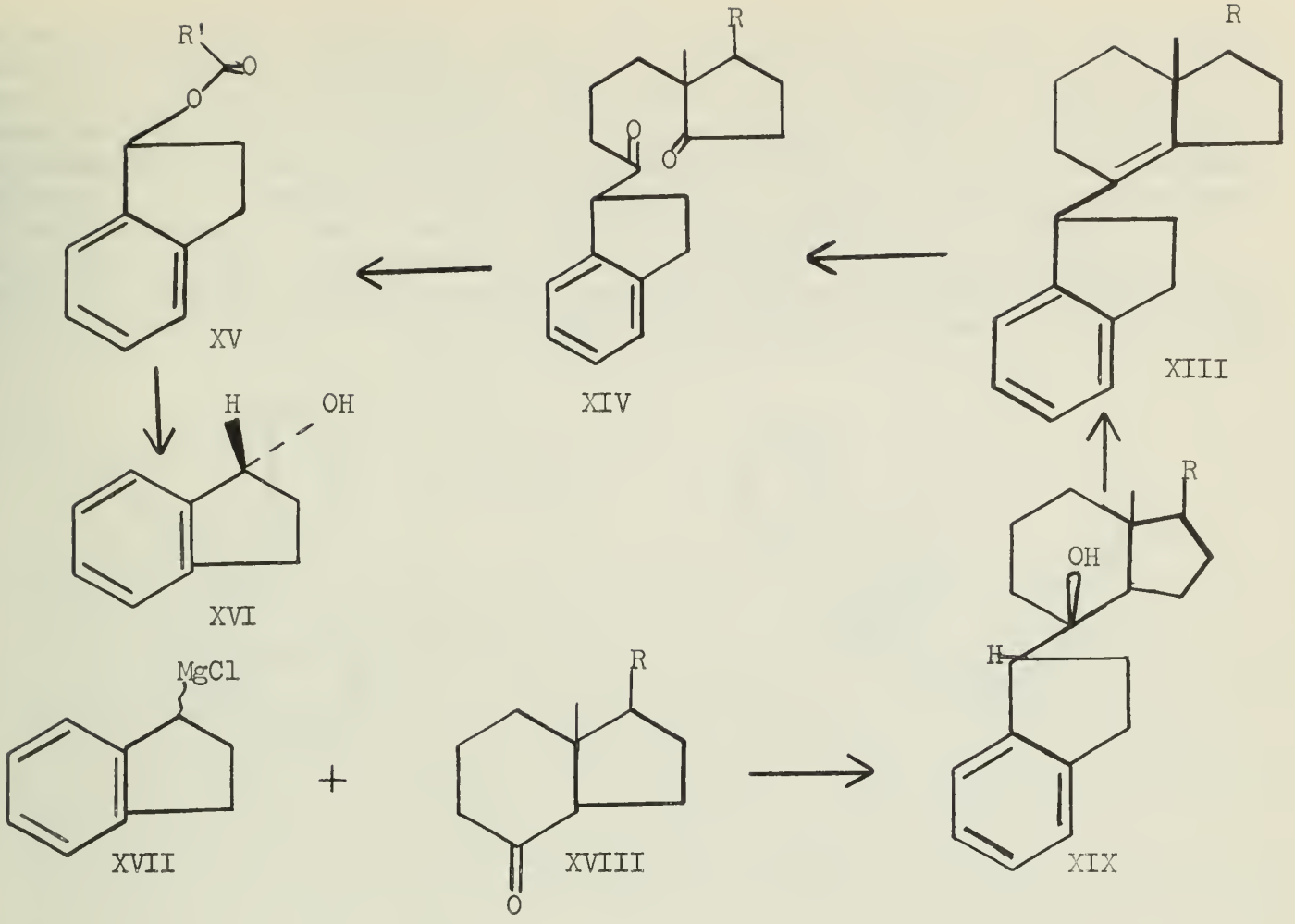


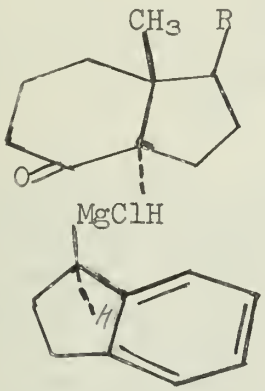
Figure 1

The structure X was put forward as the mostly likely compound derivable from calciferol and possessing the required structural features. Confirmation of this was obtained by the degradation[13] outlined in Figure 1.

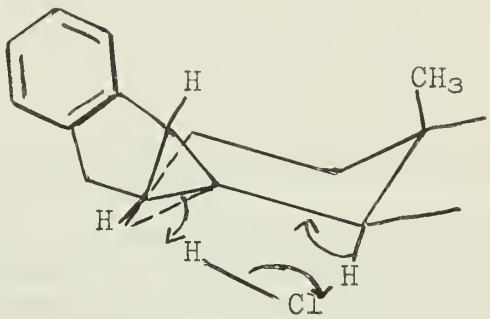
Beginning with 22-dihydrosuprasterol-II (X), the hydroxyenone XI could be obtained by chromic acid oxidation in pyridine or epoxidation followed by Oppenauer oxidation. The ultraviolet, λ_{max}^{EtOH} 263 mu (ϵ 13,100), and infrared, 1670 cm^{-1}, are consistent with the assigned structure. Lithium aluminum hydride reduction followed by dehydration at -15° with thionyl chloride in pyridine gave the aromatic derivative XII. The NMR spectrum showed 4 benzenoid protons. Treatment with hydrogen chloride in chloroform caused rearrangement to a mixture of components, the major (80%) being XIII. The ultraviolet spectrum of the mixture ($\lambda_{max}^{Cyclohexane}$ 273, 266, 259 mu (ϵ 1,760, 1,930, 1,990)) was similar to that of indane, indicating the double bond was not in conjugation. The NMR showed less than 0.2 vinyl protons, suggesting a tetrasubstituted double bond. The structure was established by dehydration of the minor alcohol (XIX) obtained from the reaction of racemic 1-indanyl magnesium chloride (XVII) and the ketone (XVIII) available from vitamin D_2. The product was identical with XIII and could also be degraded by the present scheme to the same product. Osmylation followed by treatment with lead tetraacetate gave the diketone XIV with ν_{max} 1740 cm^{-1} (5-membered ring ketone) and 1710 cm^{-1} (6-membered ring or open chain ketone). Treatment with peracetic acid caused rearrangement to the ester XV which could be reduced with lithium aluminum hydride to (-)-1-indanol (XVI), a known compound.

The stereochemistry of suprasterol-II was elucidated by considering the stereochemistry of the Grignard reaction and probable mechanism of the cyclopropane ring opening. Assuming that the five and three membered rings are cis fused, there are four possible structures for suprasterol. Two were eliminated by assigning the absolute configuration of (-)-1-indanol from the results of the Grignard addition.

Assuming the angular methyl group shields the topside of the ketone, the racemic Grignard can add in two manners, the more hindered one being shown in XX. This is expected to give the minor alcohol which leads to (-)-1-indanol. Therefore, by assuming retention of configuration for the subsequent steps, (-)-1-indanol can be assigned the absolute stereochemistry shown in XVI. Only two of the possible structures give 1-indanol of this configuration. A choice between them was made by rationalizing the fact that the opening of the cyclopropane ring gave only unconjugated olefin. This suggests that a carbonium ion is not involved. A cyclic six membered transition state, shown in XXI, rationalizes the specificity. Such a transition state is only possible for the compound shown of the two giving



XX



XXI

the correct 1-indanol. Although stereochemical assignments based upon Grignard additions are not always reliable, the assignment made has been confirmed by an x-ray study of the 4-iodo-5-nitrobenzoate.[14]

Bicyclo (3.1.0) hex-2-enes, such as suprasterol-II, are often obtained upon irradiation of trienes or 1,3-cyclohexadienes. Such products obtained from the latter can be rationalized as arising from further irradiation of the expected triene, although the triene may not be observed in every case.

ISOPYROCALCIFEROL-PHOTOISOPYROCALCIFEROL

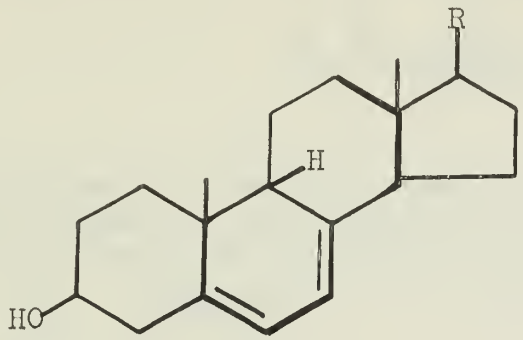
The other photochemical isomerization observed for 1,3-cyclohexadienes, although not observed in as many examples, is formation of a new sigma bond with loss of a pi bond to produce a bicyclo (2.2.0) hex-2-ene. This is illustrated in the vitamin D series by the photochemical reactions of pyrocalciferol and isopyrocalciferol.

Heating calciferol to 180° leads to two new isomers, pyrocalciferol and isopyrocalciferol (XXII). These can be irradiated to yield two new products, photopyrocalciferol and photoisopyrocalciferol.[15] The similarity of these products is shown by the fact that they undergo similar transformations in the following reactions, although only photoisopyrocalciferol will be discussed.

That photoisopyrocalciferol possesses two double bonds was suggested by microhydrogenation of the alcohol and its acetate.[15] Titration of the tetrahydroproduct with perbenzoic acid did not lead to the consumption of any perbenzoic acid.[16] Titration of the photoproduct itself with perbenzoic acid showed two double bonds. More recent studies by NMR have shown that the compound possesses four vinyl protons,[17] two being on the trans double bond in the side chain. The infrared showed absorptions at 970 cm^{-1} and 748 cm^{-1} (doublet), characteristic of trans- and cis-disubstituted double bonds respectively. That the tetrahydrophotoisopyrocalciferol was saturated was also suggested by its low end absorption (ϵ_{205} 250) in the ultraviolet. Its stability to hydrogen chloride in chloroform ruled out

the presence of a cyclopropane ring. Thus, photoisopyrocalciferol possesses five rings and two double bonds.

It was shown that the double bond is not in ring A by oxidation of photoisopyrocalciferol with chromium trioxide in acetic acid.[16] Neither the ketone nor its semicarbazone had absorption in the ultraviolet above 226 mu. This rules out a



XXII

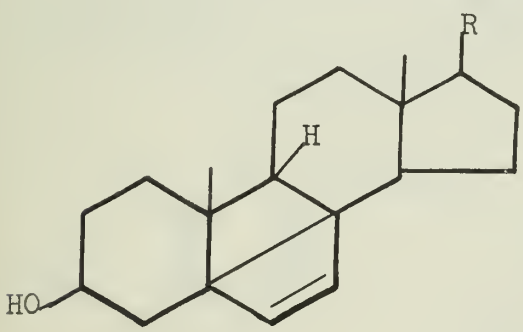
double bond α, β or β, γ to the alcohol because under these conditions the double bond would be expected to migrate into conjugation.

Upon heating to 180°, photoisopyrocalciferol is reconverted to isopyrocalciferol.[15] This indicated that the double bond should be placed in ring B, in the 6-7 position. The results of ozonolysis of photoisopyrocalciferol acetate are consistent with this.[17] After treatment with hydrogen peroxide, a tricarboxylic acid with the correct neutralization equivalent can be isolated. Treatment with acetic anhydride and distillation of the solvent gives an anhydride (ν_{max} 1770 and 1825 cm^{-1}),[18] which shows the proximity of two of the acid groups.

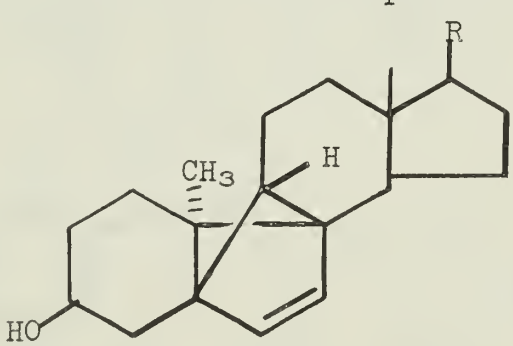
On the basis of these considerations, the structure XXIII was advanced although it was pointed out that XXIV might be possible.[17] The specificity of the thermal reconversion makes XXIV unlikely, but as no bicyclo (2.1.1) hexenes are known it cannot yet be shown that such specificity is impossible.

The product obtained upon treatment of photoisopyrocalciferone with potassium t-butoxide was consistent with structure XXIII for photoisopyrocalciferol. It had λ_{max}^{EtOH} 283 mu (ϵ 24,700), consistent with structure XXV. The same product was obtained upon treatment of isopyrocalciferone with refluxing methanolic potassium hydroxide. Both products could arise via the enol XXVI. Again this conversion favors XXIII over XXIV.

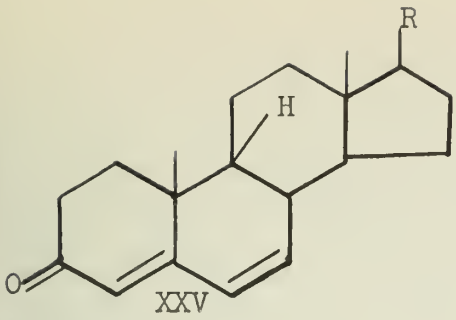
In another system[19] the bicyclo (2.1.1) hexene has been definitely ruled out. This also may be used to argue against its likelihood in the present case.



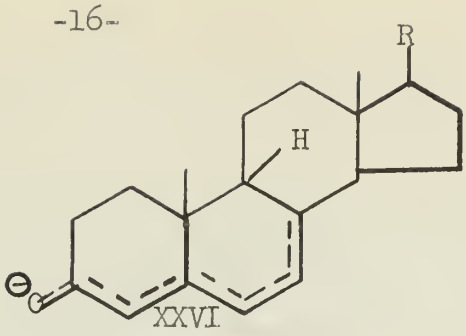
XXIII



XXIV



XXV

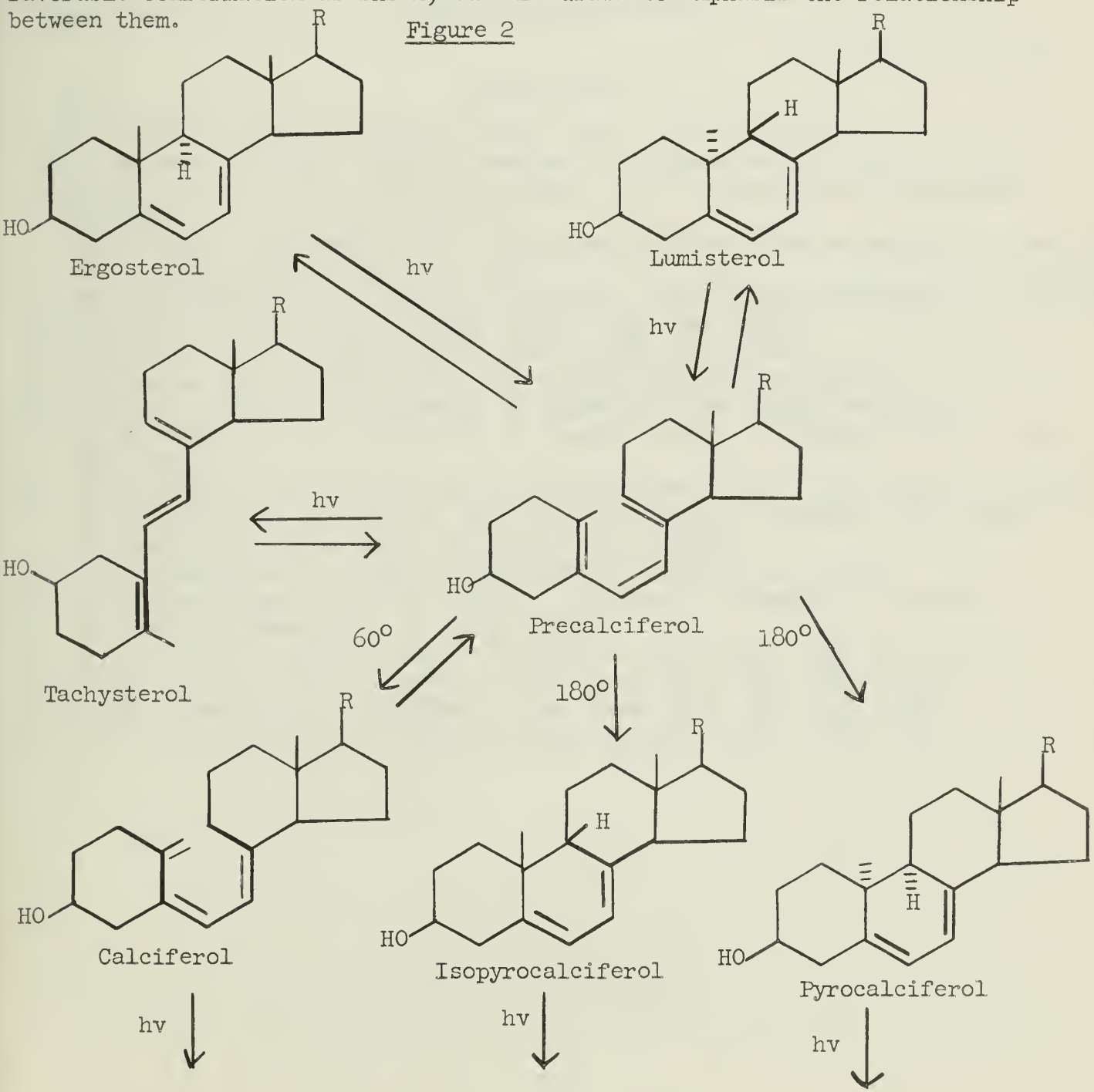


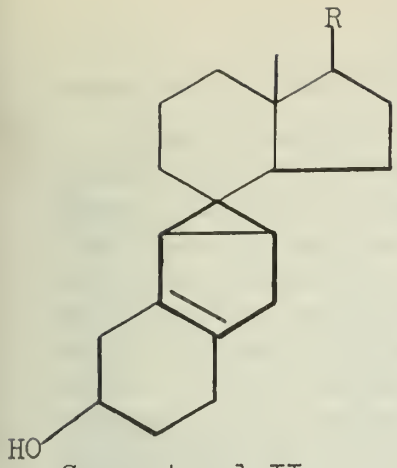
XXVI

SUMMARY

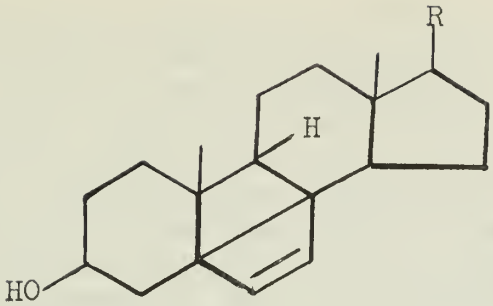
The relationship between the various compounds of photochemical and thermal origin is summarized in Figure 2. The compounds are not necessarily in the most favorable conformation as shown, but are drawn to emphasis the relationship between them.

Figure 2

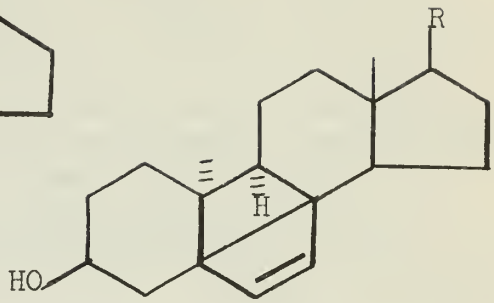




Suprasterol-II



Photoisopyrocalciferol



Photopyrocalciferol

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SOME ORGANIC INSECTICIDES AND THEIR EFFECTS

Reported by John Engelmann February 24, 1966

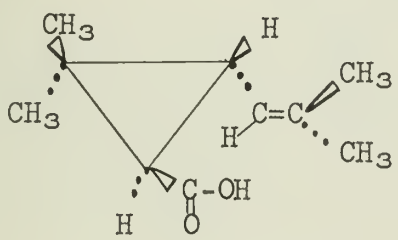
The voluminous literature on insecticides is devoted largely to empirical studies of the efficacy of specific chemicals in controlling specific insects. There is little information on the relationship between the chemical structure of the insecticides and the chemical processes which they alter within the living organism. Therefore, the latter aspect will not be discussed in this seminar; we will concern ourselves with a few well-known and widely used organic insecticides which, however, appear to affect the nervous system in ways which are not understood. These compounds are the pyrethroids and the synthetic analogs, the rotenoids, the chlorinated hydrocarbons, and the anticholinesterases; all are contact poisons which are absorbed into the body of the insect through the cuticle rather than through the alimentary canal.

The permeability of the insect cuticle determines the efficacy of these poisons. Wigglesworth has shown that by scraping the waxy layer of the cuticle with alumina before applying insecticides, he increased the toxicity of the poisons.[1-2] Other researchers have noted that the thinner the epicuticle, the more effective the contact insecticide.[3]

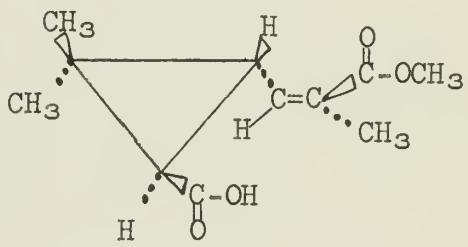
PYRETHROIDS

The natural pyrethroids are substances isolated from plants belonging to the genus Chrysanthemum, family Compositae. The majority of the pyrethrins are found in the head of the flower and only small amounts in the stem. The structure of the pyrethroids and their synthesis are very well covered in the literature and are reviewed in several places.[4-15]

Natural pyrethrin is a mixture of esters. There are two closely related acids, chrysanthemic acid (I) and pyrethric acid (II). There are two alcohols,

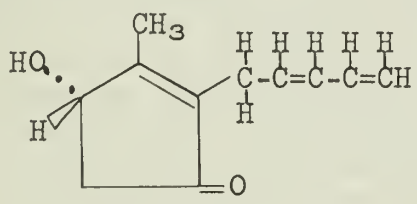


I

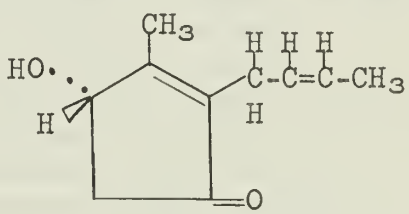


II

pyrethrolone(III) and cinerolone (IV). All possible esters are found. The esters



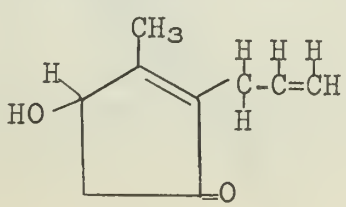
III



IV

of chrysanthemic acid are called pyrethrin I and cinerin I while the esters of pyrethric acid are called pyrethrin II and cinerin II.

Allethrin is a synthetic industrial substitute for natural pyrethrins. It is an ester of chrysanthemic acid and alcohol (V). The chrysanthemic acid has both



V

cis and trans isomers, and each of these isomers has a d and l form. Since the alcohol also has d and l forms, there are eight possible isomers of the ester. The industrial product should contain all of these isomers.

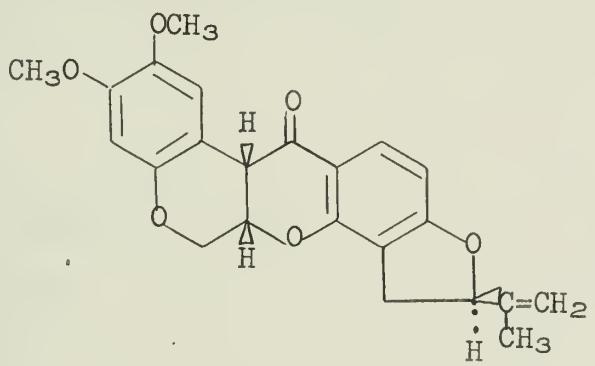
There is some controversy concerning the relative toxicity of allethrin and pyrethrin. For example, Mitlin and Babers showed that at an LD_{50} dosage, natural pyrethrins, when applied to the abdomen of the American cockroach, were 6.5 times as effective as allethrin, while against the common housefly, allethrin was 1.22 times as effective as natural pyrethrins.[16] The authors did not feel that the difference in effectiveness of allethrin and pyrethrin against houseflies was significant. In contrast to this finding, Nash concluded that natural pyrethrin, when applied to the abdomens of houseflies, was twice as effective as allethrin.[17]

The work of Mitlin seems more reliable since his allethrin was purified, while Nash states that her allethrin was only 80% pure as determined by some unspecified biological assay method. It is well to remember that different preparations of pyrethrins and allethrins can contain different proportions of the various isomers. Since the isomers have different toxicities, the potency of mixtures can vary. To be meaningful, comparisons of toxicity should be made between pure isomers rather than between mixtures of isomers.

Pyrethrins act on the nervous system of an insect. The exact mode of action of pyrethrins is not known. It has been shown, however, that pyrethrins do not affect the oxygen metabolism of nerve or muscle cells.[20]

ROTENOIDS

The chemistry of rotenoids has been extensively reviewed.[27] There are several closely related substances in naturally occurring rotenoids. The structure of the one called rotenone is shown below.



VI

Rotenone can enter the insect through the cuticle but entry through the spiracles is probably more important.[18] It can act as a stomach poison in certain insects, but the toxicity to different species is highly variable. The reason for this seems to be that some insects do not absorb rotenone from the gut.[19]

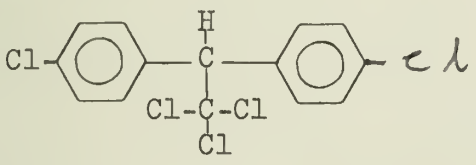
Rotenone seems to act by upsetting the oxygen metabolism of both muscle and nerve cells. The oxygen uptake of insect muscle and TTC staining of a nerve cord were depressed by treatment with 5×10^{-5}M. rotenone, while they were not influenced by 5×10^{-5}M. parathion or by 6.6×10^{-5}M. pyrethrins.[20] TTC staining is a method for assaying oxygen metabolism. In normal tissue, a red stain is produced, but if the oxidative metabolism is blocked, less stain (or none at all) is seen. The authors were able to demonstrate that the inhibition of oxygen metabolism is due to interference with the oxidation of L-glutamate to α-Keto glutamate. In addition, the authors demonstrated that rotenone had no anticholinesterase activity.

CHLORINATED HYDROCARBONS

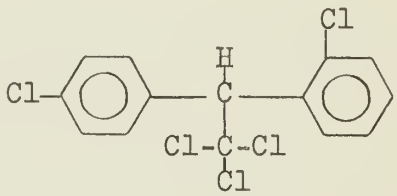
DDT was first synthesized by Zeidler in 1874 by the reaction of chloral with chlorobenzene in the presence of H_2SO_4.[21] Today, commercial DDT is prepared in the same way. The insecticidal properties of DDT were not discovered until 1939.[22]

The composition of commercial DDT was determined in 1945 by Haller and co-workers[24] and in 1946 by Forest and co-workers.[23] Their results were essentially the same. They found that around 70% of the commercial DDT was 2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane (p,p'-DDT). (VII)

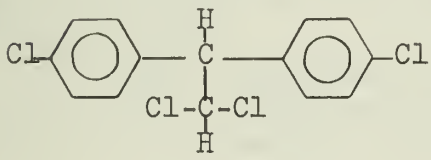
The only major impurity was 2-(o-chlorophenyl)-2-(p-chlorophenyl)-1,1,1-trichloroethane (o,p'-DDT). (VIII) There were several other impurities of interest, however. One of these was 2,2-bis-(p-chlorophenyl)-1,1-dichloroethane (p,p'-DDD). (IX) There was also a very small percentage of (o,p'-DDD). (X) Forrest speculates that these products come from dichloroactaldehyde in the chloral used as a starting material. The half condensation product of chloral and chlorobenzene, 2-(p-chlorophenyl)-1,1,1-trichloroethanol (XI) was also found. The p-chlorobenzene-sulfonate ester of the related 2-(o-chlorophenyl)-1,1,1-trichloroethanol (XII) and the bis-(p-chlorophenyl) sulfone (XIII) were also found as were several other trace impurities.



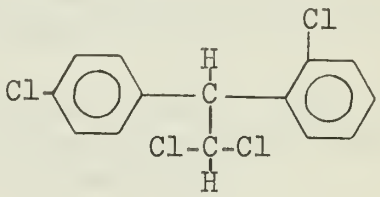
VII



VIII



IX



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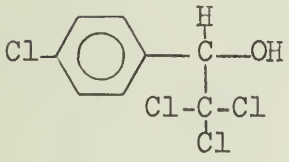
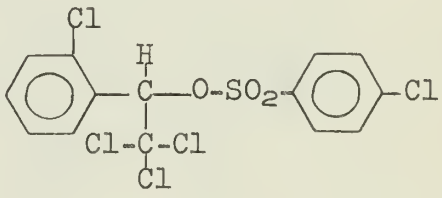


XI



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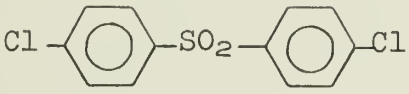


XIII

The symptoms of DDT poisoning and their sequence are described by Tobias and Kollross.[25] The insect shows: 1) hyperextension of the legs, 2) increasing tremors, 3) ataxic gait and hyperactivity resulting from stimulation, 4) the animal falls repeatedly on its back and finally fails to right itself, 5) leg movement--a fast tremor and a slow extension and flexion--continue, 6) tremors disappear, leaving only isolated motions, and 7) the heart finally stops beating.

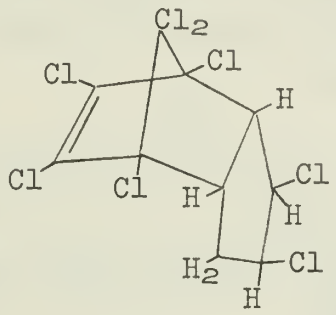
These symptoms suggest that DDT affects the nervous system. The exact mechanism of DDT poisoning is not clear. Fukami has shown that DDT has no effect on the oxygen uptake of the muscle cells or on TTC staining of nerve cords.[20] It has also been reported that DDT strongly inhibits succinic dehydrogenase.[34]

Whatever the exact mechanism, DDT apparently has an effect on the sensory peripheral nervous system.[35-36] Injection of a suspension of DDT into the leg of a cockroach changes the nature of the impulses carried by the afferent neurons. In the normal immobilized animal, the afferent neurons of the leg conduct occasional impulses. When DDT suspension is injected, however, the occasional impulses are

replaced by groups of high frequency impulses, which appear to be caused by the self-excitation of certain sensory cells. Motor neurons and the C.N.S. seem to be relatively insensitive to DDT.

Several insecticides are formed from hexachlorocyclopentadiene, but we will consider only five of these. The structures reported here are the ones accepted in the literature.

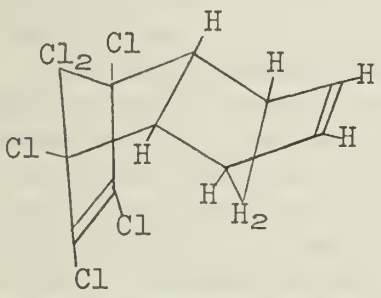
The first compound, chlordane (XIV), is formed by chlorination of a Diels-Alder adduct of hexachlorocyclopentadiene and cyclopentadiene.[26] There is a possibility for cis-trans-isomerism in the five member ring which contains the two chlorines.



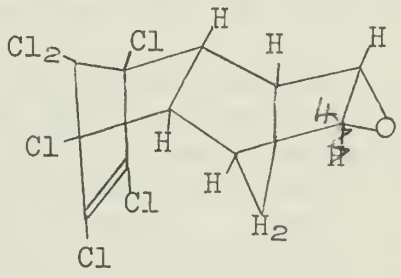
XIV

Cristol has suggested that since β-chlordane readily dehydrohalogenates with 0.04 M ethanolic NaOH while the α-compound is inert, the β-compound should have the cis configuration.[28]

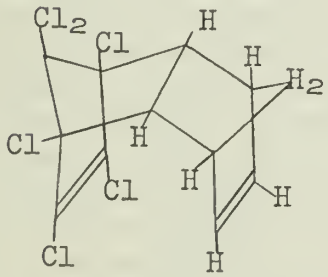
The other insecticides are aldrin (XV), isodrin (XVII), dieldrin (XVI), and endrin (XVIII). Aldrin and isodrin are isomers with the same empirical formula. Dieldrin is an epoxide of aldrin; endrin is an epoxide of isodrin.[38]



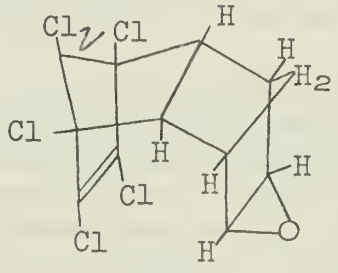
XV



XVI



XVII

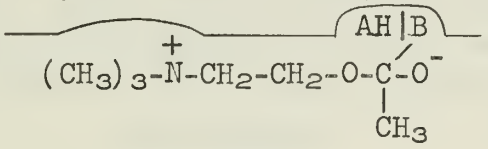


XVIII

Aldrin is prepared by the reaction of cyclopentadiene with acetylene. The resulting adduct is reacted with hexachlorocyclopentadiene.[29] Isodrin is prepared by treating hexachlorocyclopentadiene with vinyl chloride and then reacting this substance with cyclopentadiene.[30] The epoxides can be formed by reacting the parent compound with a peracid. Very little is known about the mode of action of these insecticides. It would seem likely, however, that they affect the nervous system.

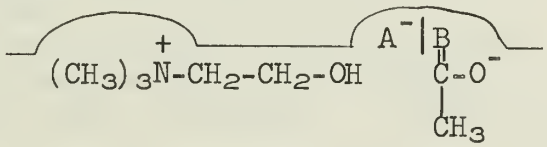
ANTICHOLINESTERASES

There are two types of anticholinesterases: the carbamates ($R\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}R'$) and the phosphate esters, which we will consider here. To understand the effects of the organic phosphate esters, it is helpful to comprehend the nature of the enzyme cholinesterase. According to Wilson, the enzyme contains two active sites.[31] One of these sites is an anionic site which can bind the $(CH_3)_3\overset{+}{N}\text{-}R$ group of the acetylcholine. The second is an esteratic site which can bind the ester portion of the molecule. A diagram of the enzyme substrate complex is shown below. Wilson proposes



XIX

that an H is transferred from the esteratic site to the choline which yields



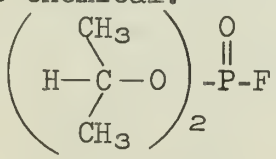
XX

The choline diffuses away, the A site recovers a proton from water and the acetyl group picks up a hydroxyl, forming acetic acid. Friess and his co-workers agree with this two-site theory except that they propose that the esteratic site attaches to the substrate through an oxygen.[32-33]

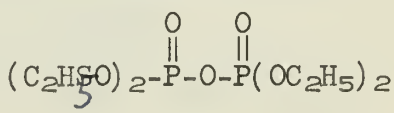
The anticholinesterases act by combining more or less irreversibly with the esteratic site of the enzyme. The esterase site is phosphorylated by the phosphate portion of the molecule. This phosphate group is not readily removed. The enzyme is thus blocked and is unable to act on acetylcholine which can then build up in concentration.

The acetylcholine has an important role in the nervous system. In mammals, the action of motor nerves on the muscles and, in the autonomic nervous system, the transmission of the nerve impulses across the synapse are mediated by actylcholine. The mediation of acetylcholine in the synapse can be described in the following manner. Suppose that a nerve impulse arrives at a synapse. A small amount of acetylcholine is released by the nerve which conducted the impulse to the synapse. This acetylcholine induces an impulse in the other nerve which leads from the synapse. The enzyme cholinesterase rapidly destroys the acetylcholine. The destruction of the acetylcholine serves to limit the response of the second nerve to a signal traveling in the first. When cholinesterase is blocked, the acetylcholine is not destroyed or only partially destroyed. The concentration of acetylcholine builds up and results in excessive stimulation of the second nerve and finally complete blockage of the nerve.

The phosphate esters which have anticholinesterase activity have widely varying structures. DFP (XXI), TEPP (XXII), and paraoxon (XXII) all show such activity *in vitro* and *in vivo*. Substances which contain a sulfur atom replacing an oxygen atom, such as parathion (XXIV), are also used as insecticides. Carefully purified samples of parathion, however, show little anticholinesterase activity *in vitro*.[37] The *in vivo* anticholinesterase activity is a result of a change in the structure of the chemical.



XXI



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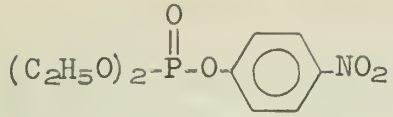
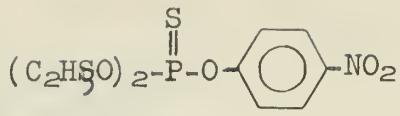


XXIII



XXIV

CONCLUSIONS

It is apparent that all of the organic insecticides discussed here affect the nervous system of the insect. These insecticides are widely used but except in the case of rotenone and the organic phosphates, the exact mode of action is unknown. More work is necessary to establish the precise mechanisms involved.

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FLASH PHOTOLYSIS

Reported by David V. Milligan February 28, 1966

Mechanistic photochemical investigations are often greatly simplified when one can obtain evidence as to the nature of the reaction intermediates. One method which permits direct characterization of such intermediates is flash photolysis (due to Norrish and Porter[1,2]). In this method the sample--gas, liquid or solid--is irradiated by a high intensity, short duration flash of light of the appropriate energy range. Then the ultra-violet and visible spectrum and rate of disappearance of the photogenerated species can be determined.

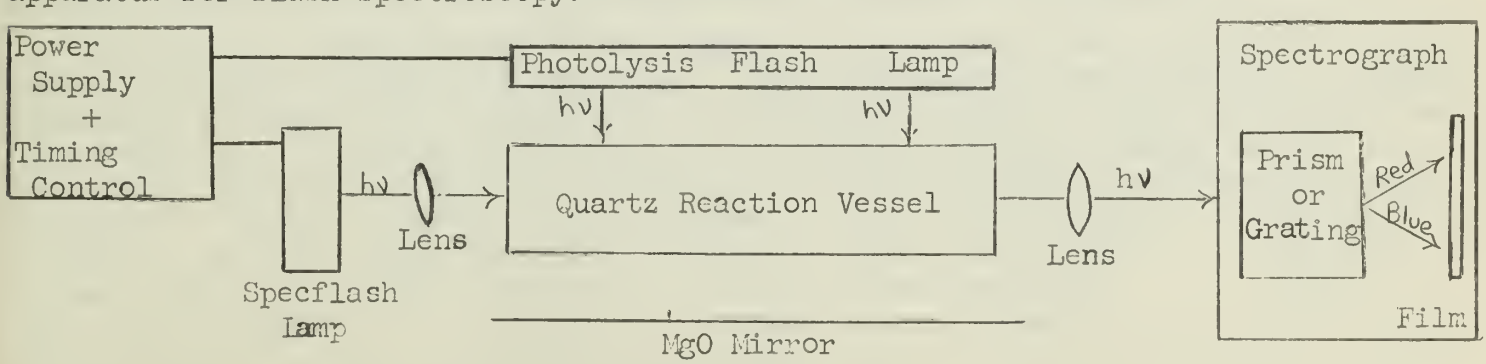
Although the subject of flash photolysis has been reviewed extensively[3-12], the viewpoint taken here will differ considerably from that in any previous review. The object of this seminar will be threefold. First, an overall description of the flash photolysis method will be given in order to facilitate general understanding. Secondly, several examples of the use of flash photolysis will be given in order to demonstrate the scope of the method, and finally, several investigations of one chemical system using both classical photochemical approaches and flash photolysis will be presented in order to show some of the possible problems encountered in the use of flash photolysis.

DESCRIPTION OF THE METHOD

The reactions of intermediates generated in a photolysis flash are usually very rapid in terms of more usual time scales.[3] Studies of fast reactions can conveniently be divided into several categories according to the time scale involved.[4] Flash photolysis is generally applicable to reactions having half-reaction times greater than five microseconds. This lower time limit stems from the finite duration of the photolysis lamp flash.[5] Studies such as those combining flash photolysis with shock tube methods[13] show promise for the elimination of this limit. A review of flash photolysis instrumentation giving a comparison of flash durations for various flash lamps is available.[12] In addition to the time scale limitations, obviously only photoinducible phenomena are amenable to study by flash photolysis.

In the study of rapid reactions two stages are especially important.[10] First, the desired reaction must be homogeneously initiated, and secondly, the ensuing reaction must be monitored. The photolysis flash serves to initiate the desired reaction by producing reactive species. In principle, the reaction that ensues can be followed by any appropriate physical analytical method which offers sufficient sensitivity, selectivity and time response and which does not alter the reaction being followed. Methods which have been used include mass spectrometry[14-16], conductivity,[17] polarography,[18,19] potentiometry,[20] and, most commonly, ultra-violet and visible spectroscopy.[3,4,7,10]

In flash spectroscopy[3] the initiating flash is followed after a set delay by a specflash of polychromatic light which passes through the sample into a spectrograph containing a prism and photographic plate. The following diagram shows a typical apparatus for flash spectroscopy.[3,12]



This method thus provides a photographic record of the optical density of the sample over a wide wavelength range at a given time after the photolysis flash. Through the use of various delay times, the changes in concentration of an absorbing species can be determined as a function of time. Alternatively, once an analytically suitable wavelength has been determined for a given species, the method of kinetic spectrophotometry[3] can be employed. In this method the specflash is replaced by a suitable ultra-violet or visible lamp which remains lighted throughout the experiment. The photographic plate is then replaced by a photomultiplier detector and oscilloscope with camera. This combination enables one to record the transmittance at one wavelength over time. These data can be easily converted to enable a determination of the desired rate constants.

THE APPLICATION OF FLASH PHOTOLYSIS

Knowledge of the ultra-violet and visible spectra of a flash photolysis-generated intermediate, combined with its rates of reaction under different conditions can often lead to unambiguous characterization of the intermediate. For example, one can usually determine whether the intermediate is a singlet, triplet or radical.[7] When two or more intermediates compete, their respective chemical roles can often be determined.

Bryce and Wells' investigation[21] into the photoreduction of 2-acetonapthone in the presence of a hydrogen atom donor demonstrates some methods used to distinguish between radicals and triplets. Although two intermediates were observed using flash spectroscopy on a sample containing the hydrogen atom donor, only the shorter lived intermediate was observed when the donor was absent. After thirty flashes without donor the solution remained unchanged indicating an electronically excited state. The shorter lived intermediate was quenched upon the addition of 1-napthol which was known to have a low-lying triplet level. Thus it appeared that this intermediate was the first triplet state of 2-acetonapthone. Subsequent triplet photosensitization using triphenylene as a sensitizer confirmed this finding. The longer lived state was thought to be a radical because of the changes observed in solution after multiple flashing, the relatively long half-life (10 milliseconds) shown by the species and the analogy of this species to the radical observed in the photoreduction of benzophenone.[22]

Flash photolysis of glasses (glass-like frozen solvents) will also serve to distinguish between radicals and triplets.[23] 2-Napthol when flash photolyzed[24] at 77°K in a glass shows phosphorescence characteristic of a triplet state. While the triplet absorption spectrum is observed to decrease, one sharp band remains until the glass is warmed. This band is characteristic of the 2-napthoxyl radical. Once the spectra of intermediates have been determined, a comparison of spectra can enable identification of these species when they are encountered again.[23] Methods similar to those above can be used to characterize an intermediate as a radical-ion,[17] nitrene,[25] carbene,[26,27] excited singlet,[28] or other reactive chemical species.[14,23]

Flash photolysis has been applied to a wide variety of investigations including the following general types:

1. The Investigation of Rates and Mechanisms of Relaxation Phenomena

"Relaxation" implies that no net change in the chemical make up of the solution occurs as a result of the investigation. Thus such studies are initiated by suddenly displacing the system from equilibrium. The system's rate of return to equilibrium is then monitored. (For a good general discussion of relaxation methods see reference 30.) Generally, the rapid addition of energy (e.g. a flash of light) provides the needed displacement. The most general reaction scheme is thus the following:

$$A \underset{\text{monitor}}{\overset{\text{initiate}}{\rightleftharpoons}} A^*.$$

Relaxation phenomena which have been studied by flash photolysis include atom recombination reactions,[31] triplet decay schemes[32] and proton transfers.[33] In relation to triplet decay, several such studies have enabled significant progress in the elucidation of the role of the triplet state in light absorption by chlorophyll.[32]

2. The Investigation of Mechanisms of Very Rapid Thermally Induced Reactions

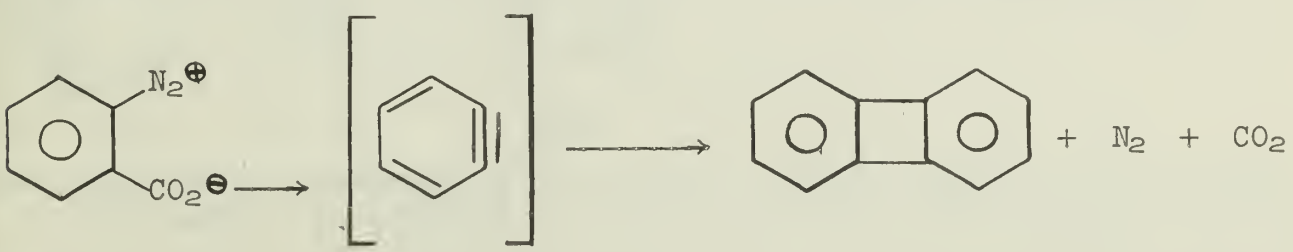
Typically in photochemical studies of gases using flash photolysis, the temperature change in the reaction vessel is much less than 10^{o} as a result of the flash.[10] This relatively small temperature rise is achieved by using a large excess of an inert gas along with a low pressure of the gas being studied; however, if the vessel is filled with only the reactive gas, then microsecond temperature increases in the order of 2000-3000^{o} can be achieved.[10] Such rapid changes in temperature provide homogeneous initiation of pyrolytic and explosive processes and have enabled the study of many gas phase reactions which are too rapid for study by classical means. By changing various conditions reaction mechanisms such as that of the oxidation of methane[34] can be determined.

Another interesting example is found in Norrish and Erhard's elucidation of the role of tetraethyl lead in the prevention of knock during the combustion of hydrocarbons.[35,36] In flash photolysis the antiknock property of tetraethyl lead was evidenced by a lengthening of the induction period between the photolysis flash and the observed explosion. The spectrum of gaseous lead oxide observed during the induction period was replaced by that of atomic lead vapor at the time of the detonation. This and other evidence led the authors to hypothesize that atomic lead intervened in the radical chain processes by reacting with hydroxyl radicals and by reducing oxygenated intermediates which had been found earlier by flash photolysis[34] to be responsible for chain branching. Both processes would yield lead oxide which would subsequently be reduced by hydrocarbon radicals to regenerate atomic lead. The failure of tetraethyl tin to show antiknock properties was attributed to the lower volatility of tin oxide which was not observed in the vapor state until after the explosion. Subsequent investigations of other antiknock compounds indicate that a heterogeneous antiknock mechanism may act in the case of iron compounds such as ferrocene.[37] The use of flash photolysis generally has made a better understanding of many explosive reactions possible.

3. Determination of the Nature of Reactive Intermediates and the Elucidation of the Mechanisms of Photochemical Processes

Flash photolysis has been used in attempts to ascertain the nature of reactive intermediates in a wide variety of investigations. For example, Porter and Ward[38] found that phenyl radicals from the flash photolysis of biphenyl could be characterized by their absorbance in the 4300-5300Å region. When a bromo-fluorobenzene was subjected to the same conditions, a bromine radical and a fluorophenyl radical were produced. The fluorophenyl radicals resulting from ortho, meta and para bromo-fluorobenzene each gave a different visible spectrum indicating that even in the excited phenyl radicals produced in flash photolysis, isomerization by hydrogen atom migration does not occur.

Additional evidence for benzyne as an intermediate has also been provided through a combination of flash photolysis and mass spectrometry.[14] The mass spectrum of the flash photolysis decomposition products of solid benzenediazonium-2-carboxylate (I) was monitored over time using a time of flight mass spectrometer.



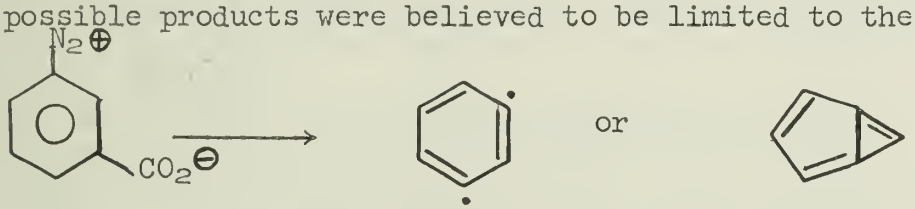
I II III

Peaks at m/e=76, 44 and 28 corresponding to molecular ion peaks from benzyne (II), carbon dioxide and nitrogen respectively were observed to appear simultaneously at a high level and then decrease while the biphenylene (III) product peak at m/e=152

increased from an initially low level to a maximum approximately 200 microseconds after the appearance of the other products. Although the observed spectra were a function of ionization voltage, only at higher voltages did the peak at m/e=76 appear as a cracking product of biphenylene. Thus, further evidence for benzyne intermediates was found.

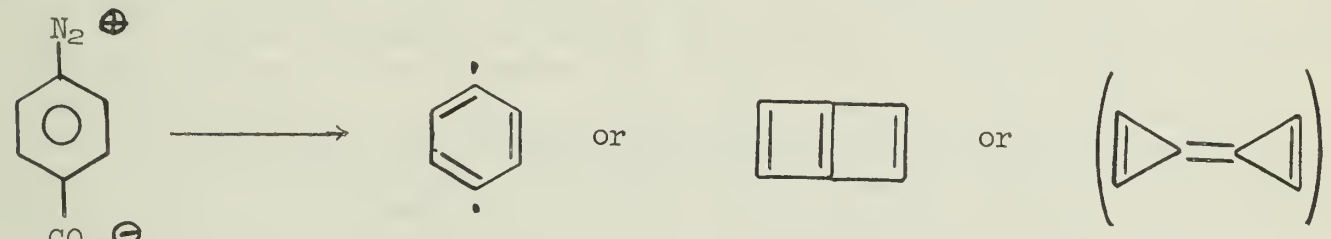
In a continuation of this investigation, Berry and coworkers[15,16] flash photolyzed the meta and para benzenediazonium carboxylates (IV and V respectively) and in both cases species showing m/e=76 were observed. The mass 76 intermediates from the ortho, meta and para compounds each showed unique mass and ultra-violet spectral properties. Surprisingly, the m/e=76 peak from the para-benzenediazonium carboxylate persisted for up to two minutes after the flash. From the available evidence including a comparison with mass spectral properties of known hexendiynes, the possible products were believed to be limited to the following:

1)



IV

2)

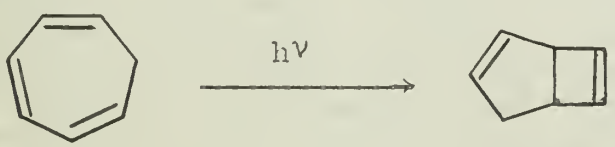


V VI

Whether the products were singlets or triplets could not be determined from the evidence at hand. Product VI was not believed likely but could not be rigorously excluded. The many reviews cited earlier can provide the reader with references to further examples of intermediate characterization by flash photolysis.

INVESTIGATIONS INTO THE PHOTOCHEMISTRY OF 1,3,5-CYCLOHEPTATRIENE

The combination of more classical photochemical methods with flash photolysis will generally enable reliable determinations of reaction mechanisms. However, the several investigations into the photochemistry of 1,3,5-cycloheptatriene serve to show some of the limitations of the method. Dauben and Cargill[39] first observed that the photolysis of cycloheptatriene (VII) in ether solution for 200 hours gave an isomeric photoproduct in 34% yield. U.V., I.R. and N.M.R. spectral evidence indicated the bicyclic structure (VIII) for this compound. The remaining products



VII VIII

were comprised predominantly of non-volatile residue assumed to be polymeric.

Srinivasan[40] in conjunction with his study of the photochemistry of simple dienes and trienes photolyzed 1,3,5-cycloheptatriene in the gas phase and found the products to be toluene (> 95%) and bicyclo [3.2.0]-heptadiene-2,6 (VIII). The following observations were made in experiments designed to determine the nature of the photochemical reaction:

1. The quantum yield for toluene decreased with increasing total gas pressure. Actually, a plot of 1/(quantum yield for toluene) versus total pressure was linear

with an intercept for zero pressure at an inverse quantum yield of 1.1±.3.

2. The quantum yield for the bicycloheptadiene (VIII) was low (≈.05) and increased slightly with increasing total gas pressure.

3. The addition of inert gases including oxygen and nitric oxide (triplet quenchers) did not alter the pattern noted in statements 1 and 2.

4. The effectiveness of quenching for the gases followed the pattern $He < Xe \approx O_2 < CO_2 \approx CH_4 < Et_2O$.

5. The ultra-violet spectrum of 1,3,5-cycloheptatriene shows an intense ($\log \varepsilon_{max} = 3.62$) first absorption region ranging from 3300 to 2250Å. (The intensity indicates a singlet; calculation of lifetime for first excited singlet state gives $t_{\frac{1}{2}} \approx 10^{-9}$ seconds meaning that in the pressure range used, collisional deactivation would not be efficient.)

6. Increasing temperature favors toluene production.

7. Cycloheptatriene undergoes thermal rearrangement to give almost exclusively toluene at 450-500°.[41]

8. In solution primarily bicycloheptadiene (VIII) and polymers are obtained. The quantum yield for formation of (VIII) is .03.[42]

These observations are in agreement with the author's postulate that "the formation of toluene occurs from a high vibrational level of the ground electronic state of cycloheptatriene..."[40] The difference in pressure dependence of the two products leads to the conclusion that they arise from different states. Thus, the first excited singlet is postulated as the precursor for bicyclo[3.2.0]-heptadiene-2,6.

Arai and coworkers[43] investigated the mercury sensitized photolysis of 1,3,5-cycloheptatriene in the vapor state. Their results were in very good agreement with those of Srinivasan, even though photosensitization with mercury generally leads to excited triplet mercury atoms (^3P) which should interact with the cycloheptatriene to yield a triplet excited molecule in line with the spin conservation rule.[44] Thus, these authors postulated that in both the non-sensitized and mercury sensitized vapor phase photolyses, the isomerization to toluene arises from triplet excited 1,3,5-cycloheptatriene. No bicyclo[3,2,0]-heptadiene-2,6 was reported. In support of a non-quenchable triplet, the authors noted that in the mercury (^3P) sensitized decomposition of ethylene, nitric oxide has been found to have no effect on the decomposition reaction of triplet excited ethylene.[45] It should be noted that although this is not the case for ethylene, with cycloheptatriene mercury lamp illumination (> 2200Å) can lead to singlet excited cycloheptatriene as well as triplet excited mercury.

Perhaps then, Thrush and Zwolenik's study[28] of the flash photolysis of 1,3,5-cycloheptatriene would provide evidence as to the nature of the intermediate leading to toluene. Upon gas phase flash photolysis of low pressures of the cycloheptatriene in the presence of an inert gas, only one transient species was detected in the ultraviolet spectral region. The spectrum of this species was found to be identical to that of the benzyl radical whose spectrum had been characterized earlier.[46] The tropyl radical which had been observed in this investigation as a result of the flash photolysis of ditropyl and ditropylsulfide was not observed. The pressure dependence for benzyl radical formation was essentially the same as that observed by Srinivasan[40] for toluene. The observed similar quantum efficiencies for benzyl radical formation shown by cycloheptatriene and toluene combined with a consideration of the energetics for both the rearrangement and benzyl radical formation reactions led the authors to postulate that the excited toluene molecules formed from the cycloheptatriene rearrangement split to give benzyl radicals. The lack of fluorescence (or phosphorescence) shown by cycloheptatriene upon irradiation seems to preclude the formation of toluene in an electronically excited singlet state since toluene itself does show fluorescence. Whether or not toluene's lowest triplet state would show phosphorescence was not questioned although indications are it would not.[47] In either case if the excited toluene molecules split immediately ($t_{\frac{1}{2}} < 10^{-10}$ seconds) after formation to give benzyl radicals, then neither phosphorescence nor fluorescence due to toluene would be observed.

The lack of fluorescence shown by 1,3,5-cycloheptatriene does seem to verify the rapid internal conversion of electronically excited singlet species to give a vibrationally excited ground state molecule; however, if the cycloheptatriene triplet did not phosphoresce, the same observation would hold for efficient intersystem crossing to give a triplet. Thus, although the flash photolysis results seem to indicate a vibrationally excited ground state singlet as the precursor for toluene, the lack of observation of a triplet does not preclude its existence. For an intermediate to be detectable by flash photolysis it must have an ultraviolet visible spectrum (or other monitorable property) which is resolvable from those of the reactants, products and other intermediates. Furthermore, that intermediate must have a half-life sufficiently long to permit its detection.

A further question is raised as a result of the observation of benzyl radicals. If these radicals are also produced in the low intensity photolyses, then the mechanism is surely more complex. If this is not the case, then one has another example of the increased complexity of reaction possible in flash photolysis as a result of the high intensity flash necessary for such studies. This complexity usually stems from reactions due to "hot" species.[48] Furthermore, a comparison of low intensity photolysis products with the products resultant from multiple flashing will not generally prove enlightening since the high concentrations of reactive species produced in flash photolysis often lead to radical-radical reactions and the like far more frequently than in low intensity photolyses.[10]

CONCLUSION

In conclusion it can be seen that flash photolysis is a very versatile method for studying photo-initiable phenomena of many types. To be amenable for study by this method, however, reactions generally must have half-reaction times greater than five microseconds and must be capable of being monitored. Among the types of investigations which have been carried out one finds studies of relaxation processes, pyrolytic and explosive phenomena and photochemical reactions. Although one can accomplish the direct observation of reactive intermediates as well as the elucidation of reaction mechanisms, confusion can arise due to the generation of "hot" species and the occurrence of radical-radical type reactions both of which become more likely as a result of the high flash intensity. Another shortcoming of the method is the need for a reasonably large investment in time and money prior to obtaining any results. If many experiments utilizing flash photolysis are intended, this drawback becomes much less significant.

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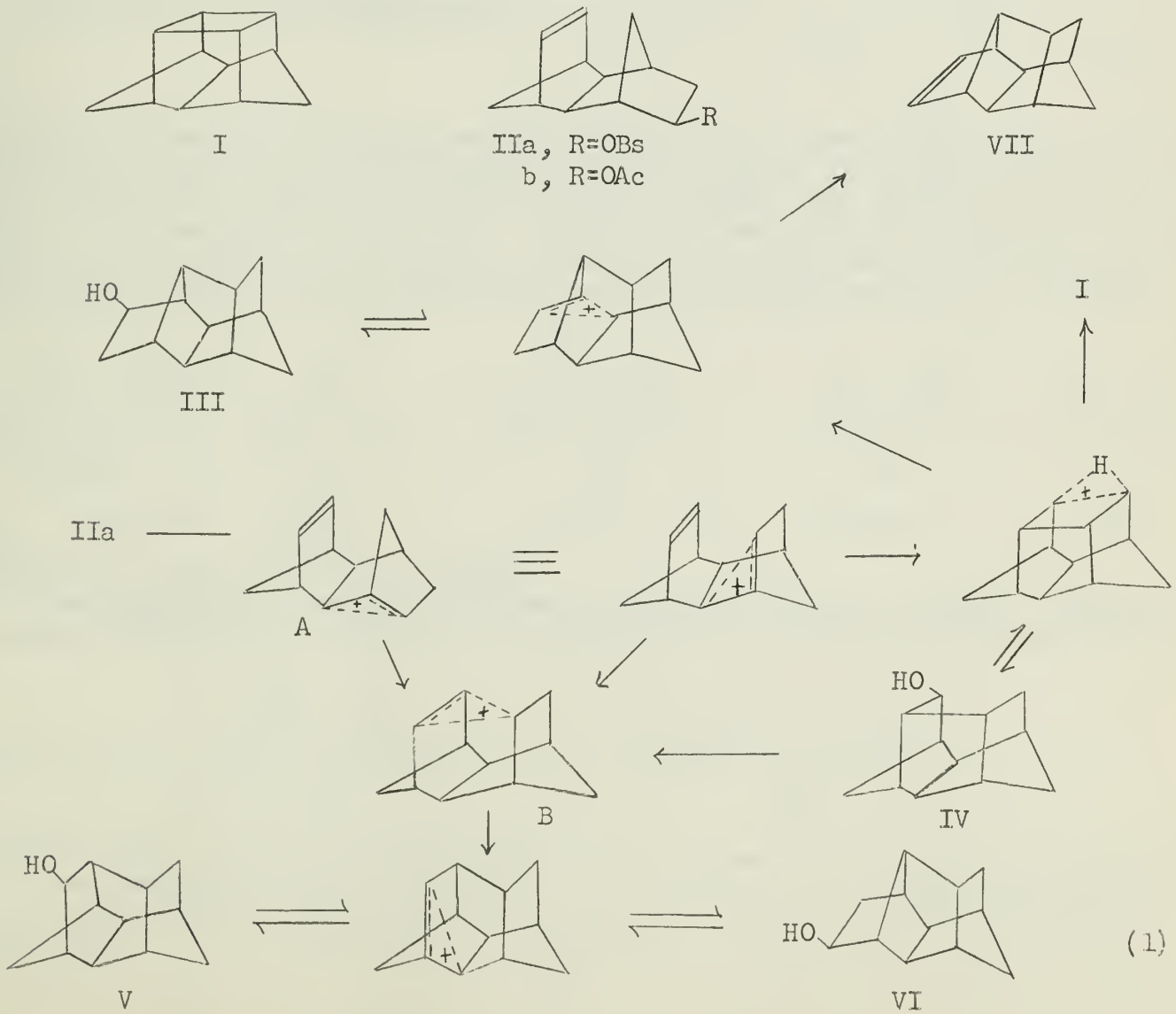
HEXACYCLODODECANE

Reported by Carl L. Mampaey March 3, 1966

In 1954, Winstein reported the synthesis of an unusual new hydrocarbon which he initially called the "birdcage hydrocarbon" (I).[1] Subsequently, it was given the systematic names of hexacyclo[7:2:1:$0^{2,5}$:$0^{3,10}$:$0^{4,8}$:$0^{6,12}$] dodecane,[1] hexacyclo[6:2:1:$1^{3,6}$:$0^{2,7}$:$0^{4,10}$:$0^{5,9}$] dodecane,[2] and hexacyclo[5:4:1:$0^{2,6}$:$0^{4,11}$:$0^{5,9}$:$0^{10,12}$] dodecane.[3] The most common nomenclature is still the earliest one however. The first part of this seminar is devoted to some of the synthetic approaches which have been used to arrive at this strained system. The second part relates some of the work which has made use of the unusual properties of the birdcage system.

SYNTHESIS BY SOLVOLYSIS REACTIONS

The first synthesis of the birdcage hydrocarbon was reported by Winstein.[1,4] The compound is a product of the solvolysis of the exo-bromobenzenesulfonate IIa. This compound is derived from the corresponding alcohol, which is obtained in a 1:4 ratio with the endo-isomer in the Diels-Alder reactions between two cyclopentadiene molecules and one of vinyl acetate and subsequent hydrolysis.[5] Acetolysis of IIa in aqueous solvent yields 30% of the expected acetate IIb and 70% of saturated materials- four alcohols and one hydrocarbon. An unsaturated hydrocarbon is also isolated.[2] The formation of the hydrocarbons and alcohols have been rationalized by a non-classical carbonium ion mechanism. In addition to spectroscopic evidence, the following facts help to derive a rationale for the products of this reaction.

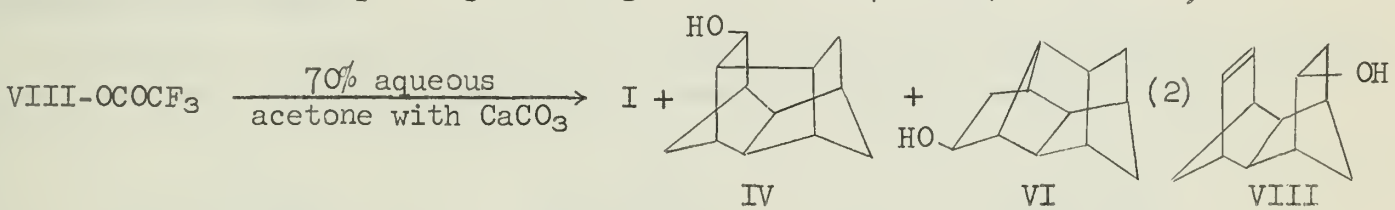


(1)

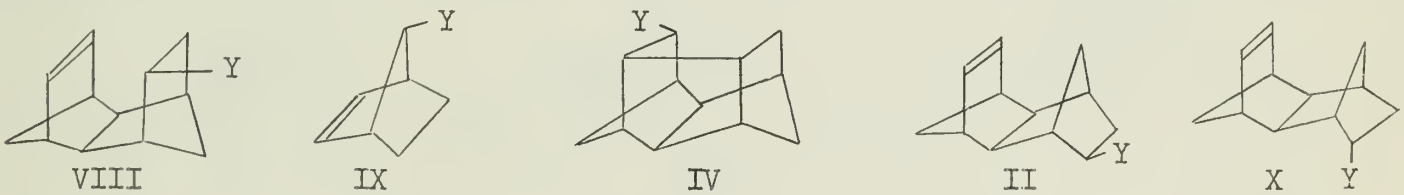
The hydrocarbon I, the saturated alcohols III and IV occur in approximately constant ratios regardless whether they are produced from solvolysis of IIa or of the bromobenzenesulfonate of IV. On the other hand, from solvolysis of the bromobenzenesulfonates of V and VI, apparently Wagner-Meerwein isomers, a mixture of the two alcohols is obtained. The hydrogen-congested half-cage compound IV-OBs is 10^2 times as reactive in acetolysis as the original bromobenzenesulfonate IIa, and nearly 10^4 times as reactive as the endo-isomer of IIa.

The structure of the birdcage hydrocarbon ($C_{12}H_{14}$) follows from a variety of evidence. This crystalline material (m.p. 165-7°) is unreactive toward bromine, potassium permanganate and ozone. The N.M.R. spectrum shows two peaks in a 10:4 ratio, in accordance with the expected ratio of tertiary to secondary hydrogen atoms. The infrared spectrum excludes the presence of CH_3 groups, but there is evidence for CH_2, a band of moderate intensity at 1454 $cm.^{-1}$, the analogous band in norbornadiene occurring at 1451 $cm.^{-1}$. An x-ray study could not be completed due to the disorder in the crystal lattice, but the molecular weight has been determined from the crystal density and the dimensions of the unit cell. A thorough electron diffraction study[6] confirms the hexacyclododecane structure I.

In the solvolysis of IIa, none of the unsaturated alcohol VIII with the endo, endo-fusion is observed in the product. This compound has been synthesized independently.[7] This material proved to be so reactive that the bromobenzenesulfonate has never been prepared. The material isolated from the attempted preparation of VIII-OBs was the corresponding half-cage derivative (IV-OBs). However, it is



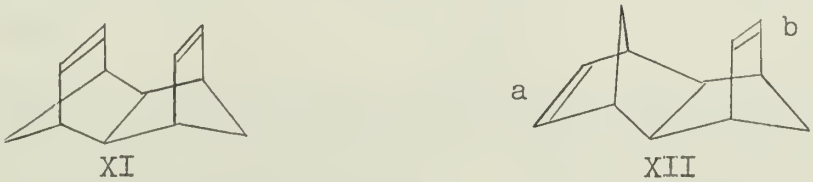
possible to prepare less reactive derivatives of VIII such as the p-nitrobenzoate and the trifluoroacetate (VIII-$OCOCF_3$). Solvolysis of the latter yields the birdcage hydrocarbon I (14%), half-cage alcohol IV (34%), and "twisted" alcohol VI (43%). The remainder of the product (9%) is a syrupy mixture of saturated alcohols. Another non-classical carbonium ion mechanism is postulated for this reaction. The reactivity of VIII can be illustrated by the following comparison of relative



	VIII	IX	IV	II	X
k_{rel}	1.26×10^6	9.5×10^4	1.75×10^4	1.15×10^2	1.00

solvolysis rates at 25°C (Y = $OCOCF_3$).

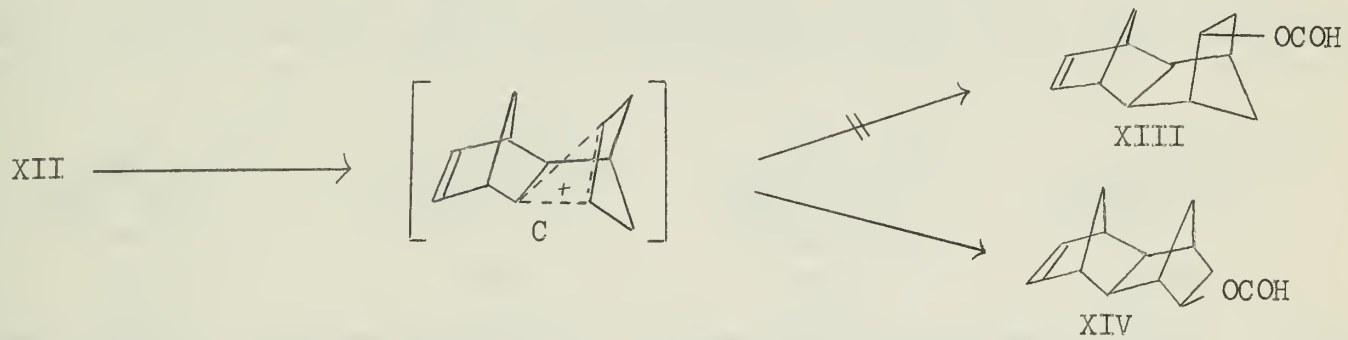
The endo,endo-diene (XI) has been synthesized[7] but has not been observed in the solvolysis of IIa. Treatment of XI with aqueous dioxane in the presence of acid



catalyst gives rise to the same products as in reaction (2), i.e., I, IV, and VI.

The exo,endo-diene XII affords another synthesis of birdcage hydrocarbon.[8] This compound is the sole stereoisomer formed by the Diels-Alder addition of norbornadiene to cyclopentadiene.[9] When XII is treated with a slight excess (1.33:1) of formic acid a total of 70-80% of monoformates is obtained. Several of the products have the same skeletal structure as those from the solvolysis of IIa, i.e., the birdcage hydrocarbon I, the half-cage alcohol IV, the "twisted"alcohol

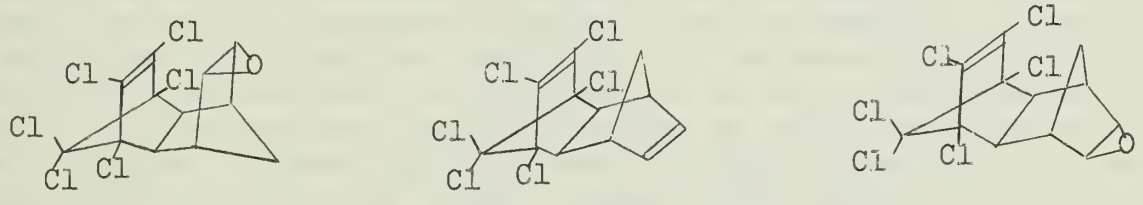
VI as well as IIa. These products can all be rationalized by the non-classical carbonium ion intermediates as those of Winstein in reaction (1) and assuming protonation on double bond (a). Due to the dissymmetry of the molecule, attack of the proton at either bond does not lead to equivalent products. Attack of the proton at bond (a) can produce a bridged ion (A) which by a Wagner-Meerwein rearrangement can produce bridged ion (B). This allows participation of the π-electrons of bond (b) in stabilization of the positive charge introduced at bond (a). The reverse is not true however, and protonation at bond (b) does not allow interaction with bond (a). The bridged ion (C) formed in this case could react with

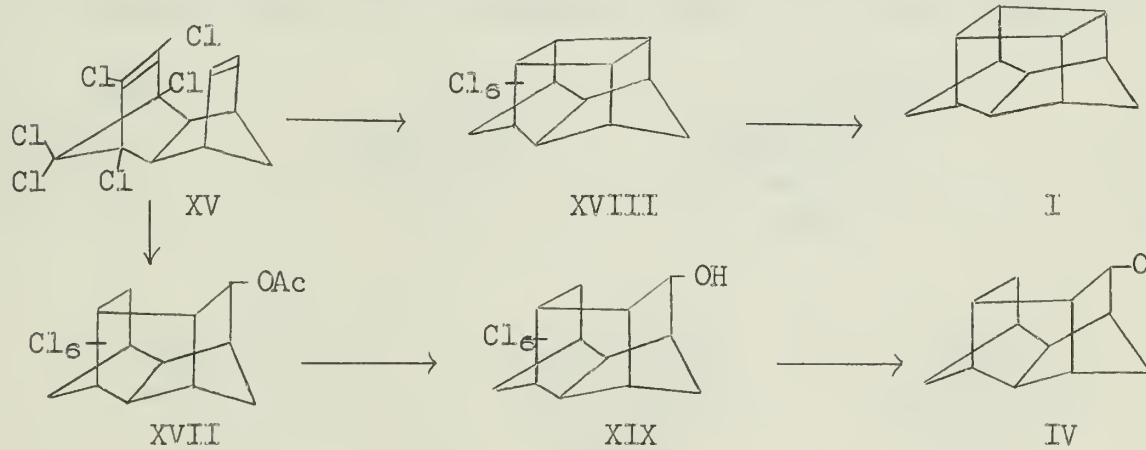


formate ion to either form XIII or rearrange to form XIV. Only the latter product is observed.

SYNTHESES FROM ISODRIN

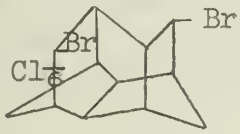
A different synthetic approach to birdcage hydrocarbon and related compounds[7] arises from the available insecticides, isodrin[10] (XV) and endrin[11] (XVI).



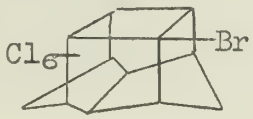


Isodrin and endrin are stereoisomeric with aldrin (XXa) and dieldrin (XXb), respectively. The basis for the assignments of the absolute configurations consists of stereochemical considerations. Aldrin[12] is made by the addition of bicycloheptadiene to hexachloropentadiene; from the known tendency for exo-addition of dienes to bicycloheptadiene and the large size of the gem-dichloro group, structure XXa was assigned. Isodrin is synthesized[10,11] by the addition of hexachlorobicycloheptadiene to cyclopentadiene; here the large gem-dichloro group in the dienophile is likely to force addition of cyclopentadiene from the endo-side, favoring structure XV. The reactions of isodrin related below yield skeletal rearrangements. Aldrin under these same conditions gives no rearrangements and this provides further evidence for the correct assignments of XV and XX.

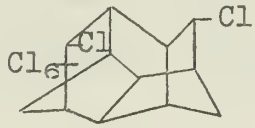
Upon treatment of isodrin XV in acetic acid containing acid catalyst, a 50% yield of the acetate XVII is produced. More prolonged refluxing leads to excellent yields of the chlorinated birdcage structure XVIII. The chlorinated half-cage alcohol XIX is readily available from the acid-catalyzed trans-esterification of the corresponding acetate XVII in ethanol. Both XVIII and XIX are dechlorinated by treatment with a lithium-tetrahydrofuran-t-butyl alcohol mixture to yield the birdcage hydrocarbon I and the half-cage alcohol IV, respectively. Isodrin can be converted to its hexacyclic isomer XVIII by other means as well.[13] Treatment with hydrogen bromide (24% yield), bromine (22% yield) as well as irradiation with a mercury arc[14] yields XVIII. Dehydration of XIX with phosphorus pentoxide also yields XVIII. The bromination of isodrin also gives an 11% yield of the dibromide XXI, which has a known skeletal structure,[2] and traces of a monobromide which was believed to be XXII. Bromination



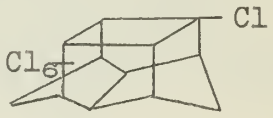
XXI



XXII



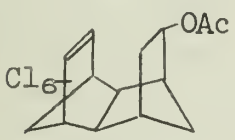
XXIII



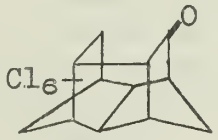
XXIV

is paralleled by chlorination, except that the products were more complex. They include XXIII and XXIV, in analogy to the bromination reaction.

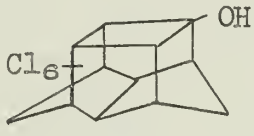
Further conjugate addition is observed with the acid-catalyzed addition of organic acids to isodrin. As noted above, with acetic acid a mixture of products is obtained which consists mostly of the rearranged acetate XVII and the normal acetate XXV. With formic acid, only the rearranged formate XVII-OCOH is isolated. Both XVII-OAc and XVII-OCOH yield the chlorinated half-cage alcohol XIX upon hydrolysis. Potassium permanganate oxidation of XIX leads to the half-cage ketone XXVI, which can also be obtained directly by the rearrangement of endrin (XVI) under both thermal and acid-catalyzed conditions.[15] The stereoisomer (XXVII) of XIX can be obtained by lithium aluminum hydride reduction of XXVI. This assignment of configuration is consistent with the known course of reduction of ketones in hindered systems by lithium aluminum hydride. When the endo-alcohol XXVII is heated with phosphorus pentoxide, the only product isolated (in low yield) is the hexacyclic compound XVII. Dehydration was also attempted with activated alumina but the product formed in this case was the ether XXVIII, the result of dehydrohalogenation. Treatment of ketone XXVI with an equimolar amount of lithium aluminum hydride rather



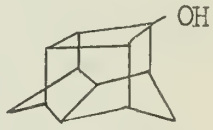
XXV



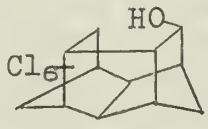
XXVI



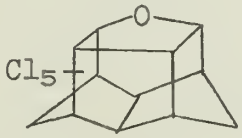
XXVIa



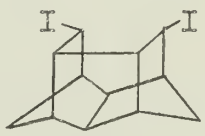
XXVIb



XXVII



XXVIII



XXIX

than an excess yields the chlorinated birdcage alcohol XXVIa. This is a base-catalyzed homoenolization which will be discussed more fully later.

Isodrin (XV) is dechlorinated to XI in two stages; first with zinc in acetic acid to reduce the two bridge chlorines and then with sodium in n-amyl alcohol to replace the four remaining chlorines. When XI is treated with iodine, conjugate addition is observed to form XXIX. The structure was verified when XXIX was treated with zinc and methanol and birdcage hydrocarbon (I) was obtained.

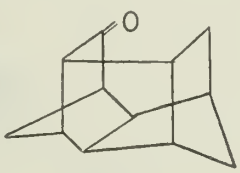
HOMOENOLIZATION

There is only one derivative of birdcage hydrocarbon known with a functional

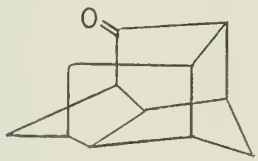
group at a cyclobutane bridgehead, namely birdcage alcohol (XXVIb).[15] This compound is derived from the hexachloro half-cage ketone XXVI. Treatment of XXVI with alcoholic sodium hydroxide or heating in pyridine readily yields XXVIa. First order kinetics are observed and the birdcage structure is confirmed by its NMR spectrum (no α-proton) and its chemical behavior. This compound is dechlorinated by the lithium-t-butyl alcohol-tetrahydrofuran procedure.[7] The solvolysis of the p-bromobenzenesulfonate of IV is of interest for practical reasons since it would serve as an indication of the feasability of carbonium ion substitution reactions in the system. It is also of interest for theoretical reasons since IV-OBs is both cyclobutyl and bridgehead. The former factor is predicted to enhance solvolysis,[16] while the latter is predicted to retard it.[17] Solvolysis in acetic acid 0.02M in sodium acetate results in first-order kinetics and an almost quantitative (92%) yield of unrearranged birdcage alcohol (XXVIb). The reactivity of XXVIb-OBs in acetolysis is nearly equal to that displayed by the bridgehead bicycloheptyl analog XXX.[18]

Recently, two different groups have reported the homoenolization-homoketonization of the half-cage ketone XXXI.[19,20] Treatment of XXXI with t-butyl alcohol

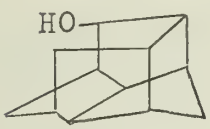
XXX



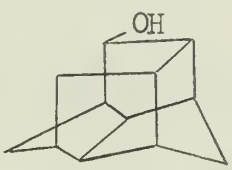
XXXI



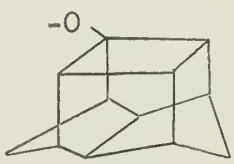
XXXII



XXXIII



XXXIV



XXXV

0.9M in potassium t-butoxide yields the new ketone XXXII quantitatively (>99%). When birdcage alcohol (IV) is treated under similar conditions, it is much more rapidly transformed (>99%) to the same ketone XXXII. Lithium aluminum hydride reduction yields the O-inside alcohol XXXIII. As expected, aluminum isopropoxide catalyzed equilibration of XXXIII yields an alcohol mixture containing >96% of the O-outside alcohol XXXIV. Available evidence is that the conversion of the half-cage ketone XXXI involves homoenolization to the birdcage alcohol XXVIb, the latter representing the "homoenol" common to both ketones XXXI and XXXII. An alternative thermal pathway for the observed isomerization can be rejected because under identical conditions, but in the absence of base, the ketones XXXI and XXXII and the alcohol XXVIb are cleanly recovered. Homoketonization of birdcage alcohol XXVIb (by way of the anion XXXV) proceeds ca. 33,000 times as rapidly as does homoenolization of XXXI at 100°C.[19] Further, the homoketonization is observed only in the direction of the new ketone XXXII, no formation of XXXI being detected. The observed product ratio favoring XXXII can be rationalized, at least qualitatively, in terms of less steric hindrance about the carbonyl groups with respect to solvation, fewer nonbonded hydrogen repulsions, and less ring strain. The steric hindrance about the carbonyl group in XXXI can be demonstrated by its lack of reactivity toward hydroxylamine. No oxime is formed at 10,000 atm., 75° under which conditions di-t-butyl ketone reacts to give the corresponding oxime in 96% yield.[21] In contrast, under normal conditions the ketone XXXII is easily converted to the corresponding oxime (90% yield).

PHYSICAL PROPERTIES

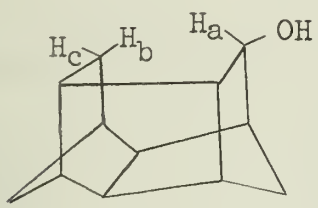
A study of the infrared absorption spectra of several birdcage and half-cage compounds reveals at least three well-defined bands in the C-H stretching region.[22] Bands at 2960, 2920, and 2886 $cm.^{-1}$ are assigned to the CH_2 asymmetric stretch, the tertiary C-H stretch and the CH_2 symmetric stretch, respectively. Each of these is approximately 30 $cm.^{-1}$ above the characteristic frequencies assigned to these bands in unstrained molecules.[23] It has also been found that these saturated strained

systems usually exhibit an anomalous, sharp absorption band in the region 3055-2980 cm.$^{-1}$.[24] This absorption is also attributed to the forced proximity of two or more methylene groups in these systems. Unusually high C-H out of plane frequencies (650-750 cm.$^{-1}$) are also observed in these strained compounds.[8]

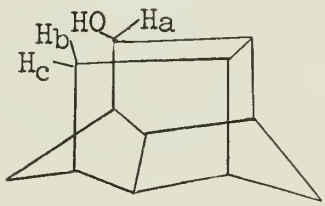
The adjacent methylene groups in half-cage compounds give rise to some unusual steric compression effects in NMR spectra.[25] These effects on chemical shifts, both intermolecular and intramolecular, have been reported.[26] In general, a low-field shift (ca. 0.1-0.6 p.p.m. for protons attached to carbon) is observed, irrespective of the nature of the atom which is in juxtaposition to the proton being examined.

Table I

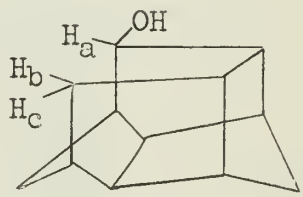
Compound	Solvent	Chem. shifts (τ values) H_a	H_b	H_c
IV	CCl_4	5.52	7.6	8.9
XXXIII	"	5.81	7.5	8.8
XXXIV	"	6.15	7.3	8.6
XXXVI	"	5.46	7.5	9.0
XXXVII	"	6.08	6.45	9.12
XXXVII-O^-Na^+	DMSO	5.75	4.72	9.40
XXXVIII	CCl_4	5.78	7.05	8.8
XXXIX	"	6.52		
XL	"	6.04		



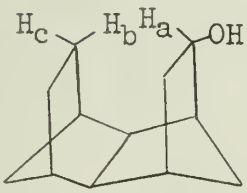
IV



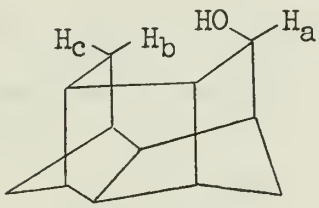
XXXIII



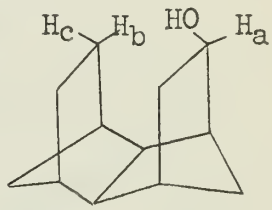
XXXIV



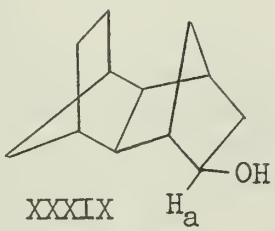
XXXVI



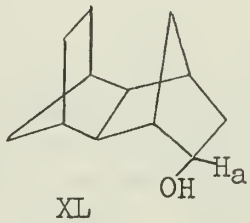
XXXVII



XXXVIII



XXXIX



XL

As is clear from the data in Table I, the inside protons are strongly deshielded (H_a and H_b relative to H_c). The α-proton, H_a, in XXXVI (τ 5.46) is at much lower field than the corresponding proton in the endo,exo-fused isomer XXXIX. If one takes the "normal" chemical shift of H_b as that of the endo-protons in norbornane (τ 8.8), the deshielding effects on H_b are given as ca. 2.4 p.p.m. in XXXVII and 1.7 p.p.m. in XXXVIII. This effect appears to be larger in the more rigid half-cage derivatives than in the endo,endo-analogs. Consistently, no effect on H_b is observed in the less congested isomeric half-cage system. The size of the effect on H_b varies with the nature of the functional group in juxtaposition, the deshielding effects being in the sequence $O^-Na^+ > OH > OMe > OAc > OBs$. With the O^-Na^+ group in the half-cage XXXVII-O^-Na^+, H_b is deshielded by as much as 4 p.p.m. A new effect was also observed. It is found that the outside H_c protons on the methylene group in juxtaposition to the inside OH group in the more rigid half-cage systems show a chemical shift to higher field. Taking the exo-protons in norbornane as reference (τ 8.6), the shielding effect on H_c is ca. 0.5 p.p.m. in XXXVII and 0.7 p.p.m. in XXXVII-O^-Na^+. The shielding effects on H_c seem to parallel the deshielding ones on H_b. A possible explanation is that the electron cloud of the oxygen tends to shift the bonding electrons in the grouping H_cCH_b away from H_b and toward H_c, thus accounting in part for the lower shielding of H_b and the higher shielding of H_c. It is also noted that no effect is visible on the outside H_a proton on the $HOCH_a$ group.

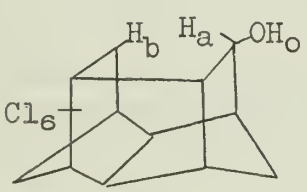
A study of the effects of steric compression on coupling constants has also been made.[27] The compounds examined are the half-cage alcohols XIX, XXVII, and XXXVII and their acetates. For observation of H_b-H_o coupling, spectra are

Table II

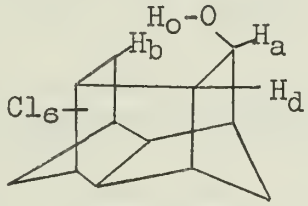
Compound	Solvent	Chem. shifts (values) H_a	H_b	H_o
XIX	$CDCl_3$	5.05	4.60	
XIX-OAc[a]	$CDCl_3$	4.20	4.52	
XXVII[b]	Acetone	5.70	2.05	4.22[d]
XXVII	$CDCl_3$	5.83	2.60	
XXVII-OAc	$CDCl_3$	5.12	3.45	
XXXVII[c]	Acetone	6.00	6.03	5.90[d,e]

[a] J_{ab} 1 c.p.s. [b] J_{ad}=5.5, J_{ao}=4.8, J_{bo}=1.1, J_{ab}=0.24 c.p.s.

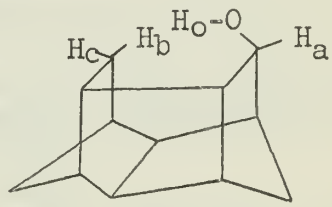
[c] J_{ao}=4.8, J_{bo} 0.5 c.p.s. [d] Temperature dependent. [e] 5.4 p.p.m. at -20°C.



XIX



XXVII



XXXVII

determined in acetone solution, conditions which are known to give very slow exchange of hydroxyl.[28] The temperature-dependent bands belong to H_o. The other bands are assigned on the basis of expected chemical shifts and complexities of bands. The deshielding of the inside protons tends to be even larger in the hexachloro compounds (XIX and XXVII) than in the unchlorinated analogs. This is the case with the deshielding of H_b on going from O-outside to O-inside compounds. Thus, Δδ is -2.0 p.p.m. between XIX and XXVII, while it may be estimated to be ca. -1 p.p.m. with the unchlorinated alcohols.[25] The most interesting coupling is that of H_o to H_b in XXVII. The value of J_{bo} is 1.1 c.p.s. in this case. Coupling of H_o to H_a is also observed (J_{ab}=0.24 c.p.s.). In the unchlorinated XXXVII however, the H_b-H_o coupling is considerably decreased (J_{bo}<0.5 c.p.s.) and J_{ab} is not observed. In both compounds, it is extremely unlikely that the coupling of H_b with either H_a or

H_o proceeds by a through-bond mechanism, as the protons are separated by five and six single bonds, respectively.[29] Therefore, the coupling most probably takes place via the unshared electrons of the oxygen atom. In both XXVII and XXXVII one can consider the possibility that the H_b-O interaction partakes of the character of a hydrogen bond. It is also likely that the chlorine atoms give rise to a buttressing effect, thus forcing H_b closer to the oxygen atom in XXVII than in XXXVII. This would be in line with the larger deshielding effects observed with the chlorinated than with the unchlorinated derivatives. On a formal basis then, the coupling of H_b with H_o can be termed "through-space". Another interesting observation was made during attempts to detect unresolved H_a-H_b coupling in XIX-OAc by double resonance. It was found that while the band H_b did not change in width on irradiation of H_a, the area of the band increased by about 45%. This observation of a nuclear Overhauser effect[30] is a reflection of a very efficient mutual relaxation of H_a by H_b and vice versa by a direct dipole-dipole mechanism.

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SPECTROSCOPIC INVESTIGATIONS OF THE CYCLOPROPYLMETHYL, NONCLASSICAL PHENONIUM AND THE CORRESPONDING CLASSICAL CATIONS IN SOLUTIONS

Reported by James E. Gano March 10, 1966

This seminar is concerned with studies of organic cations, in particular the cyclopropylmethyl, phenonium and related cations, in the antimony pentafluoride - fluorosulfuric acid - sulfur dioxide solvent systems. Recently Deno[1,2] and Druliner[3] have reviewed some of the material in this rapidly growing field. The system of nomenclature suggested by Deno will be used throughout this paper.[2]

METHOD AND REAGENTS

This discussion will concentrate on systems using antimony pentafluoride, SbF_5, and fluorosulfuric acid, FSO_3H, as both solvent and counter ion in producing cationic species. Using viscous concentrated sulfuric acid or oleums for this purpose requires temperatures above 10°. At these high temperatures, many cations are unstable.[4]

Antimony pentafluoride is a dense (2.99^{23}), colorless liquid that freezes at 7.0°, has a low dielectric constant, $\epsilon \sim 3$, and exists in cyclic and acyclic polymeric forms involving fluorine bridges.[5,6] The use of SO_2, SO_2F_2, SOF_2 or SO_2ClF as diluents in low temperature work avoids the complication introduced by the high freezing point. Olah and coworkers have reported that alkyl fluorides or alcohols dissolved in SO_2 at low temperatures form the corresponding organic cations upon the addition of SbF_5 in an excess of the 1:1 molar ratio.[4] Generally, however, the alcohol precursors give poorly resolved n.m.r. spectra. To explain the excess SbF_5 needed, Olah and coworkers have suggested the vacant p orbital of the sp^2 hybridized carbon atom interacts with unshared electrons on fluorine.[5] As mentioned by Druliner,[3] SbF_5 is very special in this property since other liquid Lewis acids in general do not form the cationic species.

Fluorosulfuric acid is a very strong acid with a Hammett H_0 value of -12.6 as compared to -11 for 100% sulfuric acid. Alcohols dissolved in neat FSO_3H or FSO_3H-SO_2 sometimes give good cation spectra, but generally these are poorly resolved and the bands are broad.[4,7]

The combination of FSO_3H with SbF_5 produces, by the following reaction, one of the most strongly acidic media known.[4] The best method for preparing organic cations

$$SbF_5 + 2FSO_3H \rightleftharpoons H_2SO_3F^{\oplus}\ SbF_5(SO_3F)^{\ominus}$$

at present seems to involve the dropwise addition of the alcohol in sulfur dioxide to SbF_5 and FSO_3H in sulfur dioxide at temperatures near -70°.

IONIZATION OR ~~CHARGE-TRANSFER~~ COMPLEX

Workers in this field have concluded that ionization occurs under the conditions described above, and suggest that the ion is present in an ion pair in SbF_5 solutions.[5] Cryoscopic measurements indicate little or no ion separation.[8] In the ionic, strongly solvating and highly polar SbF_5-FSO_3H-SO_2 medium, the ions would tend to dissociate more.

Considerable evidence suggests that ionization does occur. The change in chemical shift in going from the alcohol to the ion is much larger than expected for a ~~charge-transfer~~ complex or a protonated hydroxyl group.[2] In work with alkylcarbonyl cations, whose salts can be isolated and characterized, Olah and Pittman have presented infrared and n.m.r. evidence for both the ion pair and a ~~charge-transfer~~ complex in SbF_5 solutions. The t-butylcarbonyl salt is observed to lose carbon monoxide in solution and give a new species with the n.m.r. absorption shifted downfield from the original. That this same species can be prepared directly from t-butyl chloride or fluoride in SbF_5,[8] suggests that it is the t-butyl cation. The C^{13} n.m.r. spectrum of the t-butyl cation shows a shift 273 p.p.m. downfield from t-butyl chloride.[5] In the triphenylmethyl cation a similar shift of 129.6 p.p.m. is observed.[9] The latter resonance at -18.1 p.p.m. compares with values of 45 to 70 p.p.m. in other regular sp^2 hybridized carbon atoms thus indicating the change in chemical shift is due to rehybridization and the positive charge. Later

it will also be shown that different alcoholic precursors can form identical cations.

OBSERVATIONS OF CYCLOPROPYLMETHYL CATIONS

The tricyclopropylmethyl cation is the most intensively studied ion in this series. Its stability has permitted the isolation and characterization of its salts as well as ultraviolet and infrared studies.[10] The fluoroborate salt in liquid sulfur dioxide or the carbinol in SbF_5-FSO_3H-SO_2 solution at -65° show only single peaks at -1.8 and -2.2 p.p.m., respectively. Since the α and β protons on cyclopropylmethyl cations are usually resolved,[11] the single peak observed is anomolous. Deno and coworkers have observed similar results in concentrated sulfuric acid. Quenching the solution yields tricyclopropylcarbinol in 63% yield; therefore, rearrangement has not occurred.[10] Using D_2SO_4, no slow or fast exchange of protons, is observed in the n.m.r. spectrum. Olah and Pittman have concluded that the diamagnetic anisotropy of the cyclopropyl group results in coincidental overlap of the α and β protons. On this basis, a study of molecular models and the evidence presented later for the bisected structure of conjugated cyclopropyl rings, they assign the structure in Figure I to the ion.[11]

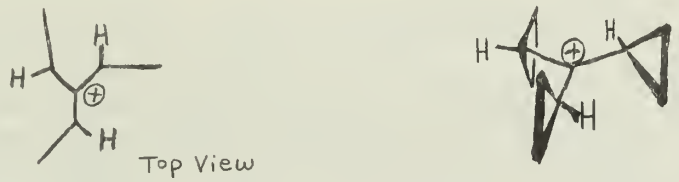


Figure I Structure of the tricyclopropylmethyl cation.

The formation of normally unstable cations in strong Lewis acid solvents has dramatically revealed the bisected structure of cyclopropylmethyl cations. Earlier evidence has come from electron defraction studies of cyclopropylformaldehyde. Bartell, Carroll and Guillory have observed cis and trans forms and established 2 kcal./mole as a minimum barrier to rotation.[14] Olah and Pittman have observed the 2-cyclopropyl-2-propyl cation in SbF_5-$SOClF$-SO_2 at -75°.[11,13] The n.m.r. spectrum and assignments are given in Figure IIa.

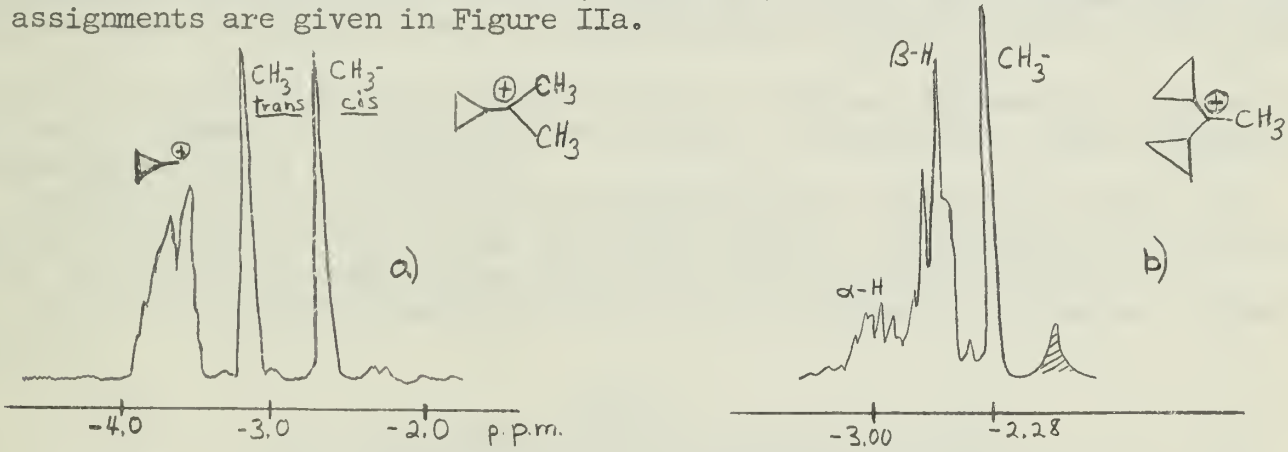


Figure II The n.m.r. spectrum of a) 2-cyclopropyl-2-propyl cation. b) dicyclopropylethyl cation.

These workers have assigned bands at -3.14 and -2.66 p.p.m. to the methyl groups trans and cis to the cyclopropyl group, respectively. This indicated the bisected structure shown. The 1,1,1-trideutero-2-cyclopropyl-2-propyl cation has an identical spectrum but the methyl peaks are only half as intense. The lack of coalescence of the two methyl peaks upon warming to -35° indicates a minimum barrier to rotation of 8-10 kcal./mole. Deno and coworkers simultaneously attempted the preparation of this ion from the alcohol in neat FSO_3H at -50°; however, the spectrum suggests the formation of a rearranged species.[7] Apparently, the possibility of free rotation of the cyclopropyl group and coupling of the methyl groups with the α proton was eliminated on the basis of the large coupling constant of 32 c.p.s. Such an elimination is somewhat questionable in this unusual system. Fortunately, Deno

prepared the 1,1-dicyclopropylethyl and corresponding α,α'-dideutero compound in neat FSO_3H.[7] The spectrum in Figure IIb shows a single peak for the methyl group which is unchanged in the dideuterated compound; therefore, eliminating the free rotation explanation.

The dicyclopropylmethyl cation has been prepared and its n.m.r. spectrum is shown in Figure III.[7,11,13] Olah and Pittman reported -8.14 p.p.m. for the center

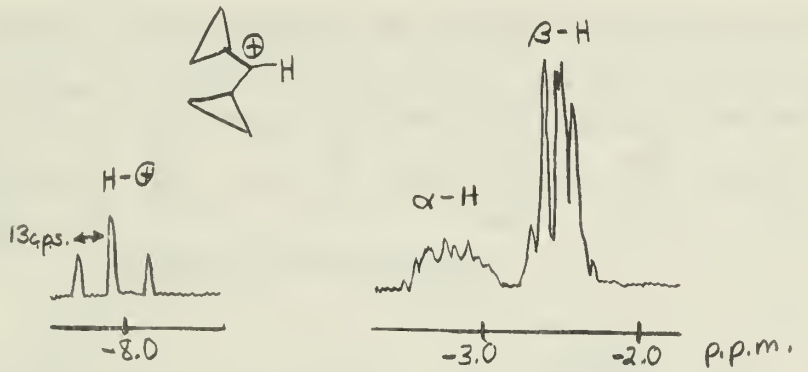
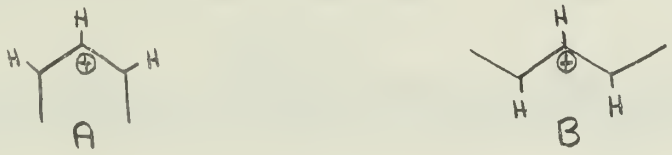
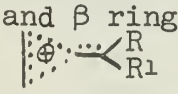
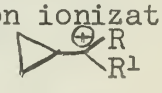


Figure III N.m.r. spectrum of the dicyclopropylmethyl cation in SbF_5-FSO_3H-SO_2 at -60°.

of the symmetrical triplet. Deno reported -8.24 p.p.m. in neat FSO_3H thus showing good agreement. The same value for the alcohol precursor in SO_2 is -1.73 p.p.m. The observed triplet indicates either structure A or B below. Olah and Pittman have chosen structure B on the basis of steric hinderance in models and the value of J_{HH} which favors trans coupling.[11]



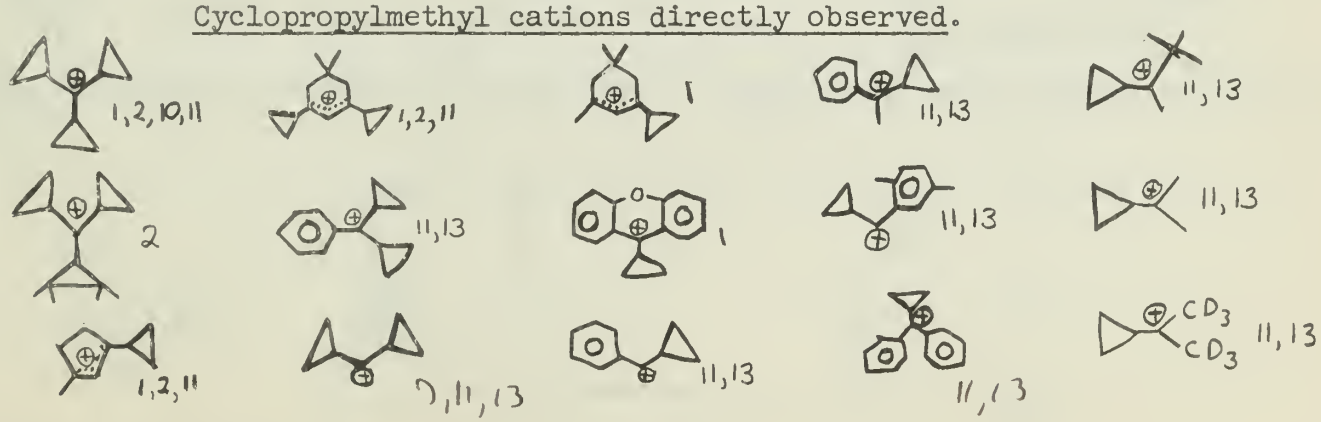
Significant charge delocalization into the cyclopropyl rings is indicated in all cases by large downfield shifts of both the α and β ring protons upon ionization. Thus, as Winstein suggested for similar reasons,[14]  rather than 

might be a preferred notation for these ions. Olah and Pittman have taken issue with this point, however,[15] noting that no evidence is available to show certain bonds are stronger than others as indicated.

Comparison of chemical shift data indicates the cyclopropyl group to be superior to phenyl in stabilizing positive charge.[13] Separating the delocalization effect and the diamagnetic anisotropy effect is difficult, however.

All of the cyclopropylmethyl cations directly observed so far are listed in Table I.

Table I
Cyclopropylmethyl cations directly observed.



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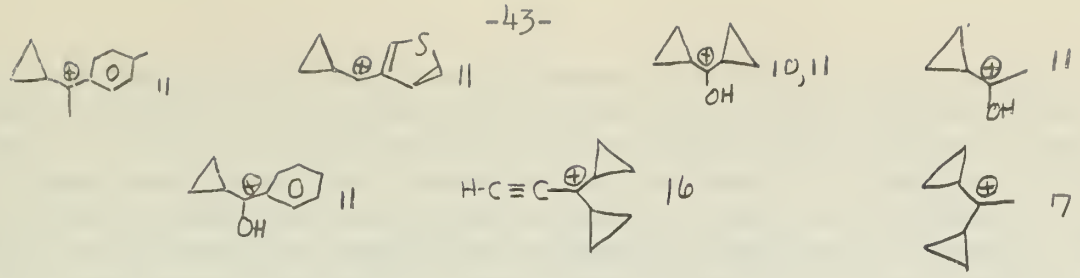
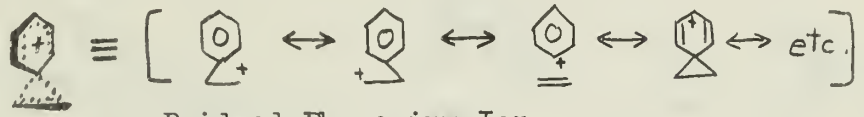


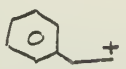
BRIDGED PHENONIUM, CLASSICAL 2-PHENYLETHYL AND RAPIDLY EQUILIBRATING 2-PHENYLETHYL CATIONS

As shown below, various possible structures can be written to describe 2-phenylethyl cations. Considerable controversy has centered on the question of whether



Bridged Phenonium Ion

Rapidly Equilibrating Classical Ion



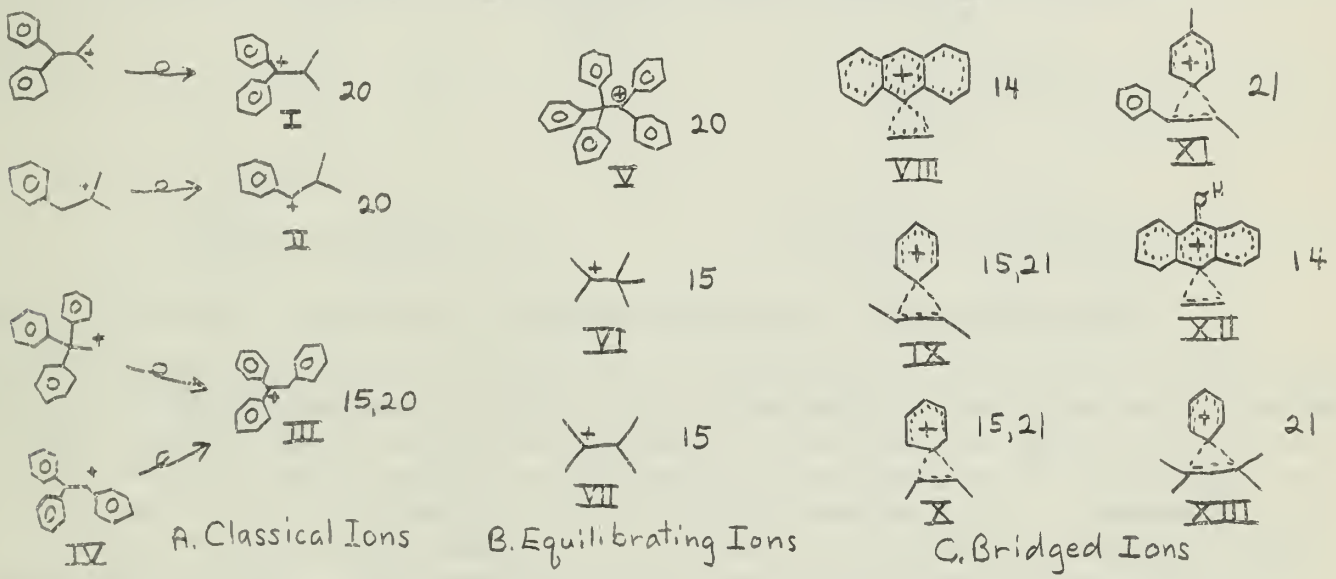
Nonequilibrating Classical Ion

such ions are merely transition states or occur as stable intermediates.[17,18,19] No attempt will be made to consider the chemical evidence pertaining to these species. Instead, a careful examination of the n.m.r. and ultraviolet data of the stable intermediates will be presented.

Table II lists the ions reported. The ions in column A can be obtained from

Table II

Some related classical, classical equilibrating and bridged phenonium ions obtained form the corresponding alcohols in SbF_5-FSO_3H-SO_2 at -60°.



the α or β alcohol precursor.[20] Their n.m.r. spectra are well resolved as shown in Figure IV.

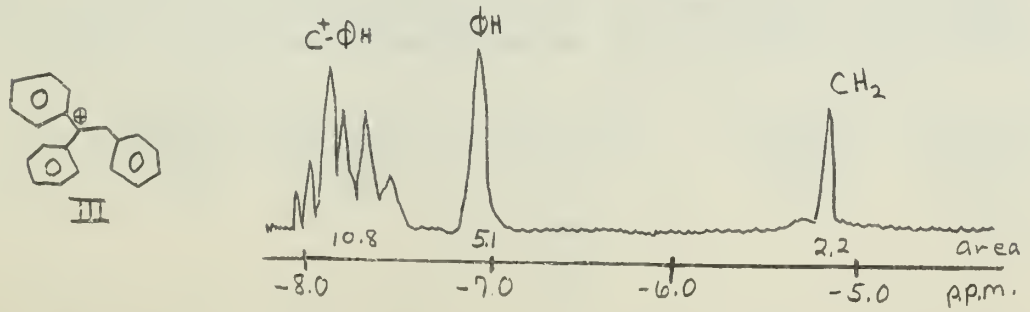
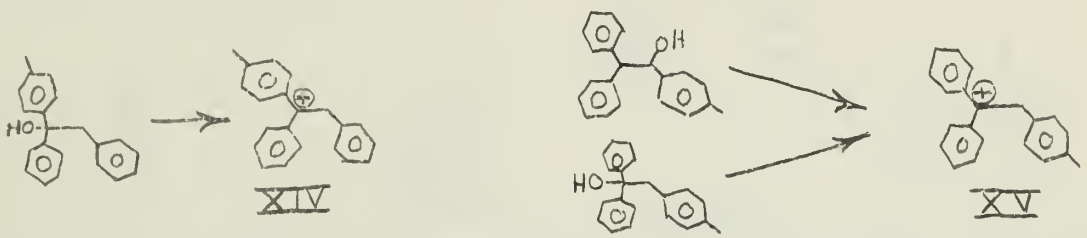


Figure IV The n.m.r. spectrum of 1,2,2-triphenylethanol in SbF_5-FSO_3H-SO_2 solution.

Possible mechanisms for the rearrangement of the β alcohols to the α cations are 1,2-hydride shift; 1,2-hydride shift preceded by rapid equilibration of the phenyl group, 1,2 shift of the phenyl group or elimination and rapid reprotonation. Olah and Pittman have found that formation of the ion corresponding to III from 1-deutero-1,2,2-triphenylethanol yields an n.m.r. spectrum identical to the undeuterated ions except the benzyl proton peak is one-half as intense, thus a 1,2-hydride shift must have occurred.[20] Rapid equilibration of the phenyl group before the hydride shift is eliminated by comparison of the ions from 1,2-diphenyl-1-p-tolylethanol; 1,1-diphenyl-2-p-tolylethanol and 2,2-diphenyl-1-p-tolylethanol. The results are shown below.[15]



Elimination to an olefin and rapid reprotonation was not mentioned by the authors, possibly due to Deno's suggestion that an appreciable concentration of olefin in the presence of cations leads to polymerization.[2] This idea could easily be tested by analyzing the spectrum from 1,2-dideutero-1,2,2-triphenylethanol.

The n.m.r. spectrum of pentaphenylethanol in SbF_5-FSO_3H-SO_2 is presented in Figure V.

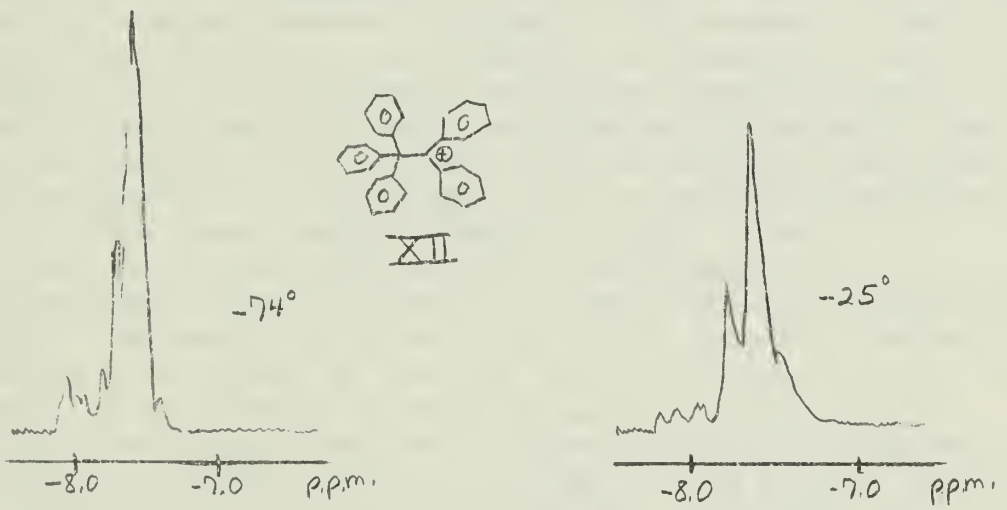
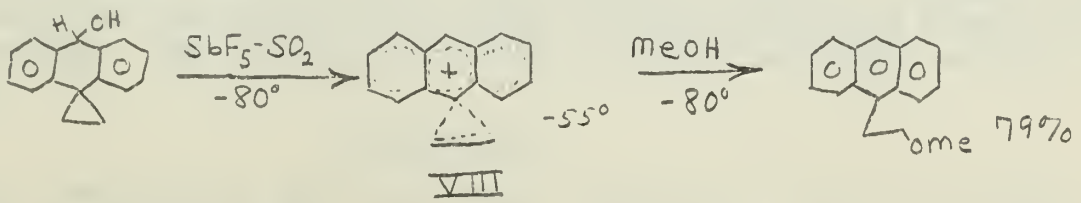


Figure V The n.m.r. spectrum of pentaphenylethanol in SbF_5-FSO_3H-SO_2.

Twenty-five protons are in the "single" band according to calibration with a known amount of tetramethylammonium chloride. The appearance of only one band invariant with temperature change lead Olah and Pittman to conclude the phenyl groups were equivalent and this was a rapidly equilibrating classical ion.[20] No reasons were given to eliminate the bridged ion or the static classical ion. Presumably, the latter would show absorption bands near -7.2 and -8.0 p.p.m. No recovery studies have been carried out. The possibility that the 2,3,3-trimethylbutyl-2 and 2,3-dimethylbutyl-2 cations are rapidly equilibrating is under investigation.[15]

Stable bridged phenonium ions have been reported by two groups. Winstein and Eberson[14] prepared the 2-(9-anthryl) ethyl or "anthrylethyl bridged" cation shown below. The n.m.r. spectrum shows bands at -3.44 s (4H), -7.7 t (4H), -8.2 t (4H)



and -9.60 s (1H) p.p.m. The chemical shifts are in agreement with similar previously observed values. If this ion were rapidly equilibrating, the -3.44 p.p.m. peak would be expected near -8.5 p.p.m. Also, the expected rearrangement to a benzyl type cation does not occur.[14]

Olah and Pittman have reported that erythro, threo or a mixture of the two isomers of 3-phenyl-2-butanol all produce the n.m.r. spectrum shown in Figure VI after one hour in an SbF_5-FSO_3H-SO_2 solution.[21]

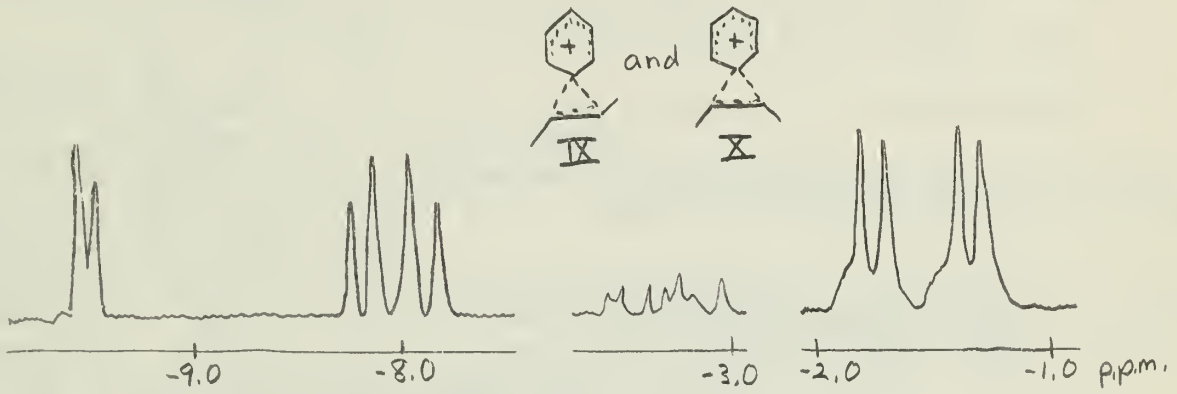


Figure VI N.m.r. spectrum of the 3-phenyl-2-butyl cation in SbF_5-FSO_3H-SO_2.

This is interpreted as a 1:1 mixture of the two possible isomeric bridged ions shown. The alcoholic precursors were recovered in 78% yields.[15] The chemical shifts are in good agreement with those observed by Winstein and Eberson.[14] While there are no major objections to the spectral assignments, some double resonance or deuterium labeling experiments would be appropriate to confirm definitely such a controversial structure. Loss of stereochemistry could be explained by ionization and then competition between rotation and bridge formation or bridge formation and subsequent reopening of the bridged ion. Surprisingly, the ion does not rearrange via a 1,2-hydride shift to the known, stable 2-phenyl-2-butyl cation.[4]

The spectra of ions XI and XIII also favor the bridged structure. Ion XIII forms from either the immediate alcohol precursor or from 2-phenyl-3,3-dimethylbutanol-2 via a methyl shift. The methyl band, at -2.20 p.p.m. does not broaden on cooling to -120°. The chemical shift would be expected near -3.31 p.p.m. if this were an equilibrating ion. No reisolation of starting material was reported.

The ultraviolet and visible spectra of several monoaryl dialkylmethyl cations show two bands appearing at 320-330 and 390-400mu.[22] The bridged ions, IX or X and XIII show only one absorption at 329 ($\epsilon \sim 23{,}500$) and 347 mu. ($\epsilon \sim 11{,}500$), respectively.[15] Absorptions with epsilon values as low as 25 could have been observed if they had existed. The spectrum is similar to that found for the cyclohexadienyl cation with an absorption at 331 mu.[23] This evidence has lead Olah and Pittman to favor the bridged structure for ion X.

Olah and Pittman have emphasized the dangers involved in transforming these results to systems under the conditions of solvolytic reactions. Consequently, although the existence of bridged ions in special solvents seems fairly certain, the question of whether bridged or open ions are short-lived intermediates in solvolysis reactions requires the consideration of other kinds of evidence.[24]

CONCLUSION

The formation of organic cations in liquid Lewis acid solutions provides a means to directly observe what were once only transient species. Strong evidence has been presented for the existence of bridged phenonium and some classical 2-phenylethyl cations. The bisected structure of cyclopropylmethyl cations has been confirmed.

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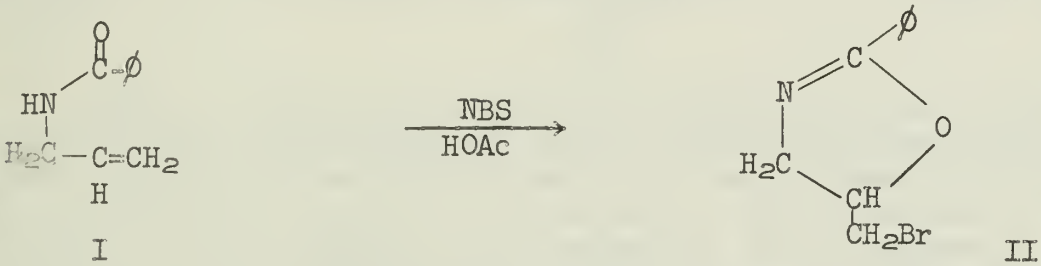
NEIGHBORING GROUP ADDITIONS TO ALKYNES

Reported by Elvin R. Lukenbach March 17, 1966

The participation of neighboring groups in reactions has been reviewed in detail by Gould and other writers.[1] Among the types of evidence for neighboring group effects are otherwise unexplained rate enhancement, stereochemistry, and rearrangements. Considerations of this sort of evidence, principally of rates of reactions, will be presented to demonstrate the neighboring group effect on nucleophilic additions to alkynes. As the groups involved in these additions have not all been studied quantitatively to assign their relative nucleophilicities, and widely varying catalytic conditions have been used to activate the alkynes, rate considerations in this subject are of a qualitative nature.

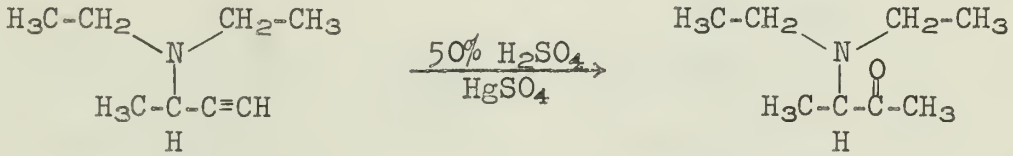
In general, neighboring group interactions depend on the nucleophilicity of the neighboring group, and so thiols, alkoxides, and amines are particularly good reagent groups. However, the favorable nature of the much smaller restriction of motion in a cyclization of this type over intermolecular reactions brings out the reactive nature of functional groups which would not ordinarily be considered good nucleophilic agents in additions to alkynes. The groups most thoroughly studied in additions to alkynes, amides, and carboxylate salts, have also been found to participate in internal displacement reactions.[2] Other groups to be discussed are urethans, ureas, alcohols, nitrogen of isocyanates, activated sites on aromatic rings, and oxygen of nitroso groups.

In a study which provides a bridge between replacements at saturated carbon and additions to the acetylenic triple bond, an alkene reaction analogous to some of the alkyne neighboring group reactions was examined by Goodman and Winstein;[3] N-benzoyl-2-propenylamine (I) is nearly quantitatively converted to 5-bromomethyl-2-phenyl-oxazolidine (II) by N-bromosuccinimide in glacial acetic acid.



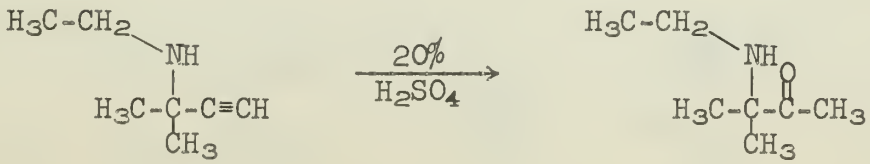
I II

That the amine group may function as a neighboring group in addition to the carbon-carbon triple bond is suggested by comparison of the following reactions. N,N-diethyl-1-methyl-2-propynylamine (III) requires fifty percent sulfuric acid plus mercuric sulfate for conversion to 3-diethylamino-2-butanone (IV).[4] These are the usual conditions for hydration of alkynes.[5] N-ethyl-1,1-dimethyl-2-



III IV

propynylamine (V) when heated with twenty percent sulfuric acid without mercuric salts is hydrated to 3-ethylamino-3-methyl-2-butanone (VI).[6] Thus the unhindered α-aminoalkyne may be helped somewhat by neighboring group participation in its hydration.



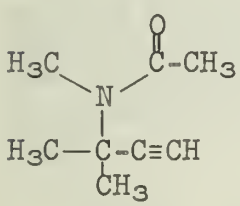
V VI

The α-aminoalkynes may be synthesized by a quite simple method. Sodium acetylide is generated by passing acetylene through sodamide in liquid ammonia. The acetylide is then added to a ketone or aldehyde, forming the α-hydroxyalkyne.[5] This may be converted to the α-chloroalkyne by thionyl chloride, and an amine plus the chloride forms the α-aminoalkyne.[7] For instance, sodium acetylide plus acetone, then thionyl chloride, then ethylamine forms N-ethyl-1,1-dimethyl-2-propynylamine (V).

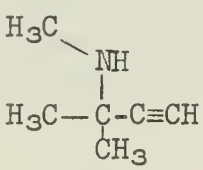
Besides the concentrated sulfuric acid and mercuric salts used as catalysts for additions to alkynes, cuprous chloride and boron trifluoride are used.[5,7,8] Copper acetylide has also been noted as a highly effective catalyst.[9]

α-AMIDOALKYNES

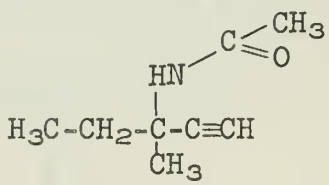
In contrast to the conditions required for hydration of the alkynes mentioned above, N-acetyl-N,1,1-trimethyl-2-propynylamine (VII), synthesized from the amine plus ketene, is hydrated in water at room temperature when a small amount of hydrochloric acid is added.[10] The reduction in the catalytic requirements for the reaction would seem to indicate that there is help from the amido group. The N,1,1-trimethyl-2-propynylamine (VIII) is completely unaffected by the same conditions. Another earlier report[11] had also noted the ease of hydration of this type of compound by reporting that the hydration of N-acetyl-1-ethyl-1-methyl-2-propynylamine (IX) was accomplished by trace amounts of sulfuric acid and mercuric sulfate in thirty percent aqueous ethanol at room temperature.



VII

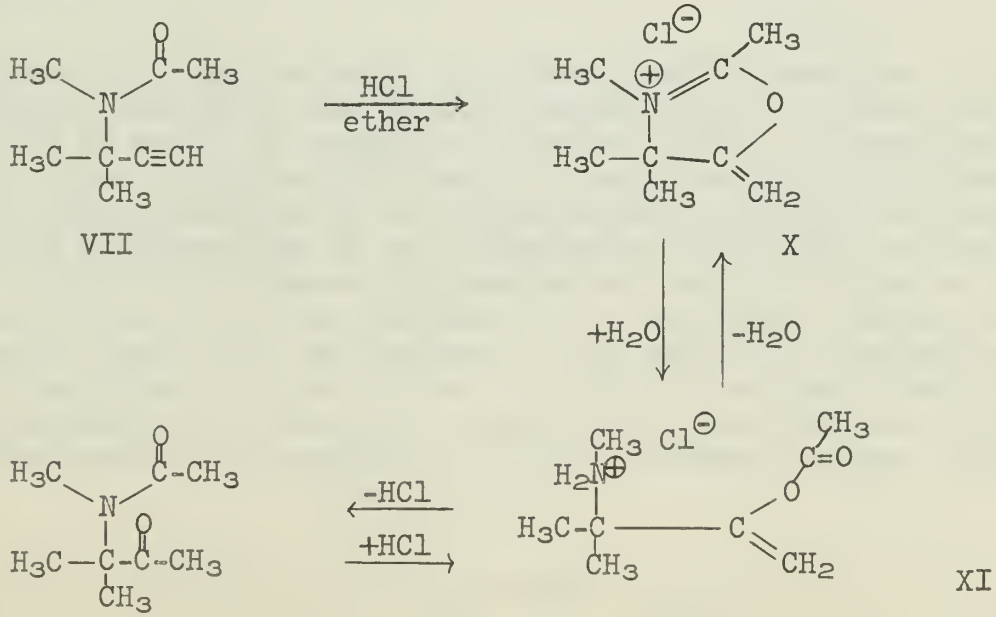


VIII



IX

In order to confirm the postulated neighboring group participation in these molecules[12] the α-amidoalkyne was treated with hydrochloric acid in ether and a compound was isolated which was shown to be 5-methylene-2,3,4,4-tetramethyloxazolidinium chloride (X). This compound is very sensitive to water, and rearranges to a new compound in its presence. This compound is the enol acetate hydrochloride of 3-(methylamino)-3-methyl-2-butanone (XI). This compound in turn rearranges to 3-(acetylmethylamino)-3-methyl-2-butanone (XII) in water, but it can be trapped as the hydrochloride in dilute hydrochloric acid. Thus the acetyl group appears to be in equilibrium in bonding with the alkynyl carbon and the amino nitrogen in water, and in the absence of water the acetyl group bonds both with nitrogen and carbon.



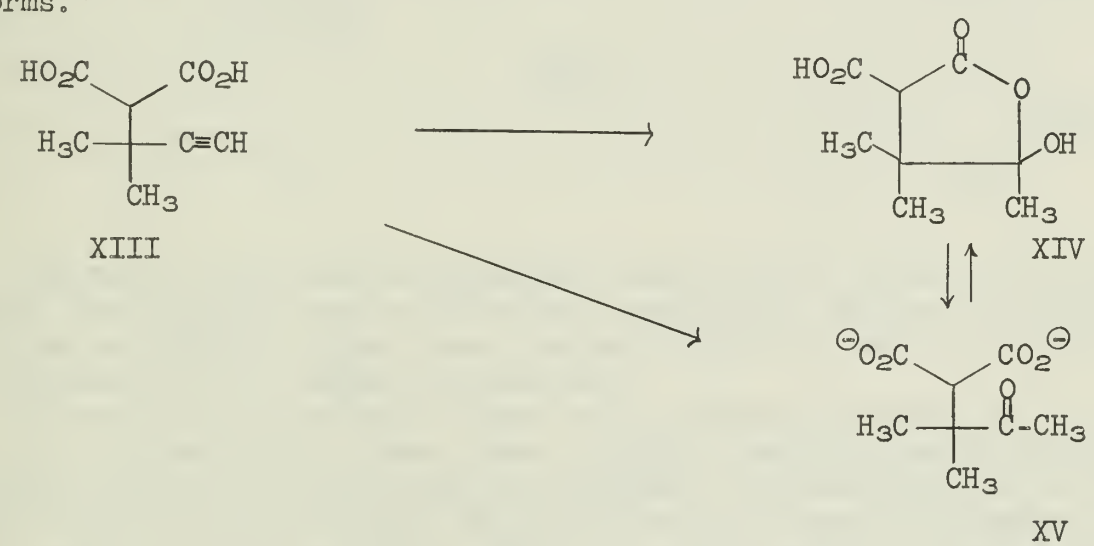
VII X XII XI

The structural assignments for the oxazolidinium chloride (X) and the enol acetate (XI) were made on the basis of infrared and NMR spectra.

The site of the hydration of the alkyne might be expected to give additional evidence for the neighboring group reaction. The five-membered ring would certainly be favored over the possible six-membered ring from addition to the other end of the triple bond, due to the linearity of the triple bond system, and so hydration should be expected to give the ketone rather than the aldehyde. However, this is also expected in simple hydration. If the other methyne hydrogen is replaced by methyl, in N-acetyl-N,1,1-trimethyl-2-butynylamine, the choice of site for hydration is not so obvious, and the fact that only the 3-pentanone is observed in the ketonic products might be taken as further evidence for the neighboring group interaction, although the effects of the different substituents on the ends of the alkyne probably cannot be predicted with confidence. Also, the yield of hydration product is low in this case and instead elimination of the amido group occurs. This is probably due to the lessened ability of the proton to reach the end of the alkyne and so catalyze the nucleophilic addition of the amide carbonyl or water.[12]

PROPARGYLMALONIC ACIDS

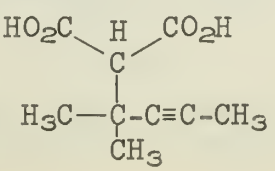
The carboxylate anion is a better nucleophile than the amide carbonyl, so it would be expected that it would act as a better neighboring group than the amide. This appears to be the case as (1,1-dimethyl-2-propynyl)-malonic acid (XIII). synthesized from the alkynyl chloride and sodiomalonic ester, when warmed in a fifty percent aqueous ethanol solution which is 1.5 N in sodium hydroxide produces 2-carboxy-3,3-dimethyl-4-hydroxy-4-pentanolactone (XIV). If the propargylmalonate or the lactone is dissolved in 6 N sodium hydroxide, disodium 2-carboxy-3,3-dimethyl levulinate (XV) results, and on reduction of the concentration of base the lactone reforms.[13]



Structural assignments are on the basis of infrared and NMR spectra.

The extreme ease with which the cyclization and hydration occur, without the benefit of any acid or metal ion catalyst, in contrast with the need for boron trifluoride-mercuric oxide catalysis for straight bimolecular addition,[5] seems a good indication of the aid to reaction which the carboxylate neighboring group provides.

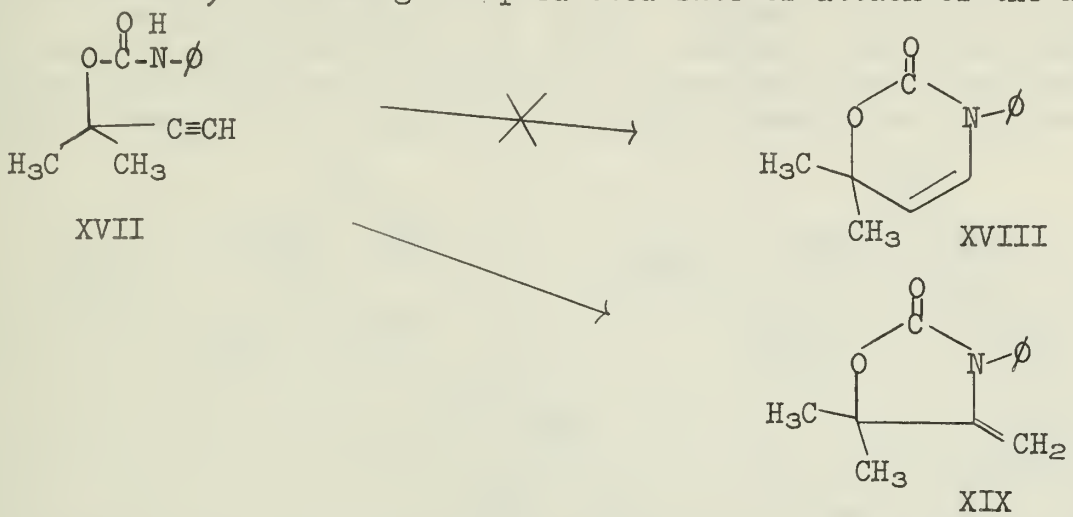
For additional demonstration of the neighboring group effect on the position of hydration, it would be of interest to examine the position of hydration of the (1,1-dimethyl-2-butynyl)-malonic acid (XVI) as, unlike the α-amidoalkyne, this compound would be expected to have little preference for one position of hydration over the other. Thus a preponderance of the product of hydration at the 2-position of the butynyl side chain might be expected over hydration at the 3-position as described previously. Unfortunately, no examination of this compound has been reported.



XVI

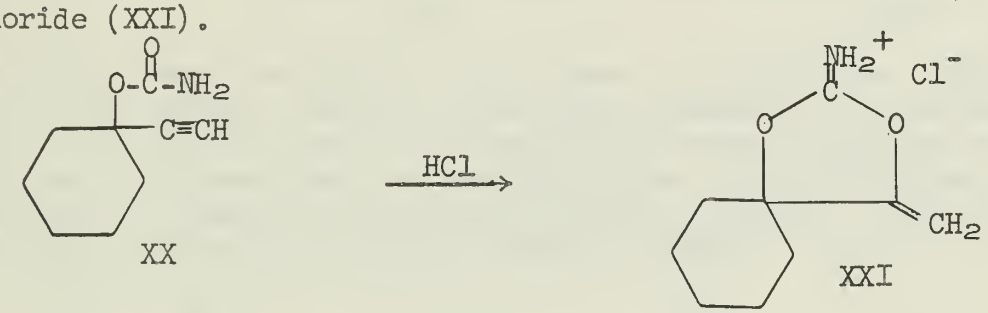
ALKYNYL CARBAMATES

It was reported[14] that 2-ethynyl-2-propyl-N-phenylcarbamate (XVII) cyclized in base to give the 6,6-dimethyl-3-phenyl-1,3,6-oxazin-2-one (XVIII). This was refuted by the work of several groups,[15-18] who showed by independent synthesis and NMR studies[15] that in fact the 5,5-dimethyl-4-methylene-3-phenyl-2-oxazolone (XIX) had been formed, confirming the predicted site of attack of the neighboring group.



XVII XVIII XIX

It has also been reported[18] that 1-ethynyl cyclohexylcarbamate (XX) cyclizes in dry ether with acid to give the 4-methylene-5-pentamethylene-1,3-dioxolane-2-iminium chloride (XXI).

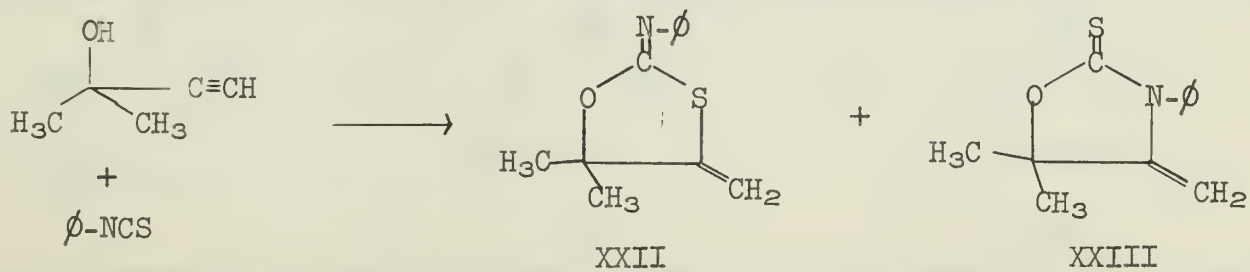


XX XXI

The acidic cyclization apparently results from attack of the more nucleophilic center, the carbonyl oxygen, with acid catalysis. The basic conditions generate a stronger nucleophilic agent from the amide nitrogen, and so it adds to the alkyne in preference to the oxygen cyclization.

It would seem that due to the weak nucleophilic nature of the attacking groups in these cyclizations, quite strong catalysis would be required to promote intermolecular addition of this type of compound, corresponding to the catalytic conditions for other nucleophiles, assuming that this type of compound would survive such conditions long enough to add, but no such additions have been carried out, so only such speculation on conditions hypothetically necessary can indicate to us the enhancement of reactivity of the neighboring group.

1,1-Dimethylpropargyl alcohol and phenyl isothiocyanate are reported to cyclize directly in the presence of base to give a mixture of products, consisting of 5,5-dimethyl-4-methylene-2-phenylimino-1,3-oxathiole (XXII) and 5,5-dimethyl-4-methylene-3-phenyl-2-oxazolethione (XXIII).[17] The structures were assigned on the basis of



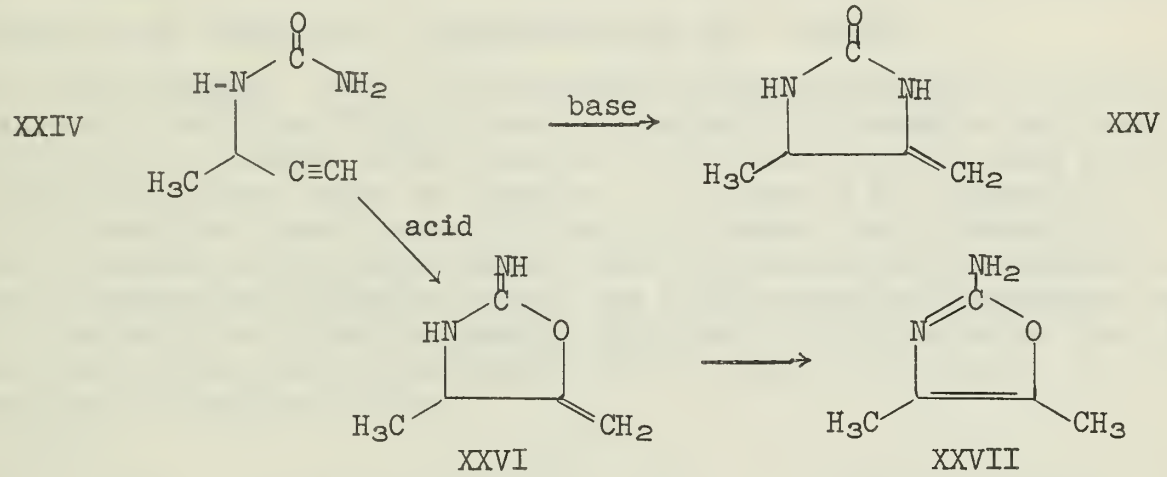
XXII XXIII

infrared and NMR spectral evidence. The oxathiole is three times as abundant as the oxazole in the products of the reaction. It might be expected, according to the

work with the carbamates, that a weaker base or none at all should favor the greater preponderance of the oxathiole, due to the high nucleophilicity of sulfur in such compounds compared with the thioamide nitrogen.

ALKYNYLUREAS

A study of the cyclization of alkynylureas shows that these compounds act in much the same way as the carbamates, to which they are similar. It was reported[19] that N-(1-methyl-2-propynyl)-urea (XXIV) cyclizes with acid to give 5-methyl-4-methylene-1,3-imidazolidine-2-one (XXV). However, recent NMR studies[20] seem to indicate that this type of compound is formed under basic catalysis, and acidic catalysis leads to the formation of 4-methyl-5-methylene-2-imino-oxazolidine (XXVI),

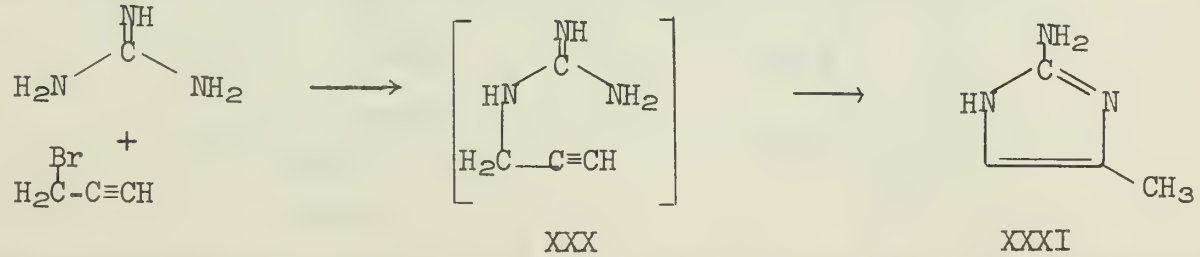


as expected from similar reactions of urethanes. In this case, where there is no gem-dimethyl group on the ring the double bond remaining from the alkynyl group can isomerize to an endo-cyclic position, giving the 2-amino-4,5-dimethyloxazole (XXVII).

Similar work has been done on the cyclization of alkynylthioureas.[19,21,22] It is reported that N-(1-methyl-2-propynyl)-thiourea (XXVIII), when treated with acid cyclizes to the 4,5-dimethyl-2-imidazolethione (XXIX).

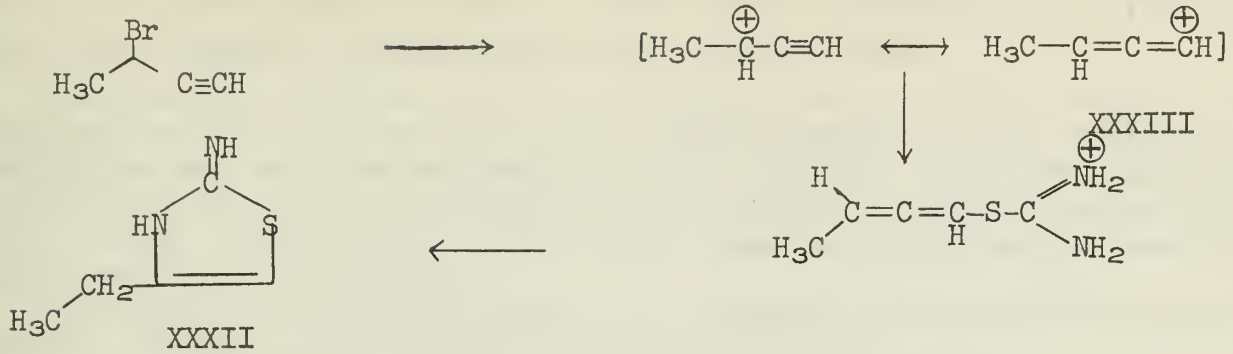
This mode of cyclization seems contrary to the expected reaction. The sulfur is a better nucleophile than the nitrogen, and the analogous reaction with the carbamates proceeded with S-cyclization. However, the evidence in both cases is not conclusive for the structures proposed, but is based on similarity of spectra with known examples of the type of compound. A more complete examination of this matter is necessary before a final decision can be made.

Guanidine adds to propargyl bromide to give 2-amino-4-methylimidazole (XXXI). This reaction presumably goes through the imino-propargylurea intermediate (XXX) in a manner similar to the other reactions of these compounds.[22]



Thiourea adds to 1-methylpropargyl bromide to give 2-amino-5-ethylthiazole (XXXII) as the major product.[21,22] This rearrangement from the expected compound results from a different mechanism,[23-25] proceeding through the α alkynyl carbonium

ion (XXXIII), and so is not an example of the neighboring group ring closure.



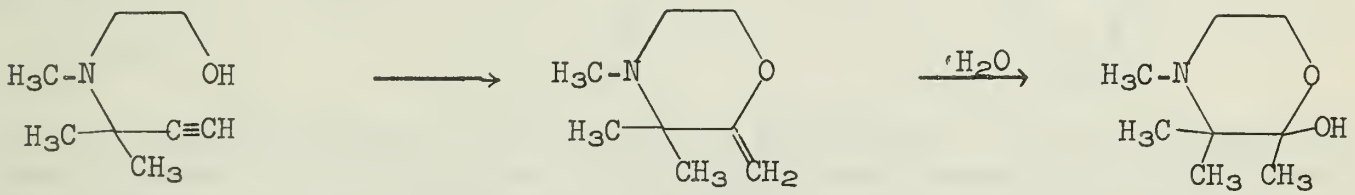
XXXII

XXXIII

N-(2-HYDROXY- AND AMINOALKYL)-PROPARGYLAMINES AND -ALCOHOLS

N-(2-hydroxyalkyl)- and N-(2-aminoalkyl)-propargylamines and -alcohols are of interest beside the possibility of another example of a neighboring group cyclization as they have the potential nucleophile in such a position that ring closure on the other end of the alkyne might be possible. In spite of the linearity of the alkynyl group, the chain can reach back sufficiently to make this a possibility.

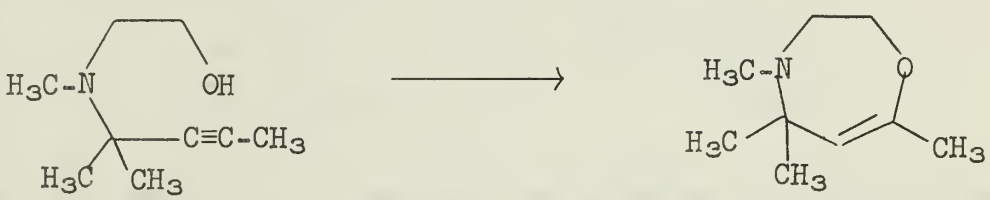
N,1,1-trimethyl-N-(2-hydroxyethyl)-propargylamine (XXXIV) cyclizes in the presence of potassium hydroxide to give the 3,3,4-trimethyl-2-methylene morpholine (XXXV). The methylene group is readily hydrated in dilute acid to the 2,3,3,4-tetramethyl-2-hydroxymorpholine (XXXVI).[26] The morpholine prepared by hydrogenating XXXV was also synthesized by the



XXXIX XXXV XXXVI

treatment of the α-hydroxyamine with ethylene oxide, followed by dehydration in acid.

N,1,1-trimethyl-N-(2-hydroxyethyl)-2-butynylamine (XXXVII), however, closes to the homomorpholine, 2,4,4,5-tetramethyl-4,6-tetrahydro-oxazepine (XXXVIII), demonstrating the possibility for cyclization of these compounds at either end of the alkyne group.[27] The structure was assigned by spectral evidence in comparison with the morpholine XXXV.



XXXVII XXXVIII

N,1,1-trimethyl-N-(2-aminopropyl)-propargylamine (XXXIX) cyclizes under the influence of sulfuric acid and mercuric sulfate to give 1,2,2,3,5-pentamethyl-2,5-tetrahydropyrazine (XL).[28]

XXXIX XL

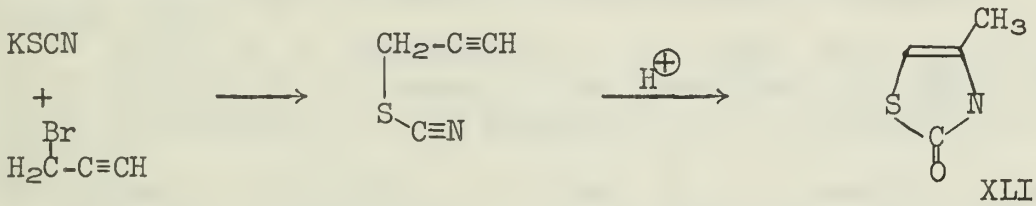
As the conditions used for the above cyclizations are quite near the conditions for the intermolecular additions of the same groups, no additional evidence for the neighboring group effect may be derived from these reactions, although it seems likely

that less active catalysis would be sufficient to accomplish the cyclizations.

ADDITIONAL EXAMPLES OF RING CLOSURE ADDITIONS TO ALKYNES

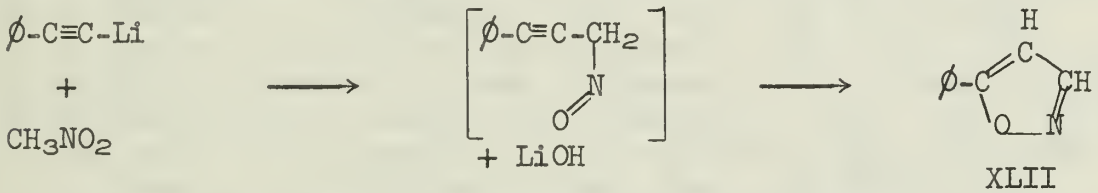
Several ring closures on alkynes have been noted without detailed study, involving groups which have not been studied in intermolecular additions, so no conclusions may be drawn on comparative rate effects. These reactions have some significance in that they involve groups which are of rather low nucleophilicities, and so would be expected to require quite rigorous conditions to cause their intermolecular addition to alkynes.

Propargyl bromide adds potassium thiocyanate, and in acid the product of this addition cyclizes to 4-methyl-2-thiazolone (XLI).[29]



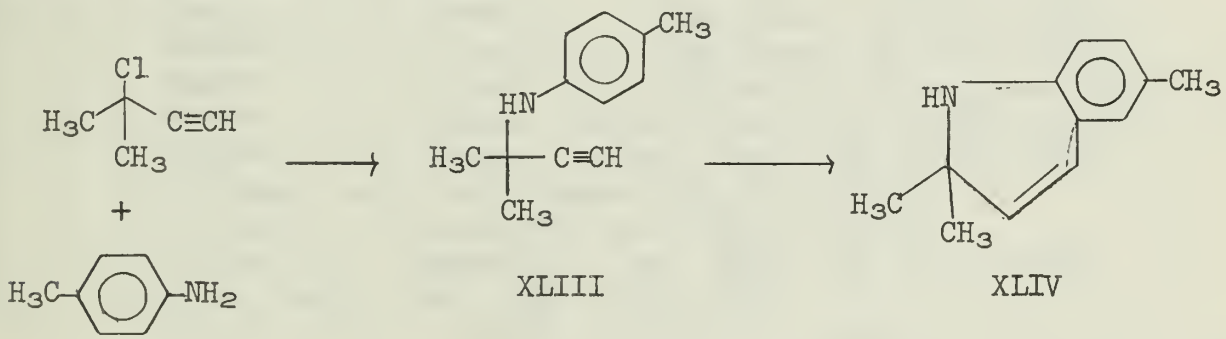
XLI

Lithio phenylacetylene adds to nitromethane to give a compound which cyclizes to 5-phenylisooxazolone (XLII) in the basic solution resulting from the addition.[30]



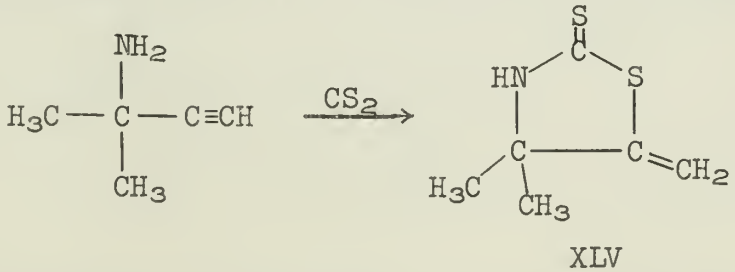
XLII

1,1-dimethylpropargyl chloride adds to p-toluidine to give 1,1-dimethyl-N-(4-methylphenyl)-propargylamine (XLIII) plus a small amount of a cyclic side product, 2,2,6-trimethyl-2-dihydroquinoline (XLIV).The propargylamine may be quantitatively transformed into the dihydroquinoline by refluxing in aqueous dioxane with cuprous chloride as catalyst.[31]



XLIII XLIV

Carbon disulfide adds to 1,1-dimethylpropargylamine to give 4,4-dimethyl-5-methylene-2-thiazolidinethione (XLV).[32,33] This reaction of addition of carbon



XLV

disulfide has been proposed as a qualitative test for α-aminoalkynes.

CONCLUSION

The wide differences between the conditions necessary for reaction of the same group with an alkyne in intermolecular and intramolecular reactions demonstrates the neighboring group effect in these compounds. The same wide difference of reactivity together with the low reactivity of alkynes toward nucleophilic agents

makes the quantitative assessment of the effect difficult. Further work on this subject could add to knowledge of the neighboring group additions and might produce further reactions of synthetic value.

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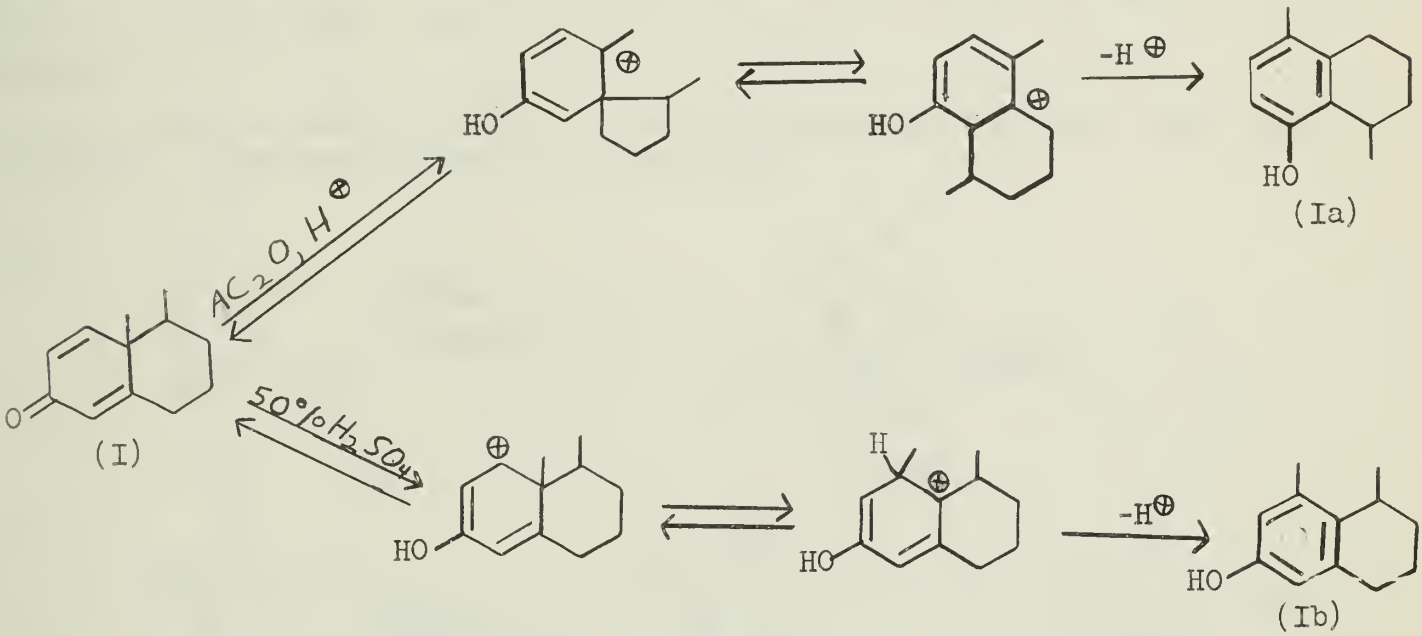
ON THE MECHANISM OF ALLYL MIGRATIONS IN ACID CATALYZED DIENONE-PHENOL REARRANGEMENTS

Reported by Gerald F. Koser March 24, 1966

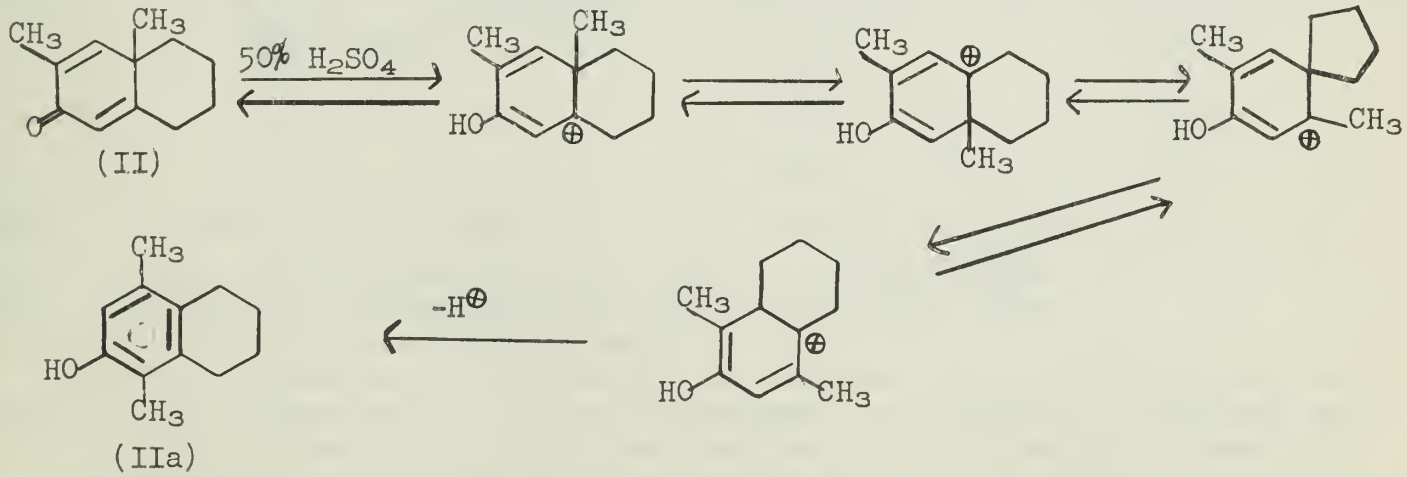
INTRODUCTION

The fact that alkyl migrations are often observed in acid-catalyzed dienone-phenol rearrangements has been known for quite some time and has been well reviewed.[1,2] However, a brief consideration of the mechanistic conclusions is of interest to this seminar. Thus, the acid-catalyzed rearrangement of dienone (I) yields two isomeric phenols, (Ia) and (Ib), by the following pathways:



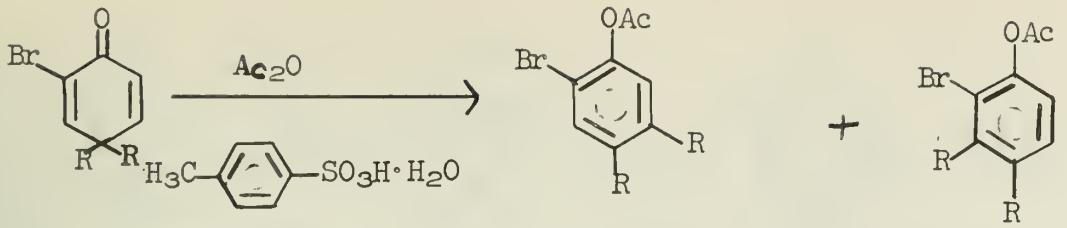
The observation that phenol (Ia) arises from dienone (I) by two successive 1,2 migrations will be of import later in the seminar.

Of more recent interest is the effect of steric interactions on the rearrangement mechanism. For example, Kropp has shown that the acid-catalyzed rearrangement of dienone (II) yields a third isomeric phenol (IIa) in addition to the two expected phenols.[3] It has been suggested that the steric repulsions encountered during the normal 1,2 shift force methyl migration to the alternate angular position.



Similarly, Bordwell and Wellman have shown that upon acid catalysis in acetic anhydride, dienones (III) and (IV) yield two isomeric products. In both cases, the major product was the acetate in which migration away from the bromine atom had occurred.[4] However, the authors have suggested that electronic as well as steric factors are involved.

Recently a series of 4,4'-di-substituted-2,6-di- t-butyl -2, 5-cyclohexadienones have been synthesized by Miller[5,6] and their behavior examined in acid solution. This



(III), R = phenyl (IIIa), R = phenyl (IIIb), R = phenyl

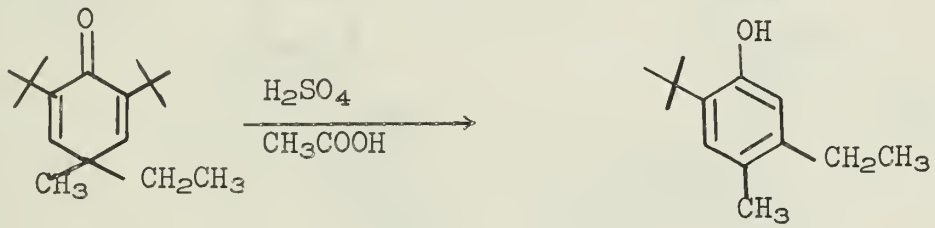
(IV), R = Methyl (IVa), R = Methyl (IVb), R = Methyl

seminar will be primarily concerned with the results of these studies from a mechanistic point of view. Of particular interest are those rearrangements in which 1,3 allyl migrations were observed.

DISCUSSION

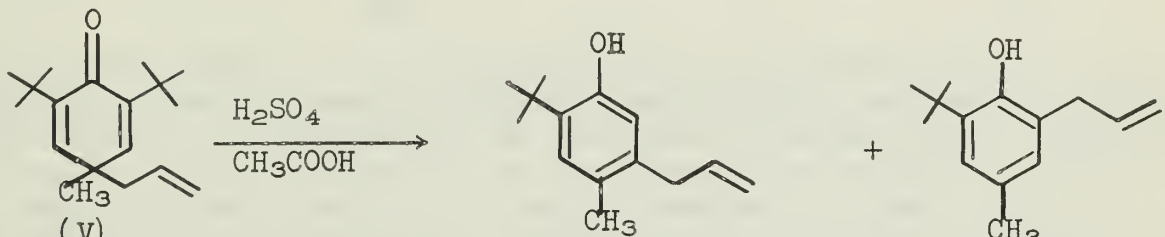
In the initial results loss of a t-butyl group as well as side chain migration was observed.[7] Consider the following reactions:

a)



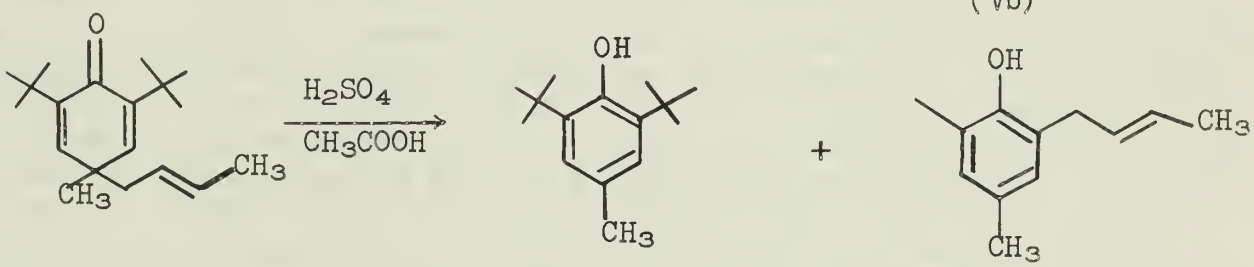
(IV) (IVa)

b)



(V) (Va) (Vb)

c)



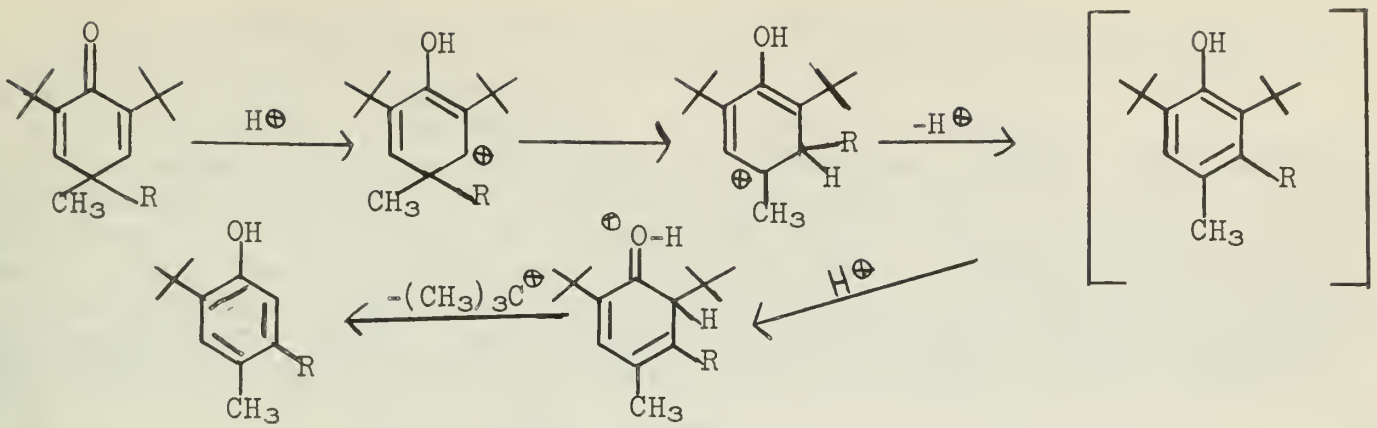
(XI) (VIa) (VIb)

These observations can be grouped into three specific categories:

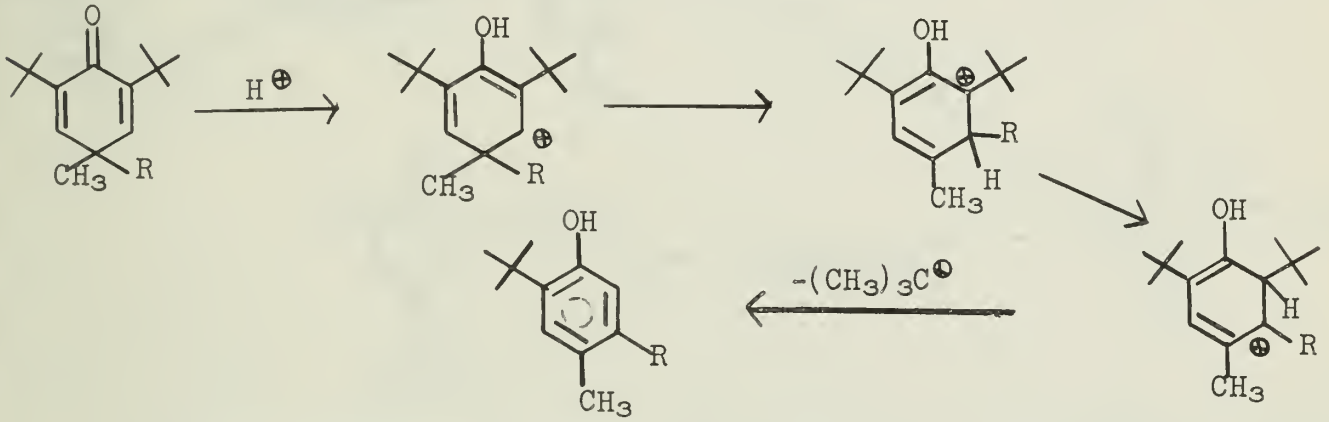
(a) 1,2 migration accompanied by the loss of a t-butyl group.
(b) 1,3 migration accompanied by the loss of a t-butyl group.
(c) loss of the migrating group itself.

The first result to be rationalized is the loss of a t-butyl group during the course of the rearrangement. Miller has advanced two plausable mechanisms, but a conclusive experiment has not yet been designed to differentiate between them.

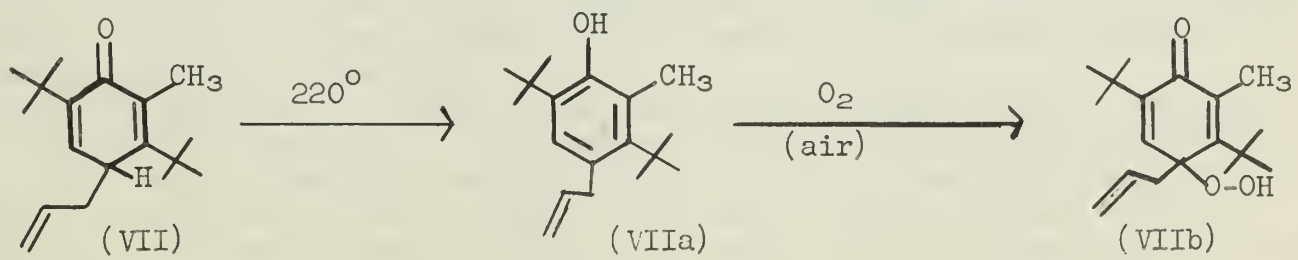
In the first, a 1,2 shift of the migrating group would occur without loss of a t-butyl group to yield an intermediate phenol. This would be followed by reprotonation at the ortho position and then cleavage to yield the product phenol and a t-butyl carbonium ion.



The second possibility would be the simultaneous loss of a t-butyl group with migration. Such a mechanism would necessarily include a 1,2 hydride shift.



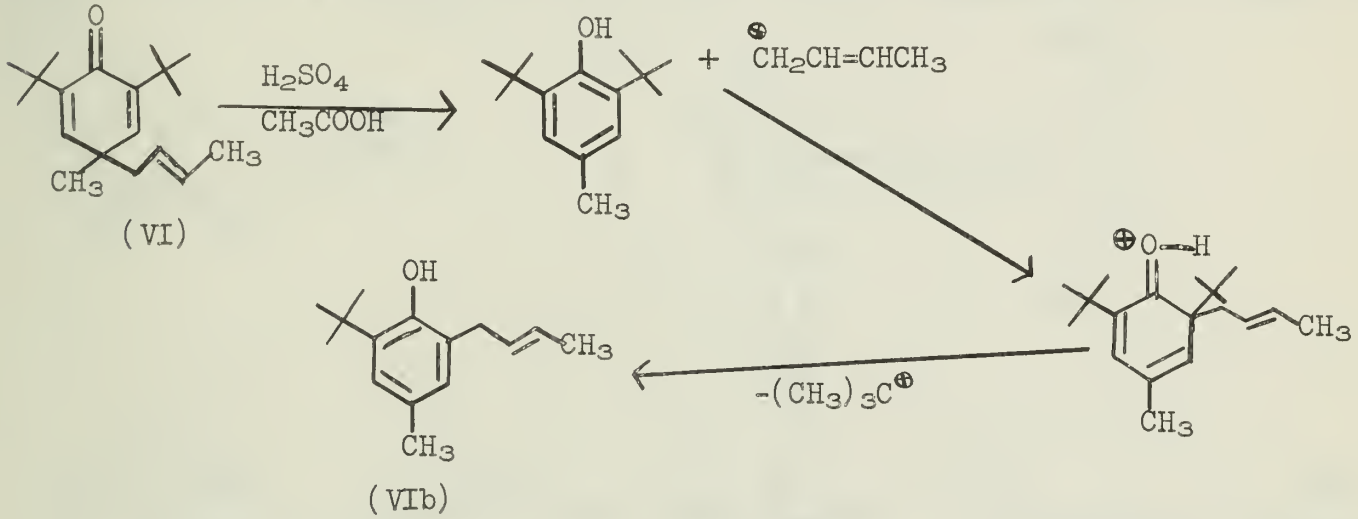
A labeling experiment in which deuterium was incorporated in the 3,5 positions of 4-allyl-2,6-di- t-butyl -4-methylcyclohexadiene-1-one (V) has been carried out and an isotope effect of 4.1 calculated on the basis of product ratio comparisons.[8] Miller has concluded from the magnitude of the isotope effect that the rate determining step is probably proton loss and reprotonation rather than hydride migration. However, it must be pointed out that the di-deuterated dienone was contaminated with 27.4% monodeuterated dienone and 6.9% undeuterated dienone, thus complicating the calculations. Normally, the loss of a t-butyl from the ortho position of a phenol requires far more rigorous conditions than these.[9,10] In fact, Miller has pointed out that 2,6-di- t-butyl -phenol and 2,6-di- t-butyl -4-methylphenol are stable indefinitely under these conditions. Miller has suggested that steric interactions between the migrating group and the t-butyl group may facilitate protonation at the ortho position since the t-butyl group would be removed from the plane of the ring. Several illustrations of steric strain aiding "ketonization" can be found in the literature.[11] For example, Miller has shown that 4-allyl-3,6-di- t-butyl -2-methylcyclohexadienone (VII) is unusually stable toward thermal tautomerization to the corresponding phenol (VIIa). This is presumably due to the fact that the allyl group would be forced into a coplanar relationship with the adjacent t-butyl group. Likewise, when the phenol (VIIa) is obtained, it rapidly undergoes autoxidation to the corresponding hydroperoxide.[12]



A perhaps even more intriguing question is that of the nature of the 1,3 migrations undergone by the allyl and crotyl groups of dienones (V) and (VI). The points to be resolved may be categorized as follows:

(a) Are the rearrangements intermolecular or intramolecular?
(b) Do the observed products of 1,3 rearrangement arise from two successive 1,2 migrations or a direct 1,3 migration?
(c) If the mechanism is intramolecular, is it cyclic in nature?
Such a rearrangement would be analogous to the "Cope" and "Claisen" rearrangements[13] in that internal inversion of the migrating allyl group should be observed. Alternatively, does it proceed through an intermediate such as a π complex which collapses in such a manner that the migrating groups retain their original stereochemistry?

In an attempt to answer the first question, consider the following intermolecular pathway suggested by Miller. Such a mechanism could be applied as an explanation for the observed product (VIb) when dienone (VI) is subjected to acid catalysis.

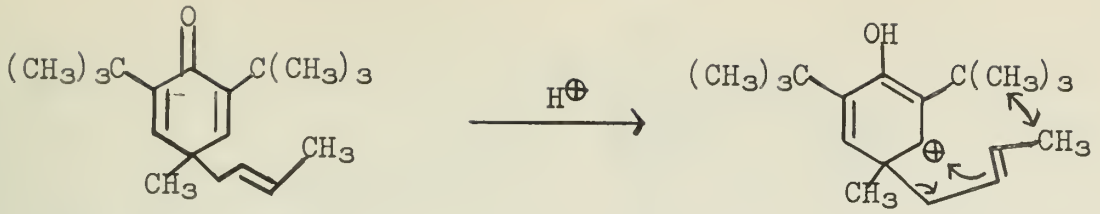


(VI) (VIb)

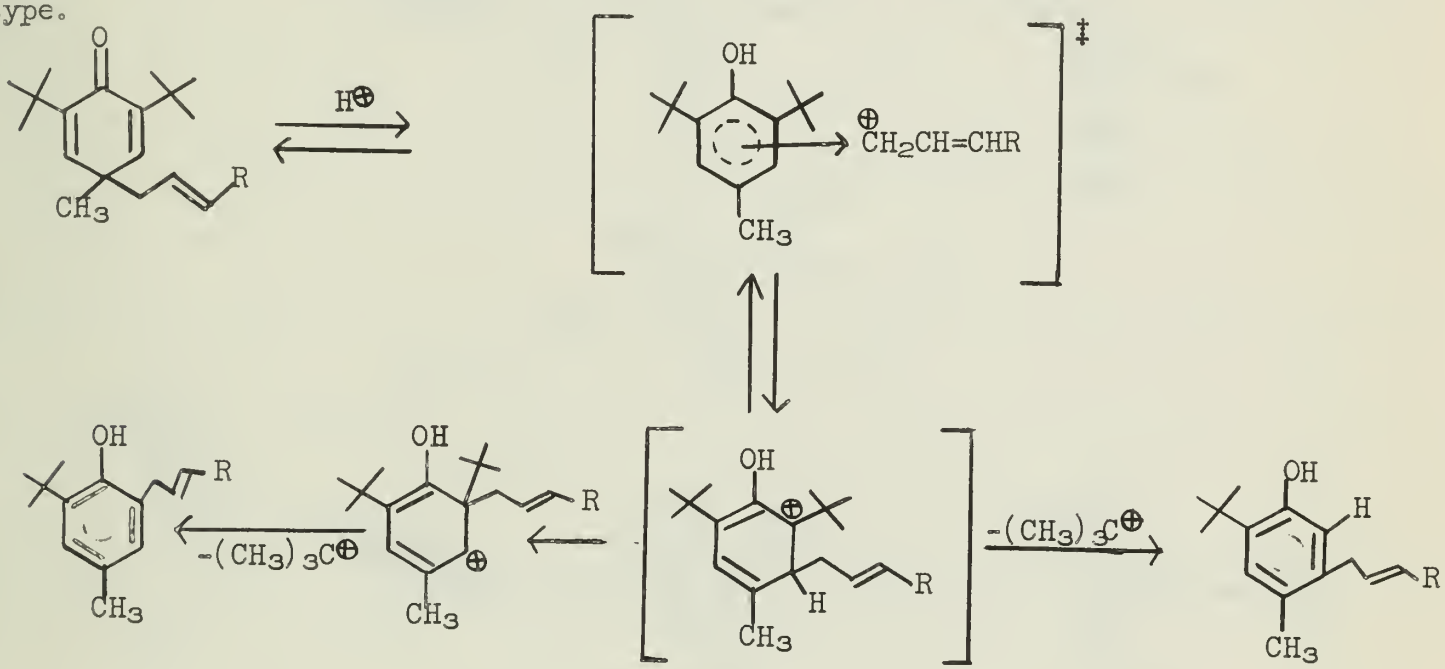
Two experimental facts seem to support such a mechanism. These are the actual isolation of 2,6-di- t-butyl -4-methylphenol in 46% yield and the higher relative yields of "1,3 products" arising from those dienones whose dissociation would result in the most stable "migrating" carbonium ions. However, an intermolecular mechanism was finally excluded on the basis of two further experimental controls. Attempts to alkylate 2,6-di-t-butyl-p-cresol with carbonium ions generated from allyl alcohol, crotyl alcohol, and methylvinylcarbinol under similar reaction conditions failed to yield any results. Secondly, attempts to trap any dissociated allyl carbonium ions by running the rearrangement of (V) in a 50 mole excess of phenol also produced negative results, although o-t-butyl phenol was isolated in 28% yield. Although the assumption that phenol would serve as an effective trap for allyl carbonium ions is probably valid, this point should be demonstrated unambiguously in a separate control.

The second question was answered in part by the labeling experiment referred to earlier in this seminar in which deuterium was incorporated in the 3,5 positions of dienone (V). If the product phenol (Vb) arises from a direct 1,3 migration of the allyl function, one would expect no significant isotope effect. On the other hand, if (Vb) is formed via two successive 1,2 allyl migrations, a measurable isotope effect should be apparent. Although the exact magnitude of the deuterium isotope effect is uncertain, there is little doubt that the ratio of "1,3 product" (Vb) over that of "1,2 product" (Va) significantly increased. Thus, in summary, experimental evidence seems to support an intramolecular mechanism involving two consecutive 1,2 allyl migrations.

With this conclusion in mind, Miller has suggested that a cyclic mechanism with allylic inversion is unlikely. The observation that the rearrangement rate of dienone (VI) is approximately one hundred times greater than that of dienone (V) would not be expected when one considers the steric repulsions that would be encountered by the methyl group of the crotyl moiety with the adjacent t-butyl group. Instead, such a rate enhancement indicates that the migrating group bears a considerable amount of positive charge in the transition state. Thus, Miller

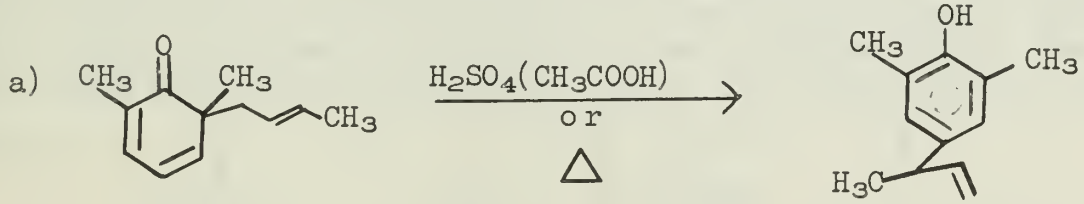


favors a mechanism in which the product of 1,2 migration is formed via a π complex which collapses to a classical carbonium ion without allylic inversion. The resulting intermediate could either lose a t-butyl group to give the "1,2 phenol" or be transformed into a second carbonium ion by an allyl migration of the Wagner-Meerwein type.



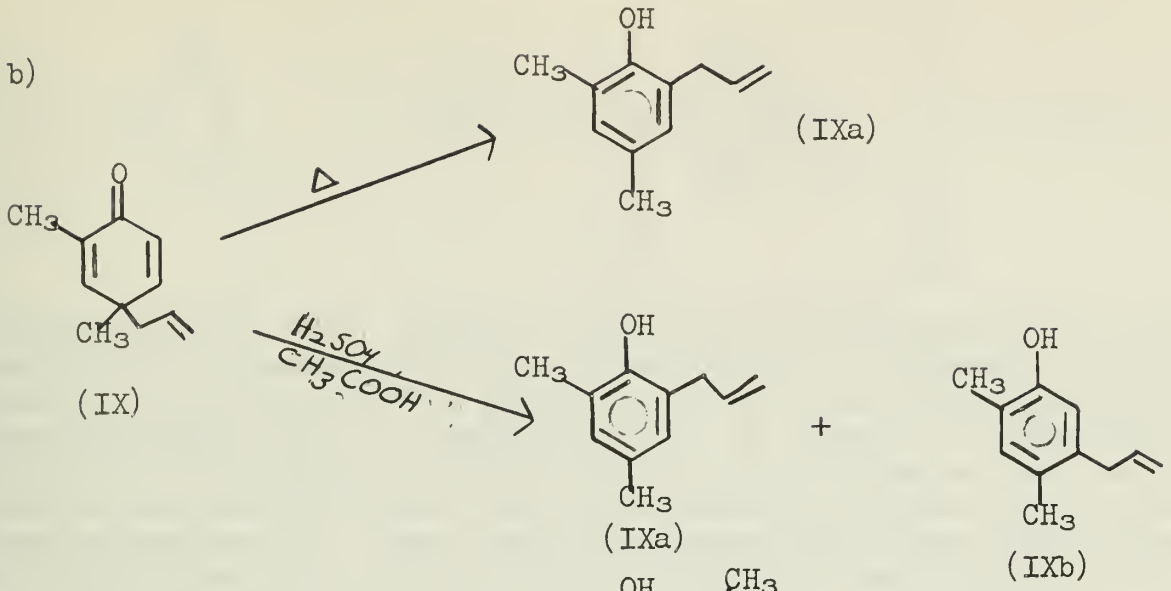
However, since the product phenol of 1,2 migration was not isolated as a rearrangement product from dienone (VI), the cyclic mechanism cannot be excluded. A conclusive experiment would be one in which the terminal carbon of the allyl group of dienone (V) were labeled with ^{14}C.

The possibility that inversion of an allyl or crotyl group might occur in acid-catalyzed dienone-phenol rearrangements prompted Miller to synthesize a number of 2,4- and 2,5-cyclohexadienones and examine their behavior in acid solution.[14] The synthesis of cross-conjugated cyclohexadienones with allylic substituents at C-4 was accomplished by thermal rearrangement of linearly conjugated cyclohexadienones and by direct alkylation of phenols following a procedure established by Schmid and coworkers.[15] Miller's results can be summarized as follows:

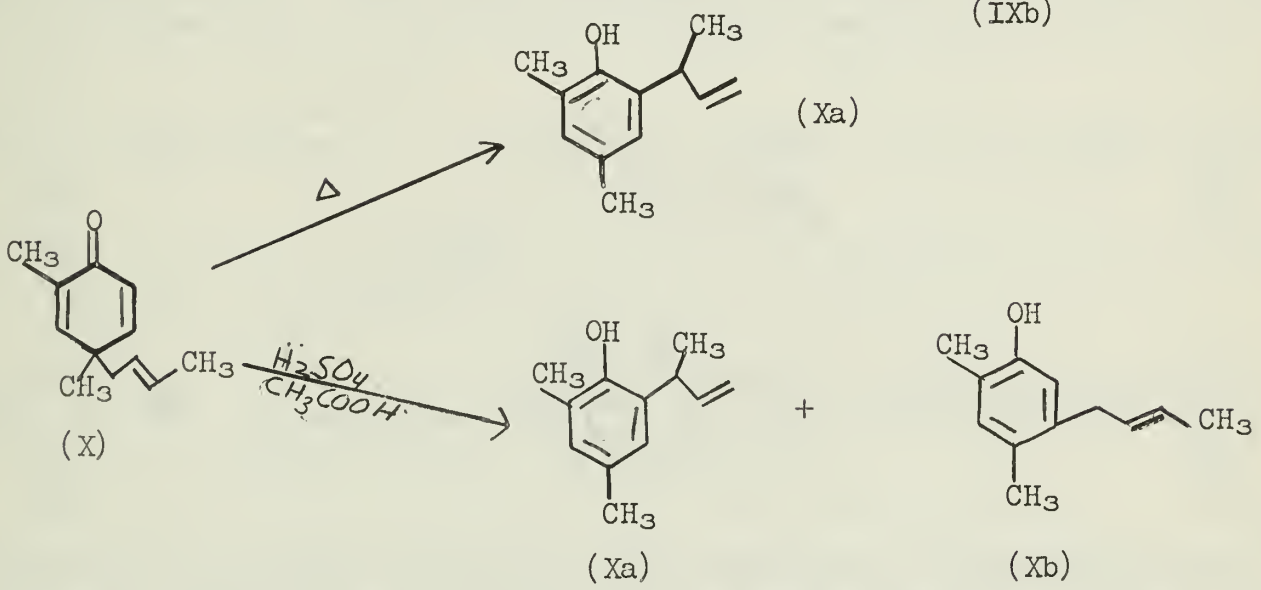


(VIII) (VIIIa)

b)

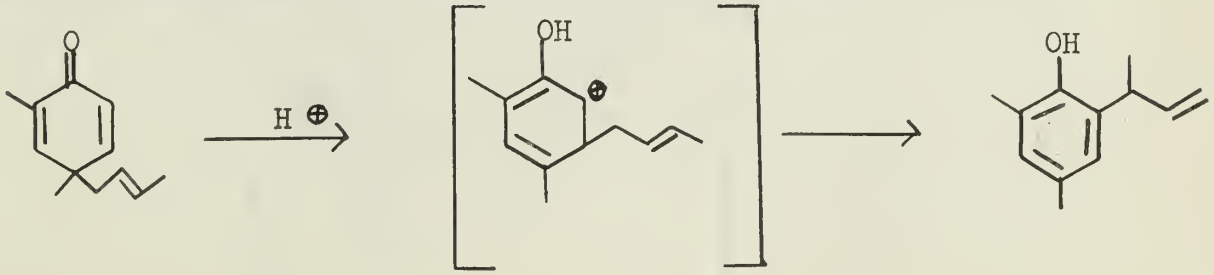


c)

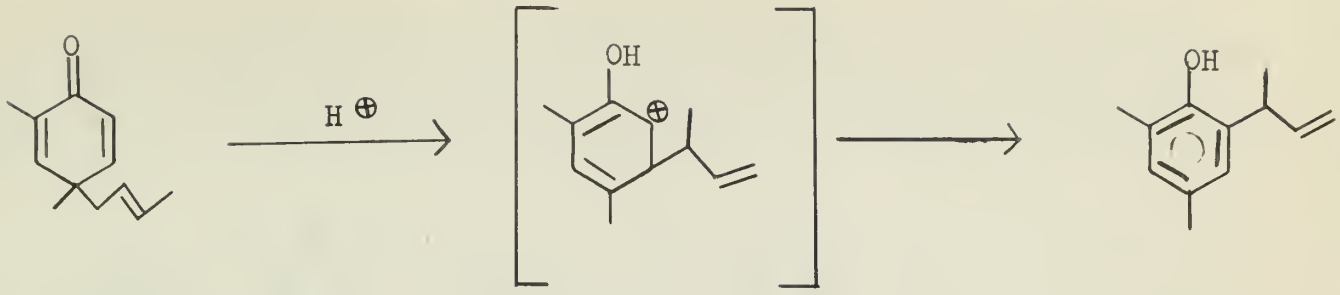


One of the most intriguing characteristics of all three reactions is that the major products of the acid catalyzed rearrangements are identical to the sole products of thermal rearrangement. In addition to this, the 1,3 migration apparently goes with inversion of the allylic group. Before proceeding any further, however, the question of intramolecularity versus intermolecularity must be resolved. Miller accomplished this by rearranging dienone (X) in the presence of six equivalents of thiophenol. As observed in the first group of rearrangements, no crotyl carbonium ions were captured, thus supporting an intramolecular mechanism. The second question to be considered is, once, again, the nature of the 1,3 migration. If two consecutive 1,2 allyl shifts were involved, only one of these would necessarily require internal rearrangement of the migrating group. The question immediately arises, then as to which of the two steps involves inversion.

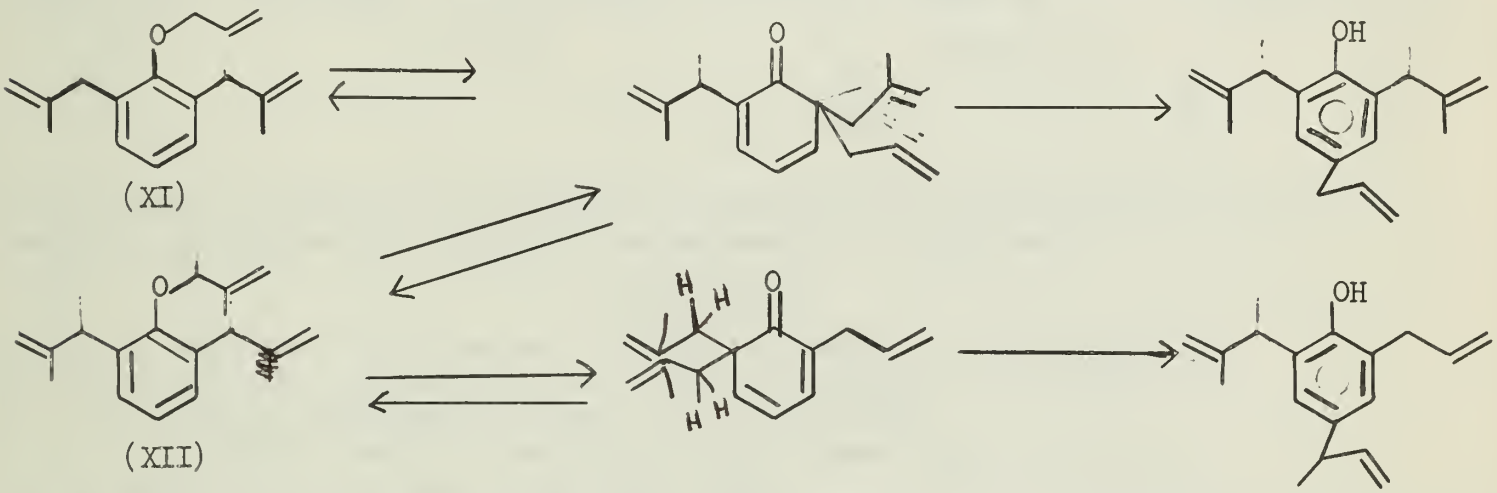
Case 1:



Case 2:



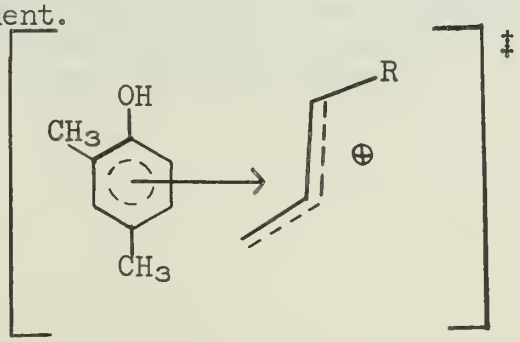
The fact that phenol (Xb) contains an uninverted crotyl group can be used in support of mechanism 1. However, Miller has suggested that the phenols arising through overall 1,3 migration could be formed in a single step via a reaction path operating independently from, but in competition with, the normal 1,2 migrations. The fact that direct 1,3 migration with subsequent allylic inversion does occur, in some instances, has been well established by mechanistic studies on the ortho and para Claisen rearrangements. Thus, Curtin and Johnson have shown that beginning with phenyl allyl ethers (XI) or (XII), the following thermal equilibria are established.[16,17]



(XI)

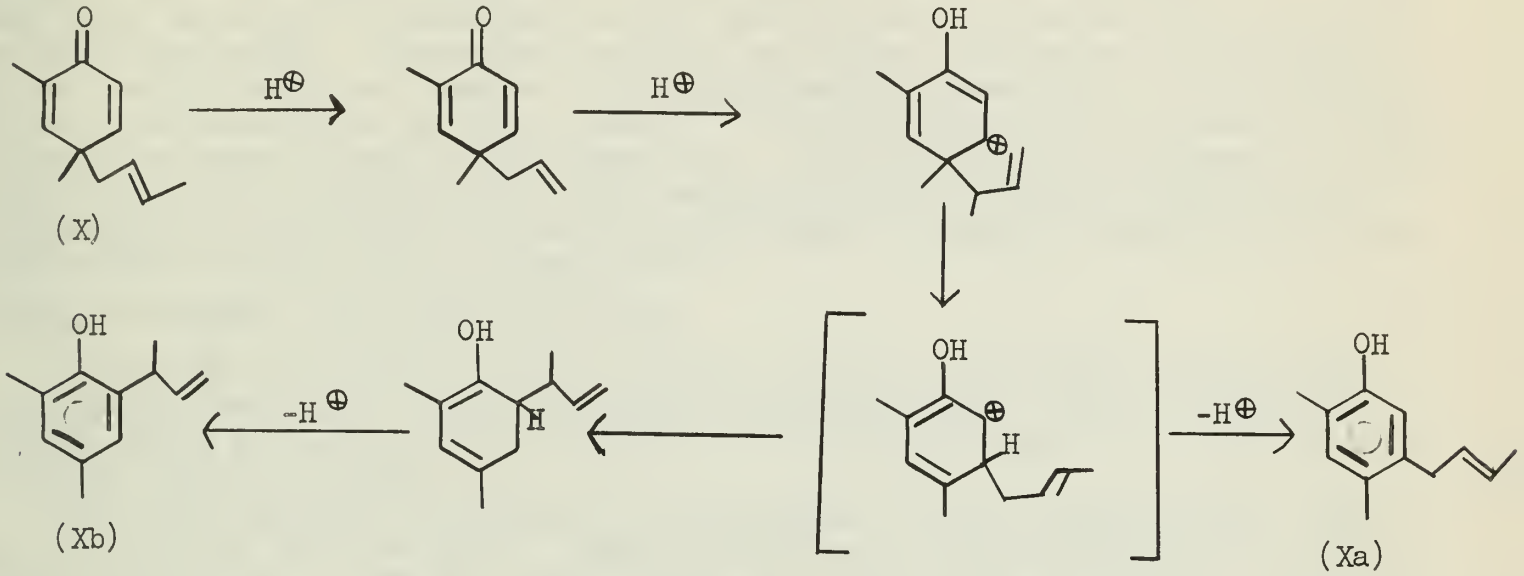
(XII)

The observations of specific interest to this seminar are the unambiguous demonstration of an o-dienone intermediate in the para Claisen rearrangement and the fact that the allyl group migrates around the ring via a series of 1,3 shifts. By means of an isotopic labeling study with ^{14}C, Schmid and co-workers have shown that the 1,3 rearrangements also proceed with inversion of the migrating group.[18] Evidence for a cyclic transition state in the para Claisen rearrangement is afforded by (1) the observed first order kinetics (2) a negative entropy of activation[19] (3) the intramolecular nature of the rearrangement and (4) the observed inversion of the migrating allyl groups. Insofar as analogies to the Claisen rearrangement can be made, Miller has preferred to represent the transition state for the latter group of acid-catalyzed rearrangements as a π complex in which the migrating group bears a considerable amount of positive charge. He has suggested that the geometry of the complex might be almost cyclic in nature similar to the transition state for the Claisen rearrangement.



Miller has previously concluded that such a π complex is a probable intermediate in the p-quinamine rearrangement.[20] However, in the absence of any further experimental data, no definite conclusions can be drawn.

It is of interest to consider an alternative explanation for the observed results of the acid catalyzed rearrangement of dienone (X) not discussed by Miller. If the crotyl group inverts before migration, the product phenols (Xa) and (Xb) could be explained by a single mechanism rather than by two separate and competing mechanisms.



This possibility should be eliminated by recovery and characterization of the remaining p-dienone after partial rearrangement to the phenols.

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THE ISOLATION, CHARACTERIZATION, AND SYNTHESIS OF SOME INSECT SEX ATTRACTANTS

Reported by Fred Falkner March 28, 1966

Since World War II insect chemistry has received an increasing amount of attention from chemists, biochemists, physiologists, and pharmacologists. Of the many areas of interest within this field, that of insect pheromones has been among the most fascinating. Pheromones are those substances secreted by one individual to the outside which are capable of eliciting specific behavioral or developmental responses in another of the same species.[1] This seminar will be concerned with that class of pheromones known as sex attractants. Interest in these compounds has been stimulated by the fact that they offer the possibility of control of vast insect populations.[2] The specificity and extremely potent biological activity of the sex attractants are also quite intriguing.[3,4]

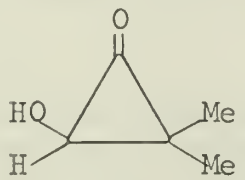
AMERICAN COCKROACH, Periplaneta americana

Of all the attractants this has provoked the most controversy and the most interesting chemistry. Initial structural assignments gave rise to a flurry of activity aimed at synthesis of the proposed structure in order to test its validity by actual biological assay.

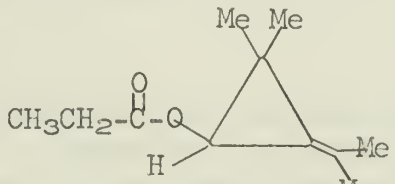
The first reported isolation of the attractant for this species was in 1962 by D. L. R. Wharton and coworkers.[5] Virgin females were kept on Whatman No. 1 paper. The aqueous extracts from this paper were made 0.1N in sodium hydroxide, acidified to pH 5, and then steam distilled. The attractant, found in the steam distillate, was then treated with lead nitrate, extracted with isopentane, and chromatographed first on alumina, then on Florisil. Vapor phase chromatography of the concentrated eluates gave an estimated 28 μg. of biologically active material with a retention time of 105 minutes. Micro-infrared analysis showed aliphatic character and an ester link.

In 1963 Jacobson[6] announced a new method of isolation for the attractant. A stream of air was wafted over a total of 10,000 virgin females, the vapors being collected in a dry ice-cooled flask containing 0.1% hydrochloric acid. Further purification by extraction with hexane, chromatography of the concentrated extracts on silicic acid, and steam distillation of the active fraction gave 12.2 mg. of a yellow liquid claimed to be the pure attractant. However, this material gave a retention time of 6 minutes rather than 105 minutes when submitted to gas chromatography under conditions identical to those of Wharton.

A single molecular formula determination gave $C_{11}H_{18}O_2$. No ultraviolet absorption was found. Infrared analysis showed an ester group and what was proposed to be an isopropylidene group by a band at 800 $cm.^{-1}$ The only reported n.m.r. absorptions were a multiplet at 7.66τ(1H) and a peak at 8.75τ(6H). A 2.2 mg. sample gave propionic acid and an unknown alcohol upon saponification. Oxidation of 4 mg. with periodate-permanganate reagent gave propionic acid, acetone, and a compound to which the structure I was assigned. Evidence cited for I included an infrared spectrum which showed hydroxyl proton absorption and carbonyl absorption as well as an ultraviolet absorption of the 2,4-dinitrophenylhydrazone derivative at 355 mμ. Further oxidation of I converted the compound to dimethylmalonic acid.

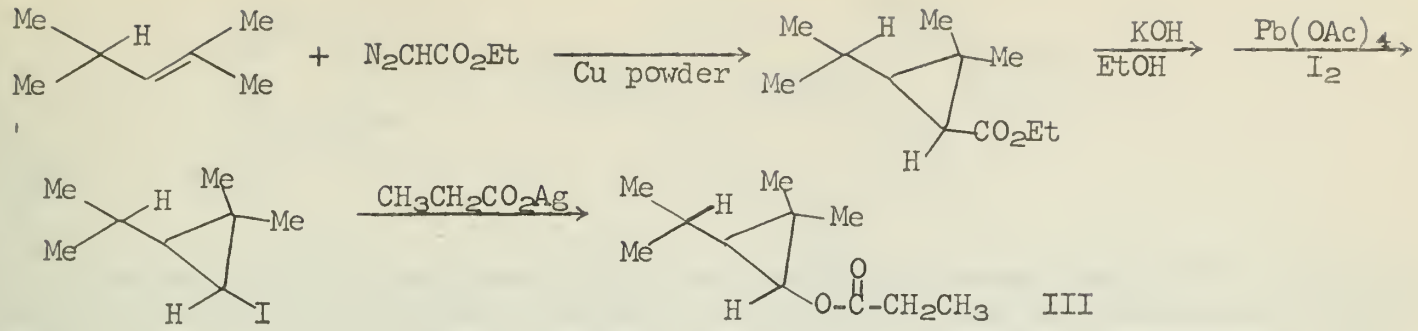


I



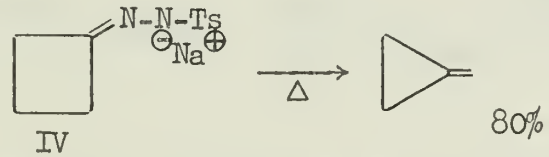
II

Compound II was proposed to be the attractant as it had properties consonant with all of the foregoing data. In an effort to confirm the proposed structure hydrogenated II was compared to an authentic sample prepared by an independent route.

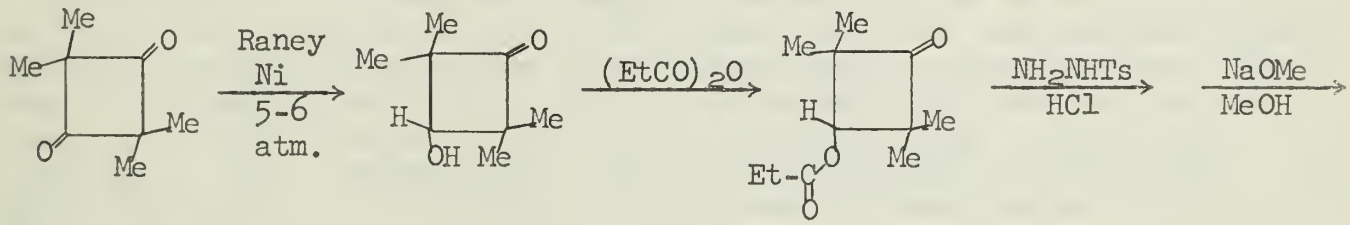


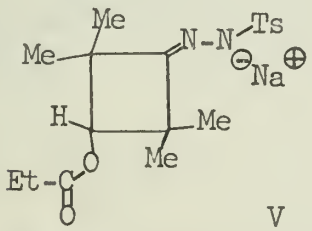
A number of objections were raised. The interpretation of the 800 cm.$^{-1}$ band in the infrared spectrum as due to an isopropylidene group was challenged.[7,8] The proton absorption at 7.66τ in the n.m.r. was found to be that of the methylene group in the propionate moiety rather than that of the hydrogen on the cyclopropyl ring alpha to oxygen as originally had been assigned.[9] The retention time of the isolated material differed drastically from that reported by Wharton although the gas chromatographic conditions were presumably identical. At that time no authentic reports of the isolation of cyclopropanones had been made. However, tetramethylcyclopropanone has recently been synthesized and has been found to be unstable in base.[10] Cyclopropanols have been found to be unstable in the presence of base, also.[11,12] Finally, the last step in the synthesis of compound III involves an almost unprecedented nucleophilic displacement on a cyclopropyl ring.

This matter was resolved by synthetic preparation of II and subsequent bioassay. Several workers attempted its synthesis. Meinwald[13] employed the Friedman-Schechter[14] application of the Bamford-Stevens reaction. Friedman and Schechter noted that heating of the sodium salt of cyclobutanone tosylhydrazone (IV) gave methylene cyclopropane as the major product.

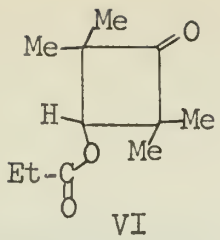


The following sequence of reactions was employed to obtain V which was then decomposed by photochemical or thermal techniques.

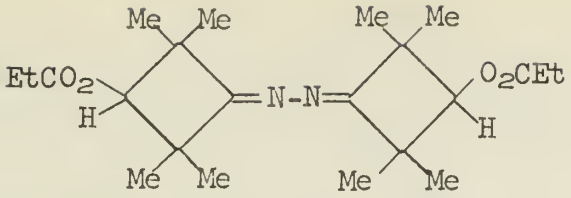




This treatment did not bring about the desired ring contraction but gave only a complex mixture of at least 11 components as determined by preparative gas chromatography. Of the three peaks collected two were mixtures which had few n.m.r. signals indicative of II, and the third proved to be 3-propionoxy-2,2,4,4-tetramethylcyclobutanone (VI). Column chromatography using silica gel, silicic acid, and alumina gave only one product which could be purified. It was identified as the bis[3-propionoxy-2,2,4,4-tetramethylcyclobutyl] azine (VII) on the basis of composition and spectral data.



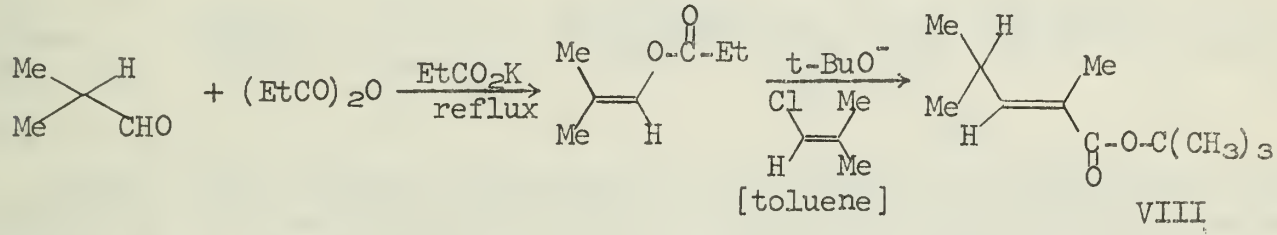
VI



VII

Another approach was taken, this time employing Tanabe's method[15] of preparing isopropylidene cyclopropanes. Scheme I was tried, but the only isolated compound proved to be a mixture of cis- and trans-t-butyl-2,4-dimethyl-2-pentenoate (VIII).

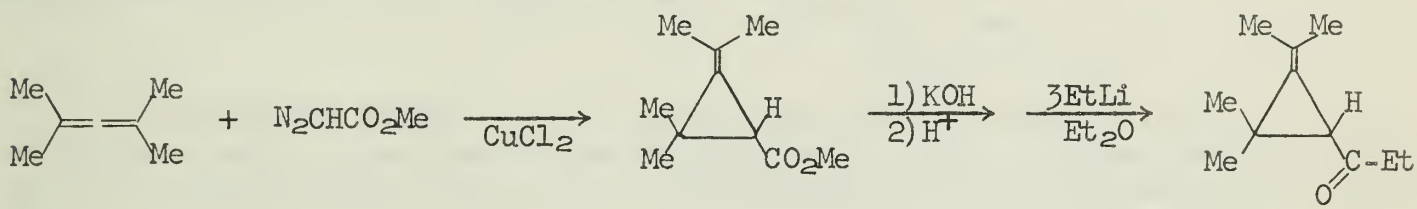
SCHEME I



[toluene]

VIII

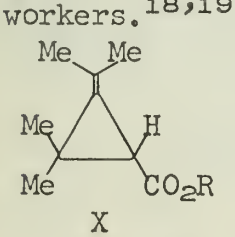
The third approach involved the observation that cyclopropanol esters could be formed by the Baeyer-Villiger oxidation of cyclopropyl ketones.[16] Although formation of an epoxide from the double bond might readily occur, it was thought that the double bond could be regenerated by Cornforth's procedure.[17] Reaction of methyl diazoacetate with tetramethylallene and subsequent treatment of the ester with ethyllithium gave the desired ketone IX.



IX

When IX was treated with trifluoroperacetic acid or m-chloroperbenzoic acid, a mixture of three components was obtained. Chromatography of the mixture after subjection to Cornforth's procedure gave no unsaturated esters.

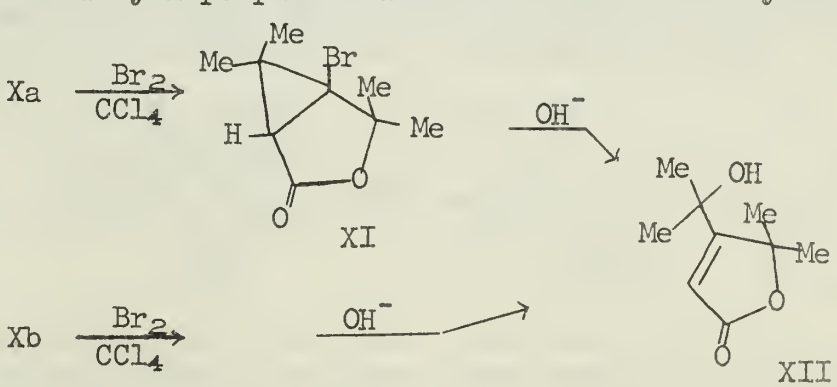
Since the double bond was thought to be the barrier to successful oxidation of the ketone, a method was sought to protect it. This led to a surprising result. Treatment of IX with bromine in carbon tetrachloride supposedly gave a labile product. The unsaturated acid Xa reacted with bromine but gave the lactone XI rather than the expected dibromo acid. Xb reacted with bromine, but hydrolysis of the ester led to XII. Meinwald also noted that XI gave XII upon hydrolysis. Nucleophilic ring opening of activated cyclopropanes has been demonstrated by several workers.[18,19]



X

a) R=H

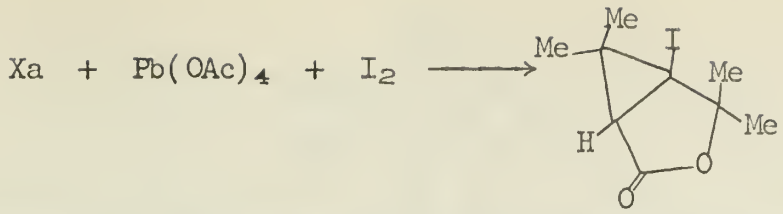
b) R=Et



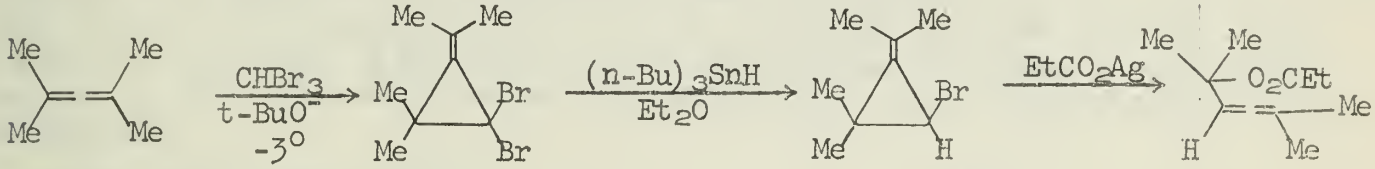
XI

XII

Since protection of the double bond did not appear to be promising, direct displacement of halogen on the cyclopropyl ring was tried. Treatment of the acid Xa with lead tetraacetate-iodine gave the iodo lactone rather than the expected iodocyclopropane.

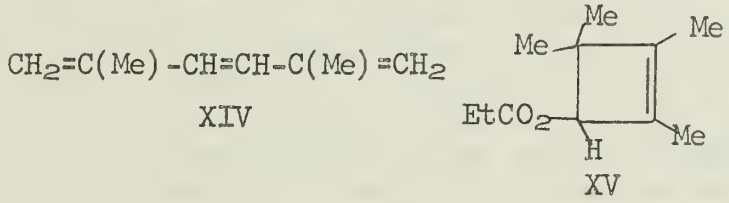


An alternate route to the preparation of the halocyclopropane was undertaken. By addition of dibromocarbene to tetramethylallene and reduction of the resulting dibromide with tri-n-butyltinhydride, XIII was obtained. However, displacement of bromine with propionate in a variety of solvents failed.



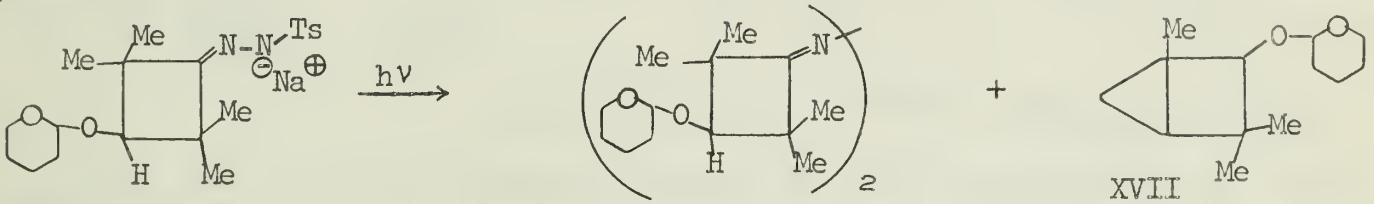
XIII

Singh[20] also attempted the synthesis of II using the cyclobutanone tosylhydrazone V. Heating the sodium salt of V in vacuum at 130-140° or in molten acetamide gave complex mixtures. The azine VII was isolated by chromatography on silicic acid while 2,5-dimethylhexatriene (XIV) and 4-propionoxy-1,2,3,3-tetramethylcyclobutene (XV) were isolated by gas chromatography.



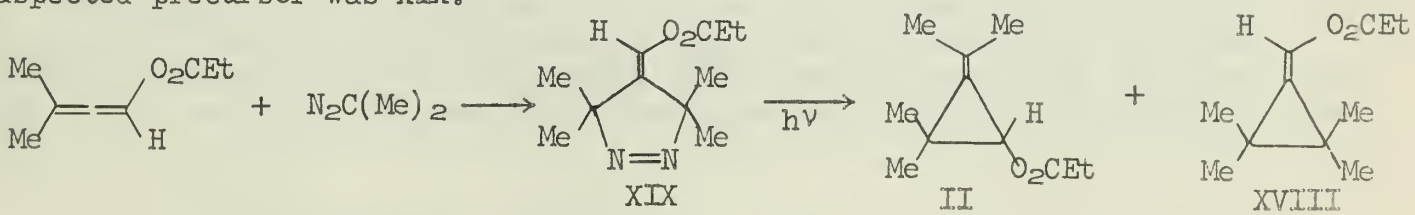
XIV XV

J. R. Chapman[21] modified the cyclobutanone tosylhydrazone by preparing the tetrahydropyranyl derivative XVI and photolyzing it. The only new product obtained was the tetrahydropyranyl ether of 1,3,3-trimethylbicyclo[2:1:0]pentan-2-ol (XVII) which was characterized by spectral data and conversion to 2,2,5-trimethylcyclopentanol.



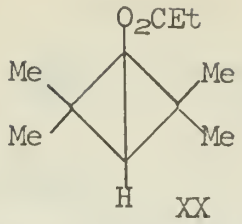
XVI XVII

The successful synthesis of II was accomplished by Day and Whiting.[22] 3-Methylbuta-1,2-dien-1-yl propionate[23] and 2-diazopropane gave a crystalline adduct. Photolysis of this adduct gave two isomers which were separated by gas chromatography and were identified as II and XVIII by n.m.r. and composition data. The suspected precursor was XIX.



XIX II XVIII

The synthetic ester was biologically inactive. There was no infrared absorption at 800 cm.$^{-1}$ Nuclear magnetic resonance peaks were noted at 5.96τ (1H) slightly coupled (J=1 cps) to a peak at 8.20τ (6H). Two methyl signals appeared at 8.82τ and at 8.93τ. The signals for the ethyl group were mentioned but were not specified. In view of the published n.m.r. data of Jacobson and coworkers, Day and Whiting proposed the bicyclobutane XX as a more likely structure.



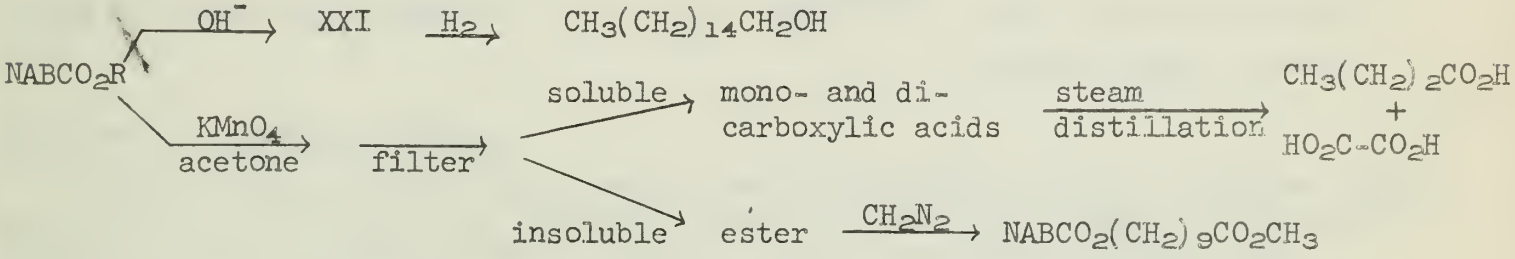
XX

However, Jacobson and Beroza[24] then eliminated XX by publishing more information concerning the n.m.r. spectrum. Their material showed a multiplet at 7.66τ(1H), a multiplet at 8.39τ(2H), a very large absorption at 8.75τ(12H), and a triplet at 9.14τ(3H). Decoupling experiments indicated that the triplet at 9.14τ was coupled to the peak at 8.75τ or to the multiplet at 8.39τ but not to the multiplet at 7.66τ. A mass spectrum of the material confirmed the molecular weight of 182. The structure of the attractant for this species remains to be determined.

SILKWORM MOTH, Bombyx mori

Butenandt[25] described the isolation and characterization of the sex attractant for this species in 1959 after 20 years of work. The odor glands of 500,000 female silkworm moths were extracted with ethanol-ether, and the raw extract was saponified. The alcoholic fraction recovered was converted to the 4'-nitroazobenzenecarboxylic acid (NAB) derivative. Column chromatography on Kieselguhr resulted in the recovery of 12 mg. of pure attractant ester. The alcohol (attractant) was active at 10^{-10} µg.

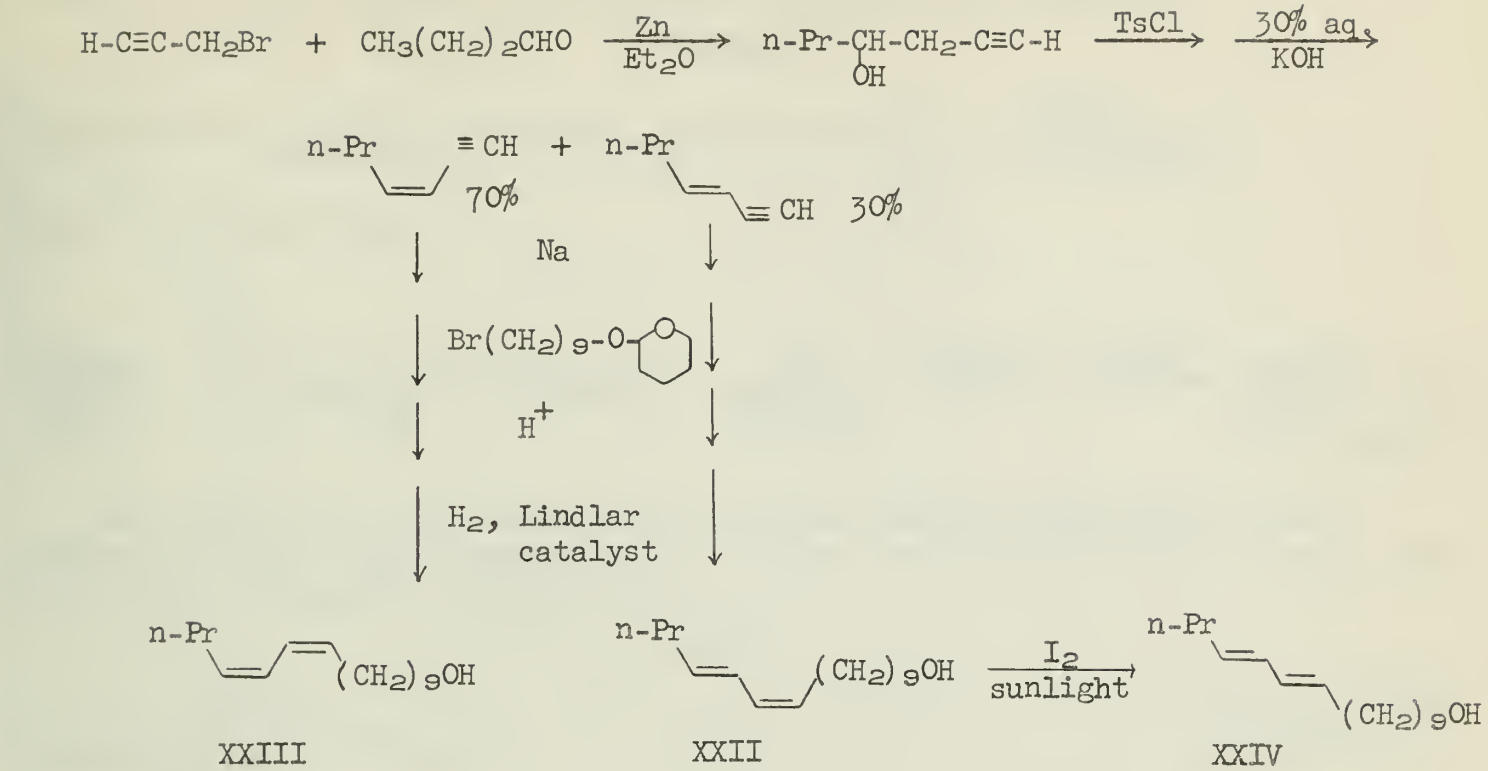
The attractant ester ($C_{29}H_{37}N_3O_4$) showed ultraviolet absorption at 331 mµ. (ε=32,700) and at 230 mµ. (ε=37,000). Infrared bands of the free alcohol were observed at 9.5-9.75µ (primary alcohol), 10.18 and 10.56µ (cis-trans diene), and 13.89µ (-CH_2-rocking). Hydrogenation of 2 mg. of the attractant gave palmitol. By a special micromethod a potassium permanganate oxidation with one milligram of the attractant ester was performed.[26]



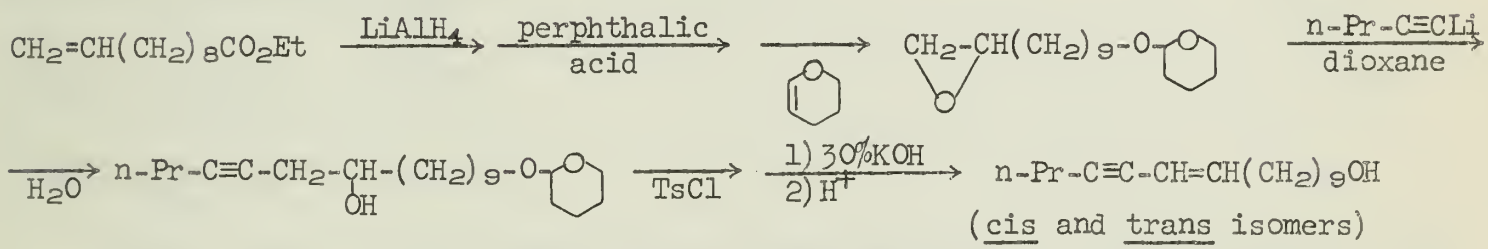
Thus, the structure of XXI was assigned as 10,12-hexadecadien-1-ol, but the geometry about the double bonds could not be deduced. Again, synthesis was employed to elucidate the geometry and confirm the actual structure of the attractant.[27] Scheme II was followed for the synthesis of the 10-cis, 12-trans isomer (XXII), the 10-cis, 12-cis isomer (XXIII), and the 10-trans, 12-trans isomer (XIV). Scheme III was employed to synthesize the 10-trans, 12-cis isomer which proved to be the attractant XXI.

The trans isomer of 10-hexadecen-12-yne-1-ol (Scheme III) was distilled from the reaction mixture and freed from the cis isomer by insertion into urea. Infrared confirmed that only the trans isomer was present in the purified solid. This isomer was then hydrogenated in the presence of Lindlar catalyst[28] to give XXI.

SCHEME II



SCHEME III

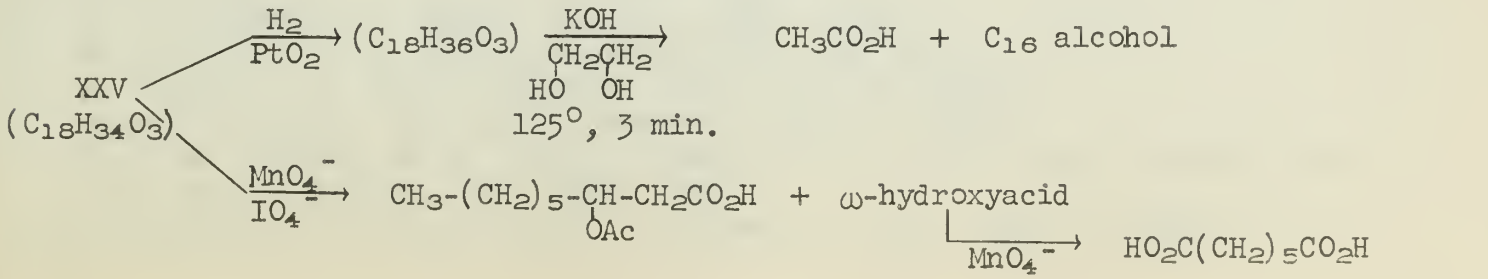


GYPSY MOTH, Porthetria dispar

The sex attractant for this species was concentrated in 1944 by Haller, Acree, and Potts[29] by extracting the abdominal tips of 12,000 female moths with benzene, saponifying the isolated material with two percent potassium hydroxide, and chromatographing the neutral fraction on alumina. However, isolation of the pure attractant eluded them.

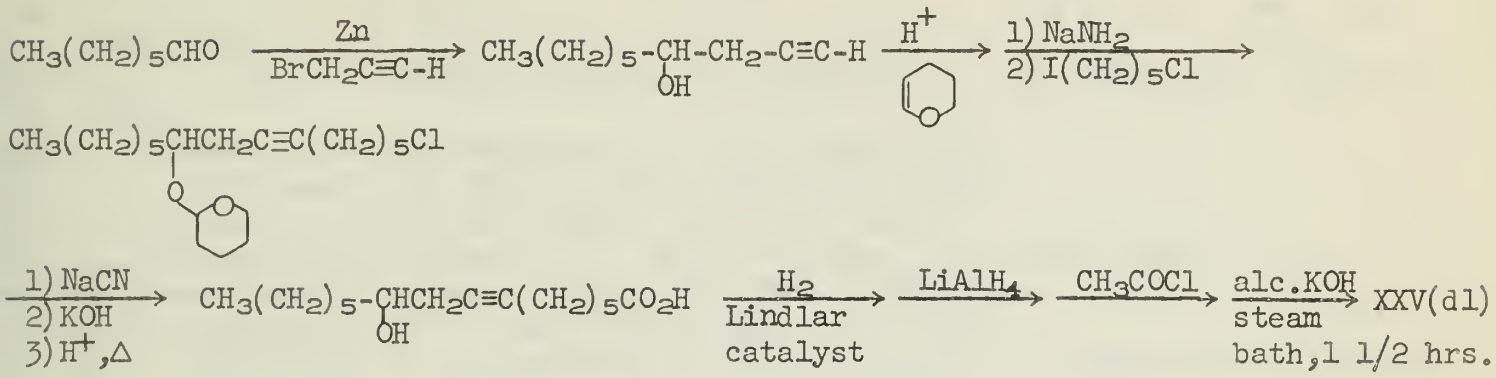
In 1961 Jacobson, Beroza, and Jones[30] chromatographed the saponifiable fraction of benzene extracts from 500,000 female moths on magnesium carbonate and magnesium oxide. A yellow oil highly attractive to male moths was obtained. Ascending chromatography on polyethylene-impregnated filter paper gave 3.4 mg. of white waxy crystals and 20 mg. of a colorless liquid. The liquid was attractive in field tests in quantities of 10^{-7} µg.

The liquid showed no ultraviolet absorption and was optically active ($[\alpha]_D^{25}$ = +7.9°). Infrared analysis showed hydroxyl absorption at 3580 cm.$^{-1}$ and 3450 cm.$^{-1}$, carbonyl absorption at 1740 cm.$^{-1}$, and cis double bond absorption at 1660 cm.$^{-1}$ and 783 cm.$^{-1}$. Hydrogen equivalent to one double bond was taken up upon microhydrogenation.



XXV was thus assigned the structure (+)-10-acetoxy-cis-7-hexadecen-1-ol, and synthesis of the dl mixture was performed as described in Scheme IV.

SCHEME IV

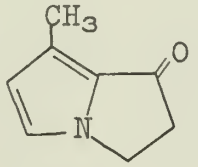


To confirm the structure and also to probe into the specificity of the attractant, these workers synthesized the related derivatives listed in Table I and tested their biological activity.[31,32]

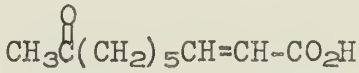
TABLE I

Compound	Level of Activity
$CH_3(CH_2)_5CHCH_2CH{=}CH(CH_2)_8OH$ (OAc, c)	$10^{-5}\mu g$
$CH_3(CH_2)_5CHCH_2CH{=}CH(CH_2)_8OH$ (OAc, t)	$10^{-4}\mu g$
$CH_3(CH_2)_5CHCH_2CH{=}CH(CH_2)_8OH$ (O-t-Bu, c)	no activity
$CH_3(CH_2)_5CHCH_2CH{=}CH(CH_2)_{10}OH$ (OAc, c)	10μg

At this time the attractants for the gypsy moth and the silkworm moth are the only two which have been characterized. Meinwald[33] isolated and characterized what he thought to be the sex attractant for the butterfly Lycorea ceres ceres. However, synthetic XXVI proved to be inactive. The queen substance (XXVII) of the honeybee Apis mellifera was thought to be the attractant for this species, but this is now in doubt as its activity is in the milligram range rather than in the microgram range. Work has been initiated to isolate the attractants from a number of insects including the cotton leafworm (Prodenia litura), the pine sawfly (Diprion similis), and the common housefly (Musca domestica). The next few years may reveal the structure of these compounds.



XXVI



XXVII

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THE CAGE EFFECT IN THE DECOMPOSITION OF AZO COMPOUNDS

Reported by Douglas T. Browne March 31, 1966

INTRODUCTION

Two radicals or free atoms formed simultaneously and at the same place in solution will remain together for a short period of time. Diffusion apart is slower than in the gas phase because of the "cage" of solvent molecules around the pair. This "cage effect" greatly increases the probability that the original partners will react with each other.[1] This seminar will deal with evidence concerning the importance of cage reactions in the thermal and photochemical decomposition of selected azo compounds.

GENERAL CONSIDERATIONS

In discussing cage effects, it is necessary to distinguish between collisions and encounters.[2] An encounter between two species in the gas phase at moderate pressure usually involves only one or two collisions.[2b] Liquid phase encounters, however, result in multiple collisions between two species constrained by the solvent "cage". The number of collisions per encounter in solution is estimated to be of the order of 10 to 10^2.[2a] At sufficiently high pressures, gas phase cage effects may also be observed.[3]

Noyes,[4] in theoretical treatments of cage effects, showed that two particles generated in a solvent cage may undergo three types of reactions. The original partners can react before diffusing apart (primary recombination), or can recombine after they have separated by several molecular diameters (secondary cage recombination). The importance of secondary recombination is uncertain at the present time.[5] Therefore, it is common to refer to any reaction of the original partners (geminate recombination) as a cage reaction without distinguishing between primary and secondary processes. The third possibility is that a radical which has diffused away from its original partner will react with a radical formed during a different event. Noyes refers to such encounters as "third degree" reactions.

The various theoretical treatments of cage effects have been reviewed recently.[6] Since most of the experimental data on cage reactions are not directly concerned with their verification, these treatments will not be discussed in detail.

AZOMETHANE

The photodecomposition of azomethane proceeds primarily according to the equation:[7,8]

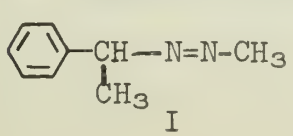
$$CH_3N{=}NCH_3 + h\nu \longrightarrow N_2 + 2CH_3\cdot \qquad (1)$$

It is possible that this process should be represented as two steps:

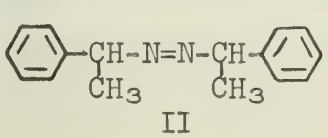
$$CH_3N_2CH_3 + h\nu \longrightarrow CH_3N_2\cdot + CH_3\cdot \qquad (2)$$

$$CH_3N_2\cdot \longrightarrow CH_3\cdot + N_2 \qquad (3)$$

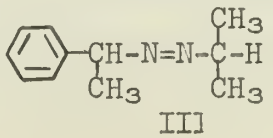
However, the fact that the quantum yield for nitrogen is unity between 25° and 200° for gas phase photolysis indicates that the $CH_3N_2\cdot$ radical, if formed, decomposes too rapidly to allow it to react with another species.[8] No evidence for the existence of $CH_3N_2\cdot$ in azomethane photolysis could be obtained under conditions (-196°) identical to those in which an e.s.r. signal attributed to $(CH_3)_2C(CN)N_2\cdot$ was produced by irradiation of azobisisobutyronitrile (VIII).[9] The only reaction in which the probable intermediacy of the methylazo radical has been shown is the thermal decomposition of α-phenylethylazomethane (I). A study of secondary deuterium and C^{13} isotope effects indicates that the decomposition occurs in two steps: first the homolysis of a C-N bond to produce an α-phenylethyl and a methylazo radical followed



I



II



III

by decomposition of $CH_3N_2\cdot$ into $CH_3\cdot$ and nitrogen.[10] Azobis-α-phenylethane (II) decomposition however involves equal degrees of stretching of both bonds in the transition state. In decomposition of α-phenylethylazo-2-propane (III) both C-N bonds are stretched in the transition state but to unequal degrees. It is suggested that the decomposition of azo compounds requires two steps when the two radicals produced have quite different stabilities.

Ethane is a major product of azomethane decomposition. In principle, it could arise from at least five reaction sequences:

$$[2CH_3\cdot]\ \text{cage} \longrightarrow C_2H_6 \qquad (4)$$

$$2CH_3\cdot \longrightarrow C_2H_6 \qquad (5)$$

$$CH_3N_2CH_3 \longrightarrow C_2H_6 + N_2 \qquad (6)$$

$$CH_3\cdot + CH_3N_2CH_3 \longrightarrow C_2H_6 + N_2 + CH_3\cdot \qquad (7)$$

$$CH_3\cdot + (CH_3)_2NNCH_3 \longrightarrow C_2H_6 + CH_3N{=}N\text{-}CH_3 \text{ or } (CH_3)_2N_2 \qquad (8)$$

Equation 4 refers to geminate recombination of methyl radicals; equation 5 to recombination outside the cage. Alternate possibilities are formation of ethane by molecular elimination (eq. 6), by induced decomposition (eq. 7), or by reactions involving $(CH_3)_2NNCH_3$ (eq. 8).

The possibility of induced decomposition may be ruled out by the temperature and concentration independent nitrogen quantum yield of unity in the gas phase[11] and by the absence of CH_3CD_3 in the products from the photolysis of a mixture of $CH_3N_2CH_3$ and $CD_3N_2CD_3$ in isooctane solution.[12] These results also make eq. 8 an unlikely possibility.

Formation of ethane by molecular elimination from azomethane (eq. 6) has been demonstrated in gas phase photolysis.[8] In the absence of radical scavengers the quantum yield of ethane is close to unity for azomethane pressures ranging from 57-275 mm. If an equimolar mixture of $CH_3N_2CH_3$ and $CD_3N_2CD_3$ is photolyzed under these conditions, ethane is formed in such proportions that $(CH_3CD_3)^2/(C_2H_6)(C_2D_6)$ is four within experimental error, suggesting that ethane is formed by random recombination of methyl radicals.[12] For gas phase photolysis in the presence of oxygen[8] or 1,4-cyclohexadiene,[7] however, the quantum yield of ethane drops to about 0.01. In the decomposition of $CH_3N_2CH_3$ and $CD_3N_2CD_3$ mixtures under these conditions, equal amounts of C_2H_6 and C_2D_6 are produced, but the ethane does not contain any detectable amount of CH_3CD_3. Thus, the ethane formed in the presence of scavenger cannot arise from recombination of "free" methyl radicals (eq. 5).[8]

A choice between a gas phase cage effect (eq. 4) and a molecular elimination (eq. 6) as the major source of the ethane formed from azomethane photolysis in the presence of scavengers is possible because of the pressure dependence of the ethane quantum yield. For 3660 A^o light, the ethane quantum yields at 66.5, 127.7 and 247.5 mm total pressure are $0.37\ 10^{-2}$, $0.66\ 10^{-2}$, and $0.69\ 10^{-2}$, respectively.[8] Thus, the pressure dependance appears to approach a high pressure limit. In contrast, the gas phase cage effect observed at higher pressures[3] appears to have no upper limit.

It is clear, therefore, that a molecular elimination mechanism can account for only about 1% of the ethane produced in the gas phase photolysis of azomethane. This leaves cage reactions (eq. 4) and "third degree" reactions (eq. 5) as the main sources of ethane. The use of radical scavengers allows a distinction between these possibilities. A suitable scavenger (S) is one sufficiently reactive toward free radicals so that the rate of scavenging (eq. 9) exceeds the rate of termination (eq. 10) by about a factor of one hundred.[2b] Since the concentration of free methyl

$$CH_3\cdot + S \xrightarrow{k_s} CH_3S \qquad (9)$$

$$CH_3\cdot + CH_3\cdot \xrightarrow{k_t} C_2H_6 \qquad (10)$$

$$\frac{\text{Rate of scavenging}}{\text{Rate of } 3^o \text{ reaction}} = \frac{k_s\,(S)}{k_t\,(CH_3\cdot)} \qquad (11)$$

radicals is usually quite low, k_t can be substantially smaller than k_s without loss of scavenging efficiency if S is present in moderate concentration. If the scavenger is present in very low concentration, however, the extent to which the scavenger interferes with "tertiary" reaction will be proportional to its concentration. As

concentration is increased, the efficiency of interference reaches a limiting value at which all tertiary reaction is suppressed. This constant scavenging value over a range of scavenger concentrations is often cited as evidence that the desired type of scavenging (i.e. total suppression of tertiary reactions with no effect on geminate recombination) has been achieved. A very reactive scavenger may also be able to compete with secondary recombination. It has been shown that, to a first approximation, this increased scavenging efficiency should vary with the square root of the scavenger concentration.[4,6]

As stated above, the gas phase photolysis of azomethane at low pressures in the presence of oxygen or 1,4-cyclohexadiene results in dramatic reduction of the ethane quantum yield as compared to the quantum yield for photolysis in the absence of scavenger. The quantum yield of nitrogen, however, is unaffected. This suggests that virtually all the ethane is formed by a "tertiary" process rather than by geminate recombination. This outcome is expected, since molecules in the gas phase are not likely to form a "cage" around a pair of radicals generated at low pressure. At sufficiently high pressure, however, a gas phase cage effect might be expected. Lyon[3] demonstrated the existence of a cage effect in the photodecomposition of azomethane in high density (0.087 to 0.260 g./cc. at 98°) propane gas. It was found that the ratio C_2H_6/CH_4 increased with increasing pressure from 0.063 to 0.10 in the density range studied. Such an increase is expected if ethane is formed by geminate recombination. However, if ethane formation were in competition with methane formation by abstraction from propane, the ratio would decrease. Addition of 1% nitric oxide as scavenger resulted in an increase of C_2H_6/CH_4 by a factor of three but little change in the ratio C_2H_6/N_2. These results strongly suggest that not all ethane and methane is formed from "free" $\cdot CH_3$. Since the formation of ethane by molecular elimination appears to reach a high pressure limit at densities much lower than those employed here, ethane is probably largely a "cage product". Assuming that all ethane is so formed, the cage effect, $100\ [2C_2H_6/(CH_4 + 2C_2H_6)]$, is 17%.

Rebbert and Ausloos[8] have recently studied the photolysis of azomethane in the liquid phase. The quantum yield of nitrogen is less than 0.1 for a variety of temperatures and solvents. This reduction in quantum yield as compared to the gas phase can be explained either by the cage recombination step:

$$[CH_3N_2\cdot + CH_3\cdot]\ \text{cage} \longrightarrow CH_3N_2CH_3 \qquad (12)$$

or by the deactivation step:

$$CH_3N_2CH_3^{*} + CH_3N_2CH_3 \text{ or solvent} \longrightarrow 2CH_3N_2CH_3 \text{ or } CH_3N_2CH_3 + \text{solvent} \qquad (13)$$

As stated previously, present evidence indicates that the methylazo radical is unstable in the gas phase. However, the lifetime of this species may be sufficiently long to allow it to undergo cage recombination in the liquid phase.

Ethane produced by the photolysis of mixtures of $CH_3N_2CH_3$ and $CD_3N_2CD_3$ in the liquid phase consists mainly of C_2H_6 and C_2D_6. In isooctane solution, for example, the amount of CH_3CD_3 formed was less than 0.3% of the total ethane formed.[12] This indicates that ethane is formed either by a molecular elimination and/or by geminate recombination but not by a "third degree" reaction. It is difficult to assess the relative importance of the two effects in the liquid phase. However, for photolysis of mixtures of liquid $CH_3N_2CH_3$ and $CD_3N_2CD_3$, $C_2H_6/C_2D_6 \simeq (CH_4 + CH_3D)/(CD_3H + CD_4)$.[8] This is an indication that ethane and methane are both formed by radical processes since it would be fortuitous that the ratios of quantum yields of the elimination and dissociative processes are the same for $CH_3N_2CH_3$ as for $CD_3N_2CD_3$. Therefore, it is likely that ethane is formed by a process involving dissociation.

It is exceedingly difficult or impossible to rule out unequivocally a molecular elimination as a source of cage products. It is possible to obtain an estimate of the importance of the extrusion mechanism only in the gas phase where cage effects are negligible and the only reactions that need be considered are "third degree" and elimination reactions. However, there is no guarantee that molecular elimination reactions are not more important in the liquid phase than in the gas phase. The most convincing argument against invoking elimination as the explanation of "cage"

products formed in the liquid phase is that entirely too many coincidences of the sort explained in the preceding paragraph would have to be invoked.[13]

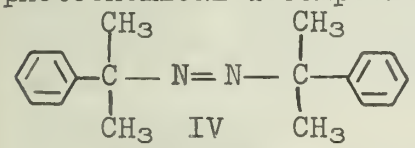
The photolysis of azomethane in the solid phase[8,14] results in an increase in the yield of ethane as compared to that obtained for liquid phase photolysis. This is consistent with a "cage" mechanism for ethane formation. However, it is possible that some of the products come from radicals "trapped" in the matrix which react on subsequent warming. Also, the amount of CH_3CD_3 formed increases from less than 1% at 77° K to about 8% at 4° K. for photolysis of a mixture of solid $CH_3N_2CH_3$ and $CD_3N_2CD_3$.[8] This effect is not predicted by cage effect theory. It may be attributable to secondary photolysis of methylazo radicals to produce "hot" methyl radicals,[8]

$$CH_3N_2\cdot + h\nu \longrightarrow CH_3\cdot^{*} + N_2$$

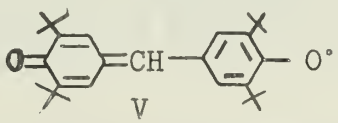
but this explanation has not been experimentally verified. A quantitative evaluation of the solid phase cage effects must be deferred until the several uncertainties and anomalies involved are eliminated or explained.

AZOCUMENE

Nelsen and Bartlett[15] have recently studied cage effects in the thermal and photochemical decomposition of azocumene (IV):



IV



V

In order to determine that the scavenging techniques employed were accounting for all radicals that escape from the cage and no others they demonstrated that the same cage effect is found over a range of scavenger concentrations and with different scavengers. For example, the cage effect in the thermal decomposition of azocumene in toluene at 40° was found to be 27.0-28.4% with di-t-butylnitroxide as scavenger, 26.3% with galvinoxyl (V), and, in benzene with 3M thiophenol, 26.4-27.4%. Thiophenol scavenges free radicals by donating a hydrogen to cumyl radicals to give cumene and relatively unreactive thiyl radicals which ultimately dimerize. Cumyl radicals and di-t-butylnitroxide probably disproportionate to form α-methylstyrene and di-t-butylhydroxylamine. The free radical galvinoxyl couples with a cumyl radical.

Di-t-butylnitroxide was used as the scavenger for most of this study. The extent of the cage reaction was determined by spectral analysis of scavenger absorption, employing the "excess scavenger" technique. If E is the efficiency of radical production, I_o and I_∞ are the initial and final initiator ($I_\infty = 0$) concentrations, and S_o and S_∞ are the corresponding scavenger concentrations then

$$2E\,[(I)_o - (I)_\infty] = [(S)_o - (S)_\infty] \qquad (14)$$

$$E = \frac{[(S)_o - (S)_\infty]}{2(I)_o} \qquad (15)$$

$$\%\ \text{cage effect} = 100\,(1-E) \qquad (16)$$

A major disadvantage of this technique is that the scavenger must be stable under the conditions required for virtually complete decomposition of the initiator. Galvinoxyl, perhaps the most generally satisfactory radical scavenger, does not meet this requirement.

The cage effect was studied as a function of temperature and solvent. If k_{diff} is the rate constant for diffusion out of the cage and k_c is the rate constant for the competing cage reactions, $k_{diff}/k_c = E/1 - E$. A plot of log k_{diff}/k_c vs. 1/T gives a straight line with slope corresponding to $E_{obsd.} = E_{diff} - E_c = 1.3$ k.cal. E_{diff} is estimated by diffusion theory to be 2.6 k.cal., giving a value of 1.3 k.cal. for E_c, the activation energy for both disproportionation and recombination of cumyl radicals.

E_{diff} was estimated under the assumption that viscosity is the dominant factor in the temperature coefficient of the cage effect. This seems to be the case in comparing results obtained in the same solvent. If the kinematic viscosity of the solvent is the only important factor determining the cage effect, then a plot of k_{diff}/k_c vs. the kinematic viscosity for a series of different solvents at the same temperature should yield a straight line. The experimental plot shows very serious scatter, indicating the importance of solvation effects on radical behavior.

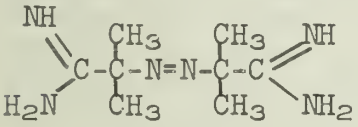
Cage effects in the photodecomposition of azocumene were 6-7% higher than in its thermal decomposition, di-t-butylnitroxide being employed as a scavenger in both cases. This may be attributable to rotation about the N=N bond in the excited state. Decomposition of the electronically excited azocumene from the cisoid rotamer would lead to cumyl radicals closer together than those resulting from decomposition of the transoid form. Radicals generated in close proximity would be expected to undergo geminate recombination more readily than those generated further apart.

It might be imagined that differences in the efficiency of radical production could result from different relative spin orientations in a newly former radical pair, provided that the radicals were close enough to permit orbital overlap. If spin inversion were slower than diffusion rates, a smaller cage effect would result from decomposition from an excited triplet state than from thermal decomposition or decomposition from an excited singlet state. The photosensitized decomposition of azocumene was studied in order to investigate this possibility.

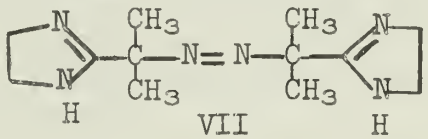
Toluene solutions containing azocumene and triphenylene or pyrene as sensitizer were irradiated with 313 mu light. For the concentrations employed, 99.6-99.97% of the 313 mu light was absorbed by the sensitizer. There is essentially no difference in cage effect between the photosensitized and direct photolysis runs. The most likely explanation of this data is that spin relaxation in solution is virtually complete before the radicals are able to diffuse apart.

AZOBISAMIDINES

The effects of interaction potentials between two "caged" radicals are difficult to account for theoretically. Thus, an experimental measure of the importance of such effects is desirable. Hammond and Neuman[16] obtained such a measure by investigating the thermal decomposition of azobisisobutyramidine (VI) and azobis-N,N'-dimethyleneisobutyramidine (VII) and their second conjugate acids. Decompositions were carried

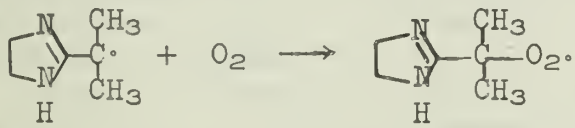


VI



VII

out in dimethyl sulfoxide for reasons of solubility. Scavenging was accomplished with an oxidation inhibitor, 2,6-di-t-butyl-p-cresol, which is known to stop two oxidation chains per molecule. In the oxidation inhibition method, the immediate scavenger of initiator fragments is oxygen (eq. 17). In the presence of antioxidants, the peroxy radicals thus formed are converted to unreactive products (eq. 18):



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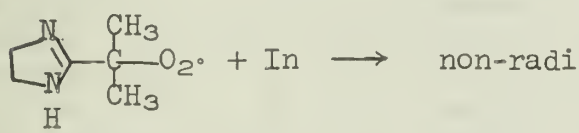


(18)

The decomposition is carried out in the presence of cumene or tetralin, which are subject to autoxidation initiated by free radicals. Inhibition periods were determined from a plot of absorbed oxygen volume *versus* time. A sharp increase in the rate of oxygen uptake occurs when the oxidation inhibitor is exhausted.

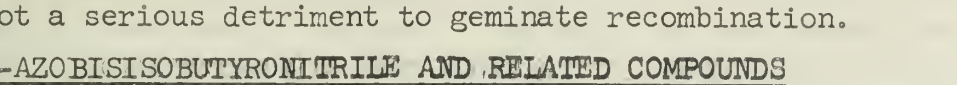
In the case of the neutral amidine (VII) the oxidation inhibition method gave unsatisfactory results, and the rate of methyl methacrylate polymerization was used to determine efficiency of radical production.

The efficiency of radical production from both azoamidines was about 0.4 and from their second conjugate acids about 0.6. The difference is real but not striking. It may be attributable to reduction of coupling rate because of electrostatic repulsion between the radicals. In DMSO, enough of the positive charges, formally carried by the radicals, might be dispersed in the solvent to allow coupling at a fairly high rate. However, the cation radicals generated in decomposition of the second conjugate acids appear to be more stable than their neutral analogous. This factor could also

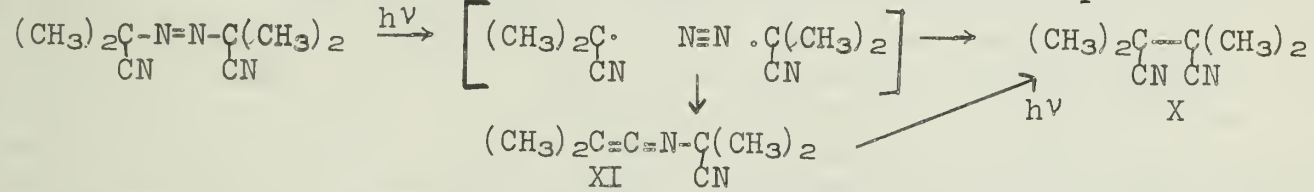
account for the reduction in geminate recombination. It would clearly be desirable to carry out the decompositions in a less polar solvent than DMSO in order to eliminate reduction of charge density on the radicals by the solvent, but solubility problems have prevented this. It may be concluded, however, that electrostatic repulsion is not a serious detriment to geminate recombination.

α,α'-AZOBISISOBUTYRONITRILE AND RELATED COMPOUNDS

The decompositions of α,α'-azobisisobutyronitrile (AIBN, VIII), ethyl 2,2'-azobisisobutyrate (IX) and several related compounds have been extensively studied.



The photolysis of VIII follows simple first order kinetics.[17] The rate is approximately the same for a variety of solvents, and there is no evidence for induced chain processes. The final products of photolysis are tetramethylsuccinonitrile (X) and small amounts of materials such as isobutyronitrile resulting from disproportionation of 2-cyano-2-propyl radicals. About 60% of the succinonitrile is produced *via* the intermediate dimethyl-N-(2-cyano-2-propyl)-ketenimine (XI). Decomposition of the ketenimine occurs at virtually the same rate as that of AIBN and also follows simple first order kinetics.



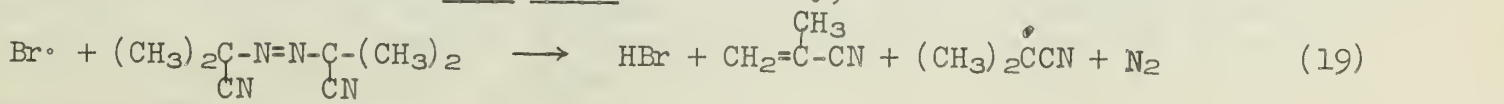
The thermal and photochemical decompositions of AIBN appear to be similar mechanistically.[17]

Early scavenging studies[18] indicated that the efficiency of free radical production from the thermal decomposition of the azonitrile is about 0.45 in CCl_4, 0.6 in benzene and chlorobenzene, and about 0.75 in nitrobenzene and nitromethane. In each solvent, the values calculated using iodine scavenger were identical with those obtained by the oxidation inhibition method, strongly suggesting that the two methods are interfering with only "third order" recombination.

Hammond and coworkers[13,19] compared the efficiency of radical production in the thermal decomposition of AIBN and the corresponding ketenimine in carbon tetrachloride at 62.5°. Efficiencies obtained by the oxidation inhibition and iodine scavenger methods were 0.35 for the ketenimine and 0.46 for the azonitrile.[13] The most likely reason for this difference is hindrance of recombination of the cyanoisopropyl radicals in AIBN decomposition by the molecule of nitrogen formed between them. However, other explanations, such as a difference in the importance of direct elimination for the two cases, are possible.

Trapp and Hammond[20] sought to discount the importance of a molecular elimination mechanism in the thermal decomposition of AIBN by decomposing the compound in liquid bromine. None of the cage product, tetramethylsuccinonitrile, is formed under these conditions. Decomposition in this medium is no more than a factor of two faster than in other media. It was determined that tetramethylsuccinonitrile is stable under the reaction conditions. However, the actual reaction products were not determined.

The dinitrile is therefore produced only from precursors which are "scavenged" by bromine. A possible interpretation is that cyanopropyl radicals are produced in a bromine cage and react with the bromine before they can undergo geminate recombination. However, there are several other possible rationales for the absence of cage product which do not rule out the occurrence of molecular elimination in other solvents. Liquid bromine may have "special" solvent properties which interfere with non-radical pathways. There may be direct reactions between bromine and the azo compound, although this is not the case for decomposition of azo-1-cyanocyclohexane in chlorobenzene containing 0.819M bromine (*vide infra*).[5] Finally, induced reactions such as



may occur.[20]

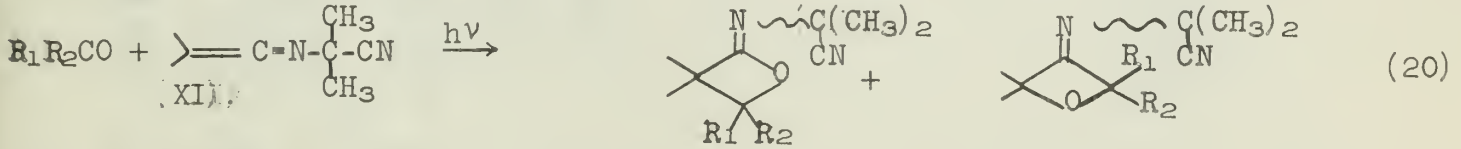
Fox and Hammond[21] have investigated the photosensitized decompositions of azo-1-cyanocyclohexane and the corresponding ketenimine, N-(1-cyanocyclohexyl)pentamethyleneketenimine. In these cases, as in the photosensitized decomposition of azocumene, the radical pair should be produced with parallel electron spins if the radicals are generated close enough together. Conventional scavengers such as iodine and α,α'-diphenyl-β-picrylhydrazyl were found to be unsuitable for use in sensitized reactions. Therefore, cumene was used as both solvent and scavenger. Since the yield of 1,1'-dicyanobicyclohexyl from photolysis of azo-1-cyanocyclohexane in cumene is the same (about 19%) in both the presence and absence of 10^{-3} M n-butyl mercaptan, it was concluded that cumene is a completely effective scavenger of free cyanocyclohexyl radicals.

As stated previously, study of the photolysis of azonitriles is complicated by the formation of ketenimines. In this study, it was necessary to measure the yield of 1,1'-dicyanobicyclohexyl resulting only from decomposition of the azo compound rather than the ketenimine. It was found that for irradiations carried out in the presence of dilute hydrochloric acid, the ketenimine was not a source of 1,1'-dicyanobicyclohexyl due to its rapid hydrolysis. Addition of acid does not destroy any components other than the ketenimine.

Irradiation of cumene solutions containing azo-1-cyanocyclohexane, water, hydrochloric acid, and triphenylene as sensitizer at 28° with 3130 A° light resulted in a 17.7% yield of 1,1'-dicyanobicyclohexyl. The corresponding yield for direct photolysis in cumene at 28° is 19.9%. It was determined that the sensitizer does not constitute part of any reaction product and is therefore presumably acting only as an agent for energy transfer. The fact that the yields of the cage product are virtually identical in direct and sensitized photolysis suggests either that both decompositions occur from the same excited state or that spin inversion is faster than the rate determining step for formation of 1,1'-dicyanobicyclohexyl. Since thermolysis and photolysis of IX are similar[22] (see below) and the quantum yield of radical production from IX is not affected by a known triplet quencher,[21,22] the latter explanation is probably correct.

The direct and sensitized photolysis of N-(1-cyanocyclohexyl)pentamethyleneketenimine were also carried out in cumene solutions at 28°. In this case, the yield of 1,1'-dicyanobicyclohexyl from direct photolysis was 24.1% and that from sensitized photolysis 8.3%. The sensitizer was apparently unchanged in the latter reaction. These results suggest that in this system the rate at which radical pairs diffuse apart is comparable to the rate of spin inversion which must precede coupling. This is the opposite conclusion to that drawn for the decomposition of azo-1-cyanocyclohexane and azocumene. Hammond suggests that separation of the two radicals by the inert nitrogen molecule results in a very weak interaction between the radicals, and, consequently, a rapid rate of spin inversion compared to cases in which the interaction is stronger. He refers to radicals resulting from ketenimine photolysis as "tight" radical pairs (R.↑↑.R) and those from the azo compound as "loose" pairs (R.↑N_2↑.R).

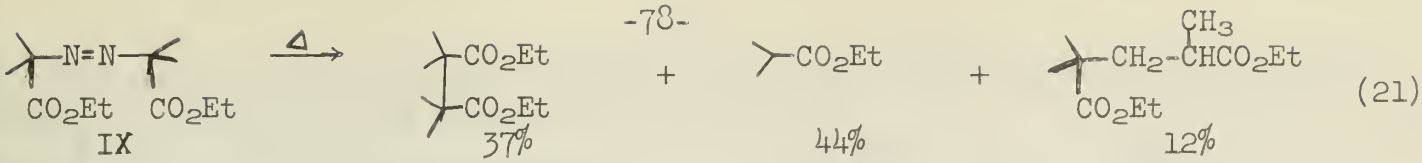
Bartlett,[23] however, has cited unpublished experimental results which indicate that photosensitized photolysis is more complex than Hammond had assumed and that the apparent decrease in cage effect may not be real. In published work,[24] Singer and Bartlett have reported the photocycloaddition of aromatic aldehydes and ketones to dimethyl-N-(2-cyano-2-propyl)ketenimine (XI). Therefore, some of the ketenimine may be taking



(20)

part in reactions other than "simple" photolysis to two cyanocyclohexyl radicals.

A comparison of the cage effects in the thermolysis and photolysis of an azo compound is of interest because it might be assumed that the fragments from photolysis would have excess energy that could favor diffusion at the expense of geminate recombination. Such a comparison was carried out for the decomposition of ethyl 2,2'-azobisisobutyrate (IX).[22] Thermal decomposition of the azo ester in chlorobenzene solution proceeds as follows:



(21)

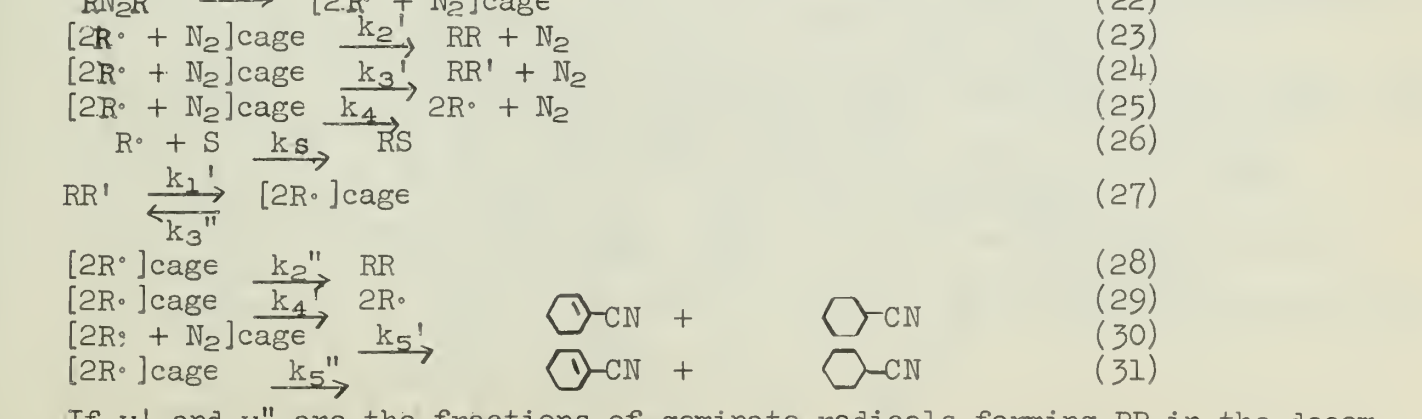
This compound was chosen for study in preference to an azonitrile because of the complication of ketenimine formation in the latter case.

The efficiency of radical production (a) from IX at 70° in chlorobenzene as measured by the oxidation-inhibition method was 0.65. Since efficiency of radical production is the same for VIII and IX at 70° in chlorobenzene and "a" for VIII in carbon tetrachloride at 62.5° is 0.45, it is estimated that "a" for IX in carbon tetrachloride at 62.5° is also about 0.45. In the photolysis experiment, the azo ester was irradiated with 3660 A° light in carbon tetrachloride at 25° in the presence of ca. 10^{-3}M iodine as scavenger. The disappearance of iodine, as determined spectrophotometrically, followed zero-order kinetics. Quantum yields for iodine consumption (ϕ_{I_2}) were then calculated and compared to independently obtained quantum yields for photochemical decomposition of the azo ester (ϕ_{EAB}). The efficiency factor for radical production, ϕ_{I_2}/ϕ_{EAB}, was 0.38. The slightly lower cage effect for thermal decomposition may be attributable to decreased solvent viscosity at higher temperature. Thermolysis and photolysis therefore seem to be essentially identical processes by the time cage effects become important. Any excess energy associated with the radicals produced by photolysis is presumably lost in processes fast compared to diffusion.[22] While the assumptions made in reaching this conclusion are reasonable, it would be desirable to carry out thermolysis and photolysis in the same solvent and to obtain an experimental estimate of the temperature dependence of cage effects in that solvent.

Many theoretical treatments of cage effects have emphasized the importance of secondary recombination. These theories all predict that scavenger interference with secondary recombination should occur at scavenger concentrations of 10^{-2}M or lower and that the decrease in the amount of secondary recombination will be a linear function of the square root of the scavenger concentration. Also, a cage effect due to primary recombination should remain after secondary recombination has been eliminated. Waits and Hammond[5] therefore studied the thermal decomposition of azo-1-cyanocyclohexane and N-(1-cyanocyclohexyl)pentamethyleneketenimine in solutions containing scavenger concentrations up to 1M in the hope of characterizing both primary and secondary recombination.

The azonitrile was decomposed at 1.00 10^{-5}M and 80° in chlorobenzene containing 3.3 10^{-5} - 1.0M bromine or iodine as scavenger. Decomposition of the ketenimine was studied under identical conditions, except that α,α-diphenyl-β-picrylhydrazyl was used as a scavenger since halogens destroy the ketenimine. It was determined that 1,1'-dicyanobicyclohexyl is stable under the reaction conditions if halogen scavenger concentration is less than 1M. The rate of decomposition of the azo compound in chlorobenzene containing 0.819M bromine was only slightly larger than that for decomposition in pure chlorobenzene. This suggests that direct reaction of the azo compound with the halogens is not important.

If RN_2R is azo-1-cyanocyclohexane, RR' is the corresponding ketenimine, and RR is 1,1'-dicyanobicyclohexyl then the thermal decompositions of RN_2R and RR' in the presence of low concentrations of scavenger (S) may be represented by the following equations:



If w' and w" are the fractions of geminate radicals forming RR in the decompositions of RN_2R and RR', respectively, and Z' and Z" are the fractions forming RR',

then the probability, ϕ, that a geminate pair which would have recombined in the absence of scavenger will react with scavenger is:

$1 - \phi = \%\ RR/100\ w'$ for RN_2R (32)

$1 - \phi = \%\ RR/(100\ w'' + s''\ \%\ RR)$ for RR' (33)

A plot of $1 - \phi$ vs. $(S)^{1/2}$ is predicted to be linear by theories of the cage effect which stress the importance of secondary recombination. This relationship is not observed for either RN_2R or RR' decomposition. Concentrations of scavengers predicted to provide substantial interference with secondary recombination have no effect on ϕ. Indeed, ϕ is not appreciably affected until the scavenger concentration level is such that interference with primary recombination is expected.

Hammond therefore proposes a model based on the assumption that geminate recombination will be prevented only if the radical pair is produced with a scavenger as a nearest neighbor. This model gives good agreement with experimental data if it is assumed that the number of nearest neighbors to substrate molecules is between 4 and 5 on the average. Therefore, it is possible to account for the effect of scavengers without invoking secondary recombination. This does not exclude the possibility of secondary recombination. Indeed, Hammond's theoretical treatment may be easily modified in such a way that the participation of secondary recombination is assumed. However, his experimental results suggest that it is not experimentally feasible to distinguish between primary and secondary recombination.

SUMMARY

Study of the thermal and photochemical decomposition of azo compounds has provided experimental evidence for the existence of cage effects. Estimates of the importance of radical structure and method of radical generation on the magnitude of cage effects have also been obtained. However, some of these results are suggestive rather than conclusive.

While many aspects of cage reactions are worthy of further study, investigations of decomposition in the presence of high concentrations of scavengers are perhaps most intriguing. It would be highly desirable to have more direct evidence that molecular elimination mechanisms are unimportant in solution. Hammond's conclusion that primary and secondary recombination are experimentally indistinguishable also clearly invites further investigations at high scavenger concentration to determine whether the failure of the half-order relationship is universal.

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THE MITOMYCIN ANTIBIOTICS

Reported by Robert A. Gardiner April 4, 1966

INTRODUCTION

The mitomycin group of antibiotics is comprised of mitomycins A, B, and C, the structures of which are shown in Table A. Porfiromycin, another antibiotic, is closely related structurally and is sometimes found in conjunction with the mitomycins. Its structure is also given in Table A. These antibiotics are active against both gram-positive and gram-negative bacteria and also show some anti-tumor activity. They are the first members of a new and unusual structural type, representing the first naturally occurring example of an aziridine produced by a microorganism. After dealing briefly with the isolation of and structural work on the mitomycins, this seminar will be primarily concerned with the studies directed toward their synthesis.

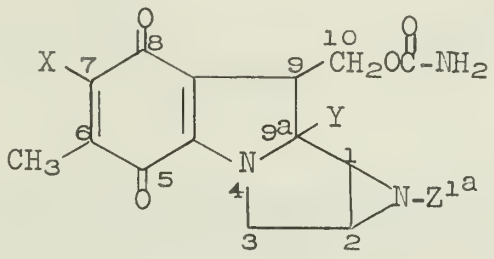


TABLE A

	Compound	X	Y	Z
I-A	Mitomycin A	H_3CO	OCH_3	H
I-B	Mitomycin B	H_3CO	OH	CH_3
I-C	Mitomycin C	H_2N	OCH_3	H
I-D	Porfiromycin	H_2N	OCH_3	CH_3
I-E	N-methyl mitomycin A	H_3CO	OCH_3	CH_3

ISOLATION

The first report of the isolation of a mitomycin antibiotic was by Hata and his coworkers[1] in 1956. They reported that a new actinomyces strain named Streptomyces caespitosus produced mitomycins A and B. In 1958 Wakaki and his co-workers[2] reported that their culture of Streptomyces caespitosus produced mitomycin C as the major antibiotic with A and B being produced only in minor quantities. From three soil isolates of Streptomyces verticillatus Lefemine and his coworkers[3] were able to isolate mitomycins A, B, and C, and in addition porfiromycin, which had previously been reported by Herr.[4]

STRUCTURAL STUDIES

Since the structure of mitomycin C has been the subject of a recent M.I.T. seminar and since the other mitomycins are closely related, only a brief structural discussion will be given here.

Initial studies carried out by Wakaki and his coworkers[2,5] led them to suggest a possible quinone structure.

Lefemine and his coworkers[3] were able to correlate mitomycin A to mitomycin C by reacting I-A with ammonia in methanol, and they also showed that N-methyl mitomycin A could be converted to porfiromycin by treatment with ammonia.

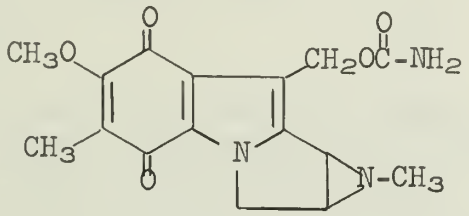
Webb and his coworkers[6] were able not only to establish the chromophores of the antibiotics but by a series of hydrolysis reactions and spectral studies were also able to assign structure I-A to mitomycin A.

Tulinsky[7] later performed an x-ray structural study on mitomycin A using the N-4'-bromobenzene sulfonyl derivative. His study confirmed the chemically assigned structure and also established that the bridgehead methoxy group is trans to the carbamoyloxymethyl and the aziridine functions. He was also able to confirm the methyl and O-methyl groups on the quinone ring.

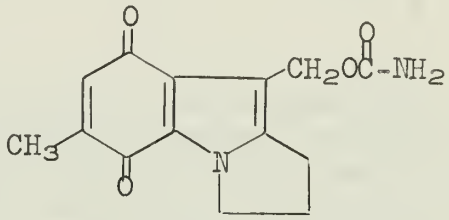
An independent structural determination carried out on mitomycin C was the subject of Taylor's seminar at M.I.T.[8] and was later reported by Stevens, Taylor, and coworkers.[9]

AZIRIDINOMITOSENES

Later degradative studies carried out on the mitomycins by Patrick and his coworkers[10] led to the isolation of so-called aziridinomitosenes. For example, the hydrogenation of mitomycin B in dimethylformamide gave a new compound called 7-methoxy-1,2(N-methylaziridino) mitosene (II), where mitosene is the trivial name given to structure III (2,3-dihydro-9-hydroxymethyl-6-methyl-1H-pyrrolo[1,2-a] indole-5,8-dione carbamate).



II

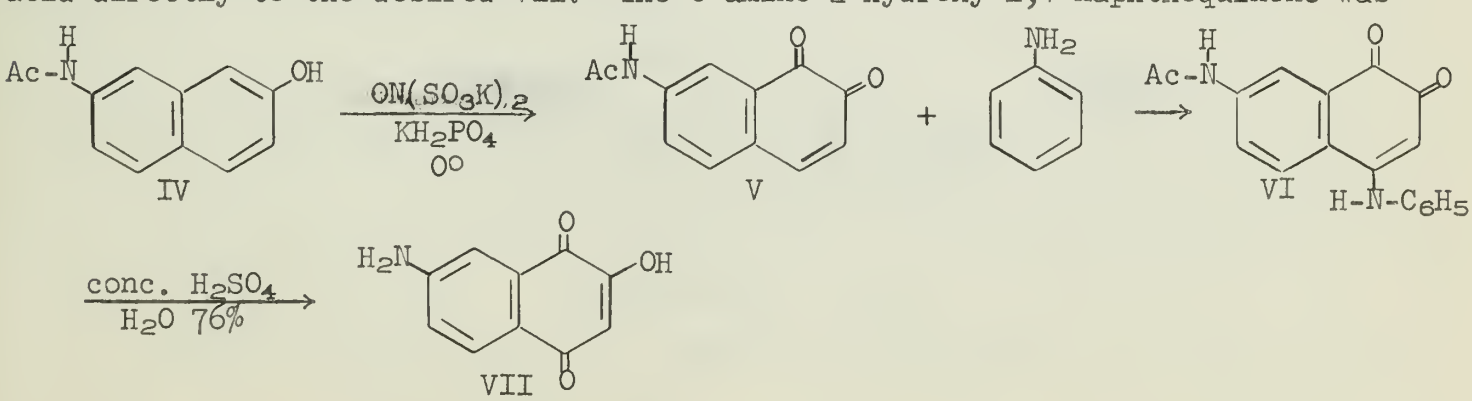


III

It can be seen that the aziridinomitosenes contain neither the 9a substituent nor the asymmetry at C-9 that the parent mitomycins contain. Because of the simpler nature of the aziridinomitosenes, succeeding studies were directed toward their synthesis. For this synthesis methods were required for the fabrication of four key structural features: (1) the indoloquinone chromophore, (2) the fundamental ring system, (3) the carbamoyloxymethyl group at C-9, and (4) the aziridine moiety fused to ring A.

SYNTHETIC STUDIES

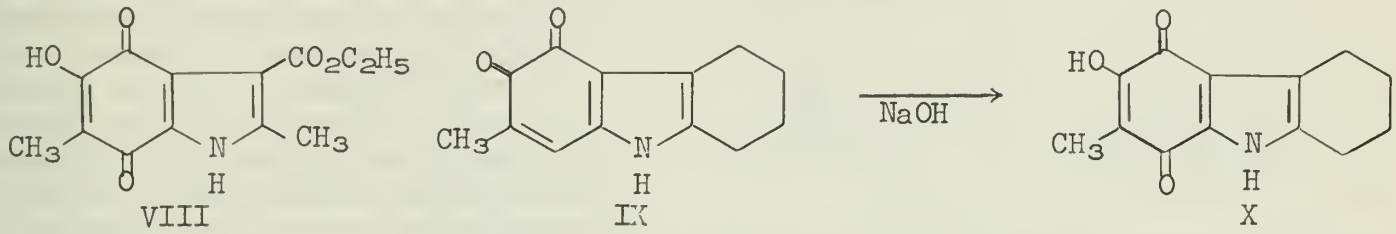
A. Model quinones. - During the course of Webb's investigation of the structure of the mitomycins, it was felt that some of the degradation products were amino-substituted 2-hydroxy-3-methyl-1,4-quinones. Remers, James, and Weiss[11] then undertook the synthesis of several naphtho- and indoloquinones to serve as ultraviolet models for these compounds. Although some of the benz-amino-2-hydroxy-1,4-naphthoquinones had previously been reported by Kehrmann and his collaborators,[12] it was desirable to devise more convenient pathways for their synthesis. The use of the Fremy's salt (potassium nitrosodisulfonate) procedure[13] for the conversion of phenolic compounds to quinones proved to be of value. This method can be illustrated by examining the synthesis of 7-amino-2-hydroxy-1,4-naphthoquinone (VII). This was achieved by first converting 7-amino-2-naphthol to the N-acetyl derivative IV via O,N-diacetylation of the hydrochloride in aqueous solution, followed by de-O-acetylation in dilute alkali. Oxidation of IV with Fremy's salt afforded an 89% yield of 7-acetamido-1,2-naphthoquinone (V). Then addition of aniline to V gave 7-acetamido-4-anilino-1,2-naphthoquinone (VI), which could be hydrolyzed in sulfuric acid directly to the desired VII. The 8-amino-2-hydroxy-1,4-naphthoquinone was



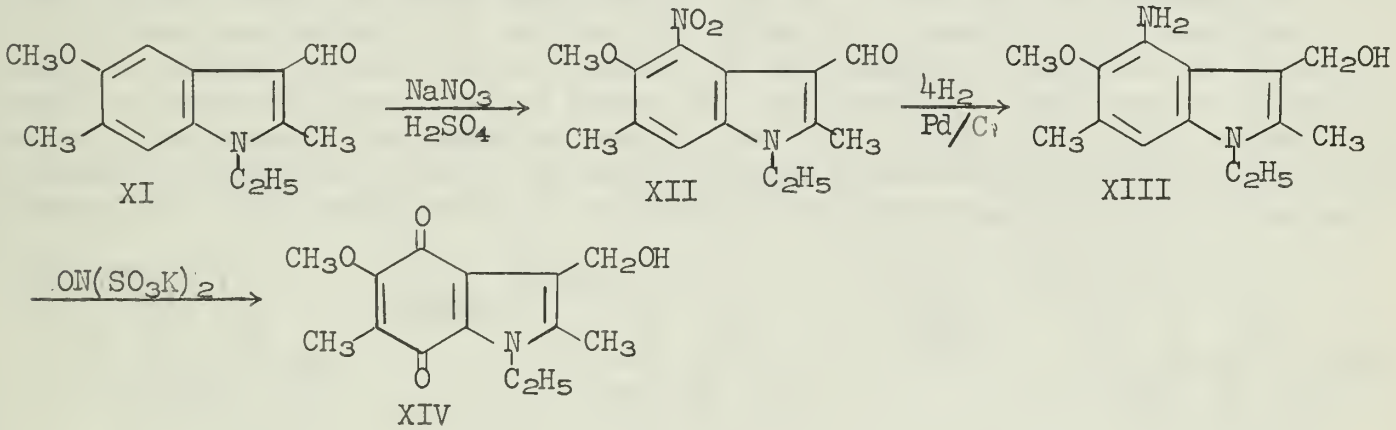
prepared in the same manner, but the 5-amino-2-hydroxy-1,4-naphthoquinone could not be prepared in this way since the Fremy's salt oxidation gave only starting material.

When the amino-hydroxy-1,4-naphthoquinones proved to be of limited use as

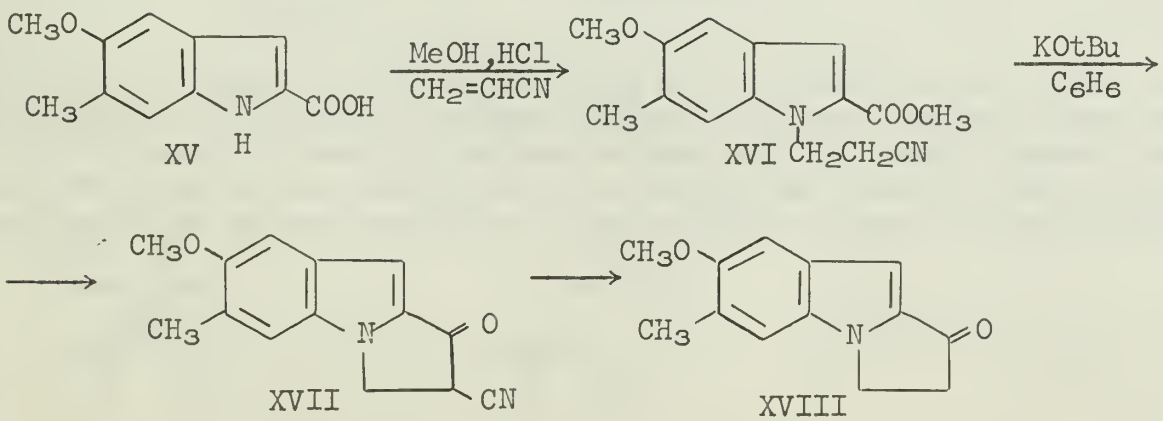
ultraviolet models, the synthesis of indoloquinones was undertaken. In 1958 Teuber and Thaler[13] reported the synthesis of ethyl 5-hydroxy-2,6-dimethyl-4,8-dioxo-3-indolecarboxylate (VIII). Although this was a reasonably good ultraviolet model, it seemed as if an indoloquinone substituted only with alkyl groups might be more appropriate. Therefore, 5,6,7,8-tetrahydro-3-hydroxy-2-methyl-1,4-carbazoledione (X) was prepared from 5,6,7,8-tetrahydro-2-methyl-3,4-carbazoledione (IX) by prolonged treatment with 0.1N sodium hydroxide solution.



Allen, Poletto, and Weiss,[14] while synthesizing indoloquinones to define the minimum structural requirements for antibacterial activity, developed an abbreviated route to the indoloquinone chromophore. This route depended upon nitration of the benzenoid nucleus in a 5-methoxy-3-indolecarboxaldehyde. For example, the nitration of XI with sodium nitrate in sulfuric acid or with fuming nitric acid in glacial acetic acid gave the nitro derivative XII. Hydrogenation of XII presumably gave the 4-amino-3-indolylmethanol XIII, which upon treatment with potassium nitrosodisulfonate furnished the indoloquinone XIV.

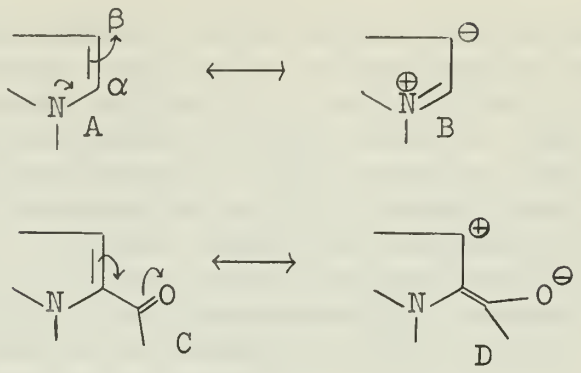


B. The pyrrolo[1,2-a]indole ring system. - The basic pyrrolo[1,2-a]indole ring system was readily available from 5-methoxy-6-methyl-2-indolecarboxylic acid (XV). Reaction of the methyl ester of XV with acrylonitrile gave the 1-β-cyanoethyl derivative XVI which upon treatment with potassium t-butoxide in boiling benzene furnished the β-ketonitrile XVII. These two reactions could be combined by carrying out the condensation of the indole ester with acrylonitrile using an equivalent of t-butoxide. In this way the β-ketonitrile XVII was furnished directly. Hydrolysis of the nitrile and then methylation followed by decarbomethoxylation gave the 1-ketopyrrolo[1,2-a]indole system XVIII.

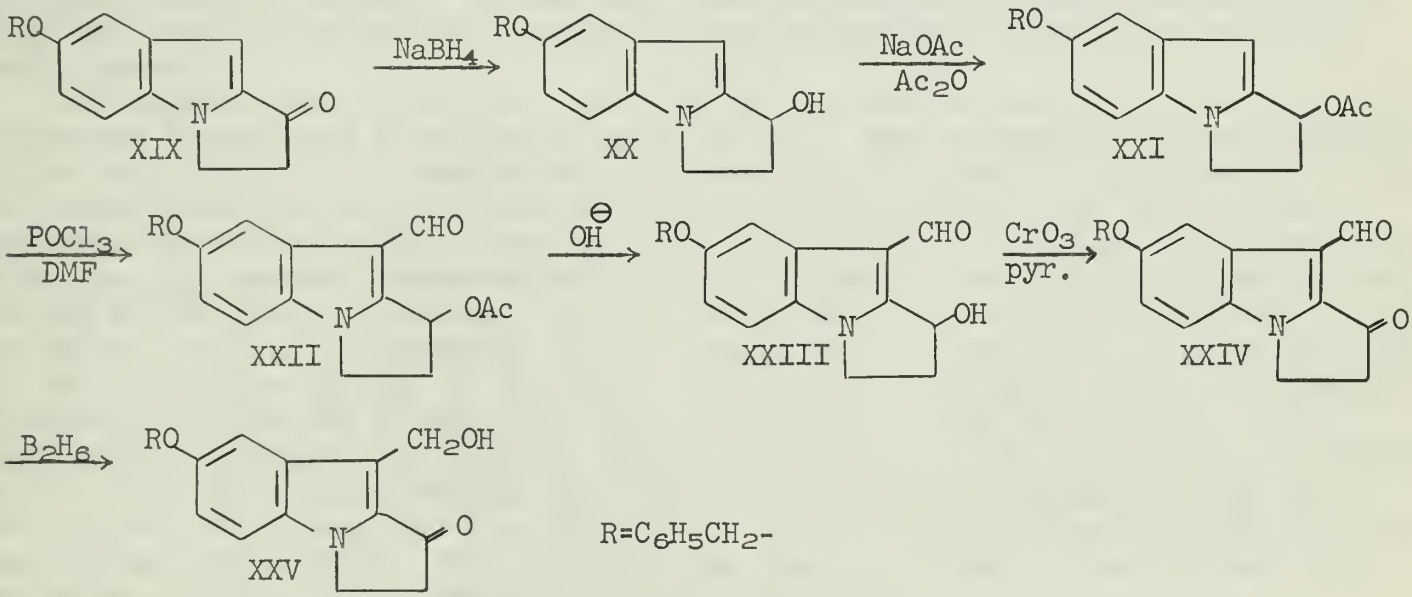


C. Introduction of the C-9 hydroxymethyl group. - Introduction of the hydroxymethyl group at C-9 was complicated by two factors. Substitution reactions at the

β-position of indoles are generally electrophilic in character and are dependent upon the delocalization of electrons from the heterocyclic nitrogen toward this position (A ⟷ B).[15] However, in this case the delocalization was opposed by the electron-withdrawing effect of the carbonyl at the indole α-position (C ⟷ D). There was also a need to stabilize the generally unstable β-hydroxymethyl group.[16] Remers[17] anticipated that such stabilization would be afforded by the 1-carbonyl. Thus for a successful reaction the effects of the carbonyl group must be balanced. It cannot deactivate the indole β-position to electrophilic substitution, and it must stabilize the hydroxymethyl derivatives which are formed.

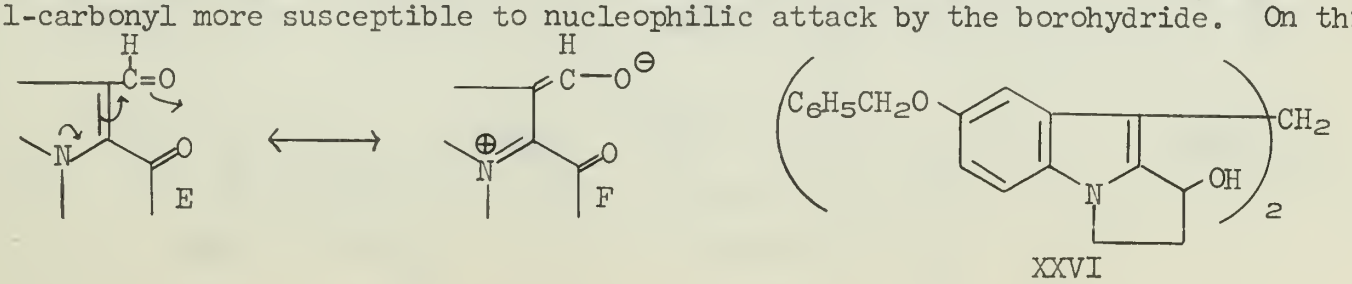


Remers and his coworkers[17] first tried direct treatment of the 1-ketopyrrolo [1,2-a]indole XIX with formaldehyde in acid but received only starting material. An attempted nucleophilic substitution with nitromethane and trimethylamine also was unsuccessful. Similarly no useful reaction was obtained by treatment of XIX with zinc cyanide and hydrochloric acid, with phosgene, or with ethyl chloroformate and silver perchlorate. A successful reaction was obtained by treatment of XIX with the dimethylformamide-phosphorus oxychloride complex (Vilsmeier-Haack conditions),[18] and the 9-formyl derivative XXIV resulted in 7% yield. A better yield resulted when the 1-one was reduced to the 1-ol derivative XX with sodium borohydride in ethanol in order to remove the deactivating effect of the carbonyl. Then after acetylation of the 1-ol the formylation could be carried out with yields up to 85%. Saponification followed by oxidation of the 1-ol with chromium trioxide-pyridine gave the 9-formyl-1-one XXIV in 25% yield overall. To receive the hydroxymethyl group it was now



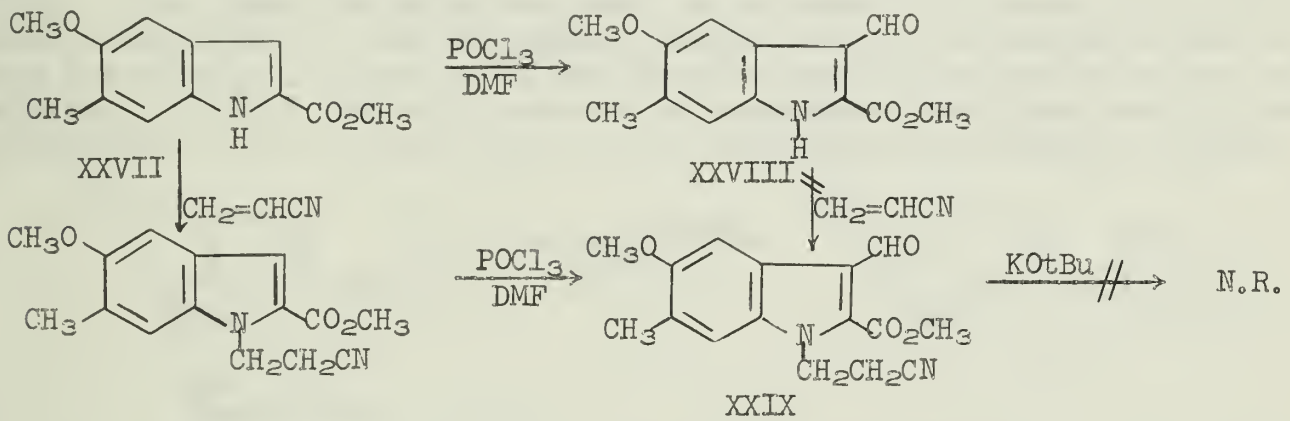
R=$C_6H_5CH_2$-

necessary to reduce the 9-formyl group without reducing the 1-one. With sodium borohydride the diindolyl methane XXVI was obtained, probably from reduction of the 1-one followed by reduction of the 9-formyl group. This sequence could be due to electron release from the indole nitrogen to the 9-formyl group (E ⟷ F), making the 1-carbonyl more susceptible to nucleophilic attack by the borohydride. On this



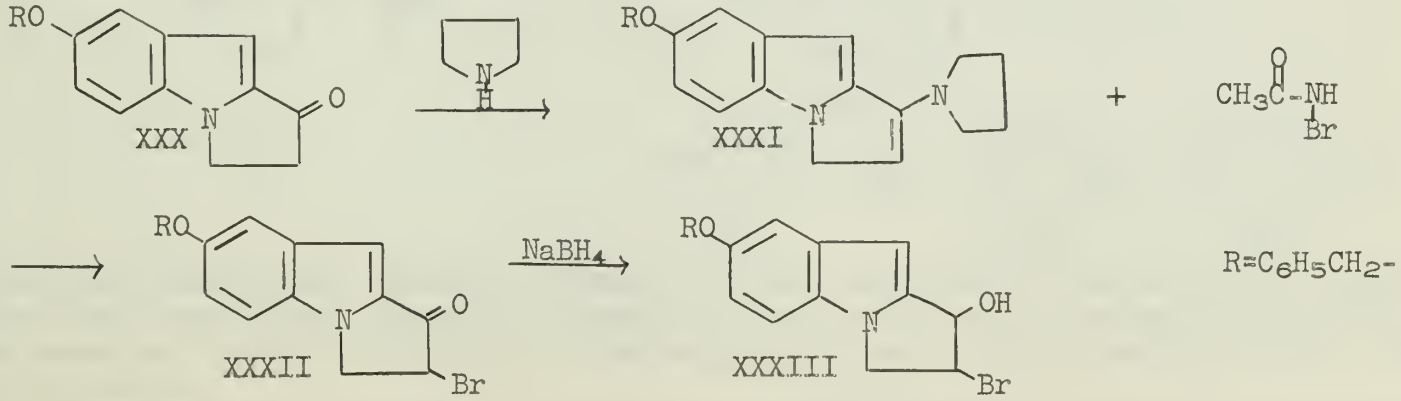
basis the 9-formyl group should be more reactive to an electrophilic reagent and in fact treatment of XXIV with diborane gave the 9-hydroxymethyl-1-one XXV in good yield.

Another attempt to introduce the hydroxymethyl group involved the Dieckmann ring closure of the adducts obtained from the condensation of an indole-2-carboxylate with acrylic esters or nitriles. This method required the introduction of the 9-hydroxymethyl group into the indole β-position prior to ring closure. Thus it was shown that the formylation of the indole-2-carboxylate XXVII proceeded easily to give the formyl compound XXVIII; however, the condensation of this product with acrylic esters or nitriles could not be achieved. For this reason the condensation of the indole-2-carboxylate with acrylonitrile was carried out first, followed by formylation to give XXIX. After reduction of XXIX to the 3-hydroxymethyl compound it was treated with potassium t-butoxide in benzene in an attempt at ring closure. However, this attempt failed as did all attempts with other bases.

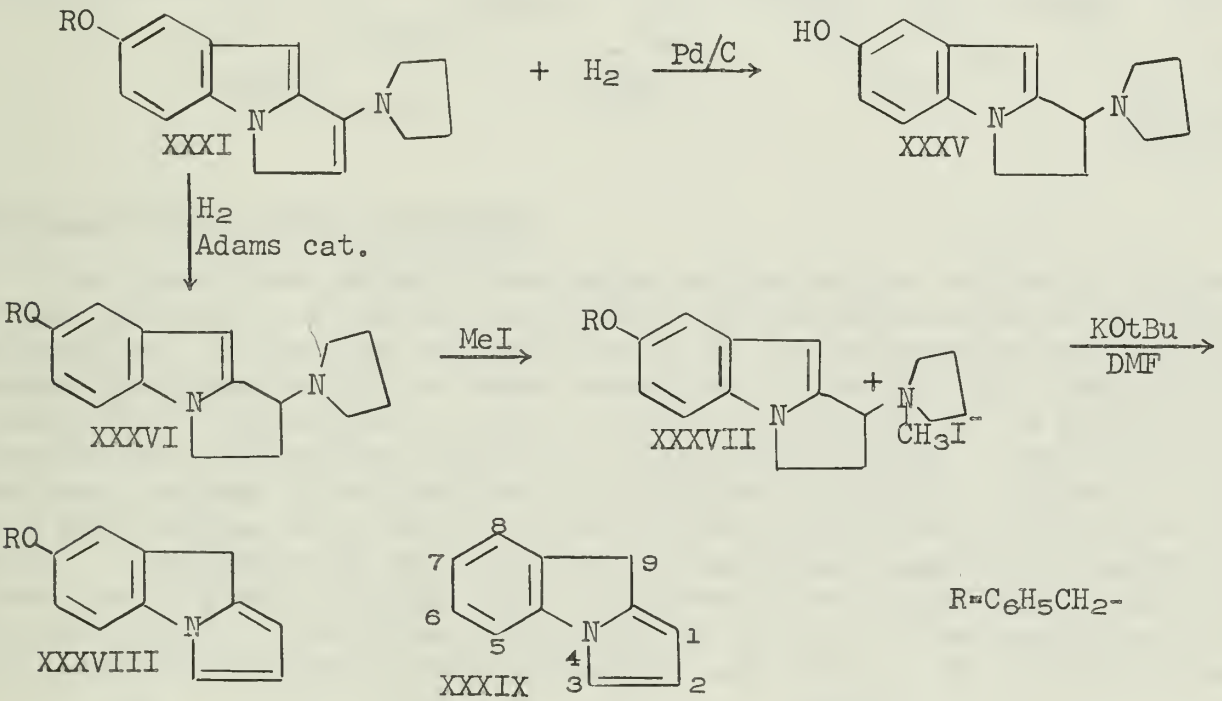


D. Attempts to introduce the aziridine moiety. - At this point the only remaining structural feature necessary for the synthesis of an aziridinomitosene was the fused aziridine moiety. To set the stage for the introduction of this moiety Allen and Weiss[19] carried out a number of transformations in the pyrrolo[1,2-a] indole system.

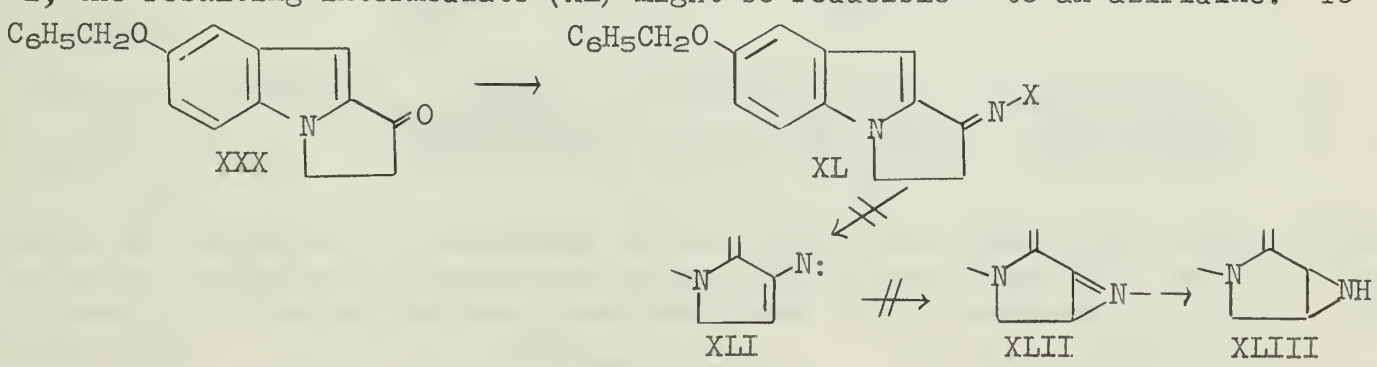
One approach which they felt would be of use involved starting with the 1-keto system and introducing a functional group at C-2. They attempted to functionalize C-2 by introduction of a bromine and by elimination to give 1,2 unsaturation. When the 7-benzyloxy-1-keto derivative XXX was treated with bromine in acetic acid, a monobromo ketone was formed. However, this was shown not to be the C-2 bromo ketone since the A_2X_2 pattern characteristic of the C-2 and C-3 methylene protons was unchanged in the n.m.r. spectrum. Then by using the 7-methoxy-6-methyl system without the ketone function, bromination could be shown to occur at C-9 by loss of the signal for the C-9 proton (τ4.10) in the n.m.r. spectrum. By using an excess of bromine a dibromo derivative was formed which had bromines at C-2 and C-9. If the 1-keto function was changed to an enamine, it was possible to obtain preferential bromination at C-2. The pyrrolidine enamine XXXI could be prepared by reaction of XXX with pyrrolidine, and subsequent treatment of the enamine with N-bromoacetamide produced the 2-bromo ketone XXXII. This ketone could then be reduced to the 2-bromo-1-ol derivative XXXIII by reaction with sodium borohydride.



Attempts to introduce 1,2 unsaturation by elimination of 1-ols which were derived from the ketones by borohydride reduction were unsuccessful. Another method tried involved elimination of a tertiary amino group from C-1. For this purpose the enamine XXXI was used and it was converted to the tertiary amine XXXV by hydrogenation using a palladium on charcoal catalyst. However, with this catalyst debenzylation occurred, but the use of Adams' catalyst gave the tertiary amine XXXVI with the 7-benzyloxy group still present. This material was smoothly transformed into the methiodide XXXVII, treatment of which with potassium t-butoxide in dimethyl formamide gave in good yield a product (XXXVIII) which had the desired $C_{18}H_{15}NO$ composition. However, this compound did not show a u.v. spectrum typical of a 2-vinylindole.[20,21] A comparison of the u.v. spectrum to that of 9H-pyrrolo[1,2-a]indole XXXIX prepared by Laschtuvko and Huisgen[22] indicated that this compound might have the 9H-pyrrolo [1,2-a]indole structure (XXXVIII), and this was confirmed by a study of its n.m.r. spectrum. The C-8 proton (τ2.83) could be decoupled from a methylene group at τ7.28. This places the methylene group at C-9 since if it were at C-3 this coupling would be improbable. Also an apparent triplet at τ3.77 (1 proton) could be split into a doublet by irradiation at the radiofrequency corresponding to the C-3 proton multiplet (τ2.74). The only proton in an environment that would satisfy these observations is to be found at C-2 in the 9H-pyrrolo[1,2-a]indole structure (XXXVIII).



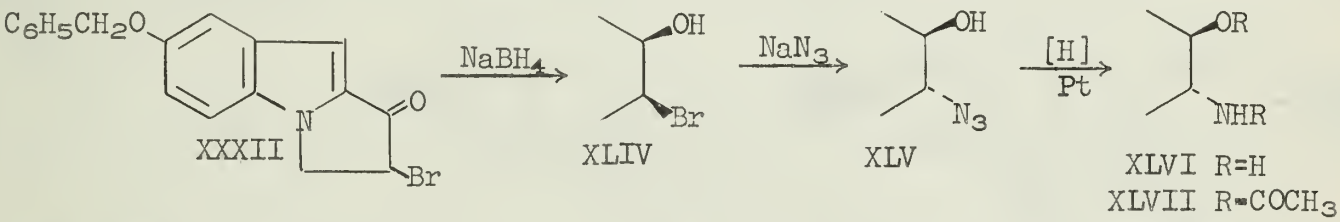
Remers, Roth, and Weiss[23] felt that one of the most direct routes to an aziridine from a 1-ketopyrroloindole (e.g., XXX) would be by conversion of the carbonyl to a C=N-X group, wherein X is a good leaving group. Then if a nitrene could be generated by proton removal from the adjacent methylene group, and if insertion occurred at C-2, the resulting intermediate (XL) might be reducible[24] to an aziridine. To test



this possibility the 1-ketopyrroloindole XXX was converted to the oxime and then to the tosyl derivative. However, attempts to generate an aziridine with either sodium ethoxide and sodium borohydride or sodium hydride and lithium aluminum hydride were unsuccessful.

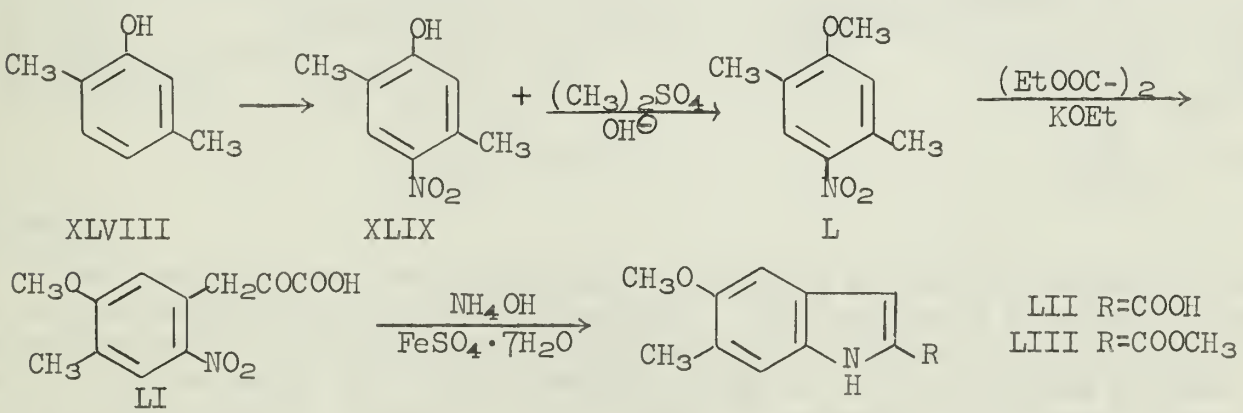
When the use of "nitrene" intermediates failed, a more classical approach was

undertaken in which trans-aminohydrins were prepared in order to attempt modifications of the Wenker aziridine synthesis.[25] Reduction of the 2-bromo-1-ketopyrroloindole XXXII with sodium borohydride in methanol afforded the corresponding bromohydrin XLIV. This bromohydrin was assigned cis stereochemistry since the bulky borohydride should add on the side opposite to the bromine. The aminohydrin XLVI was then prepared by treating XLIV with sodium azide followed by catalytic reduction of the resulting hydroxy azide XLV. The aminohydrin XLVI was assigned trans stereochemistry since the reaction of the nucleophilic azide ion with XLIV was probably an S_N2-type displacement. To transform the aminohydrin into an aziridine it was necessary to convert the 1-hydroxy function to a suitable leaving group. Treatment of XLVI with sulfuric acid or chlorosulfonic acid caused immediate decomposition. Also mesylation and tosylation studies yielded no usable derivatives. At this point sulfonate ester formation of XLVI was abandoned, and a possible new method of aziridine formation involving displacement of acetoxy by the anion derived from neighboring trans-acetamido was investigated. However, treatment of the O,N-diacetate XLVII with lithium hydride or sodium hydride in tetrahydrofuran was unsuccessful, with starting material or the equivalent being recovered in each instance.

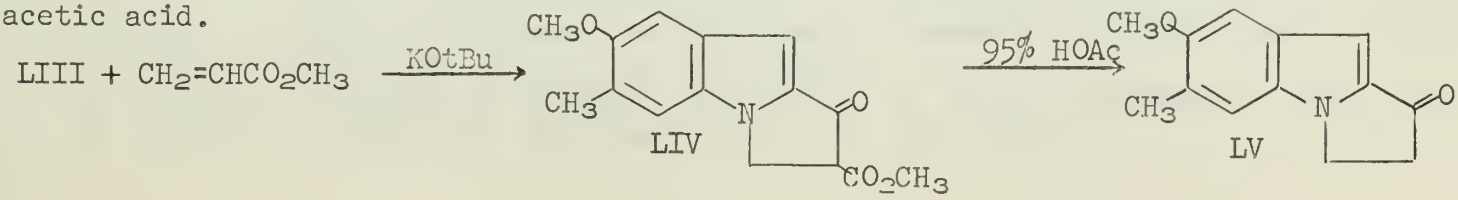


PREPARATION OF 7-METHOXYMITOSENE

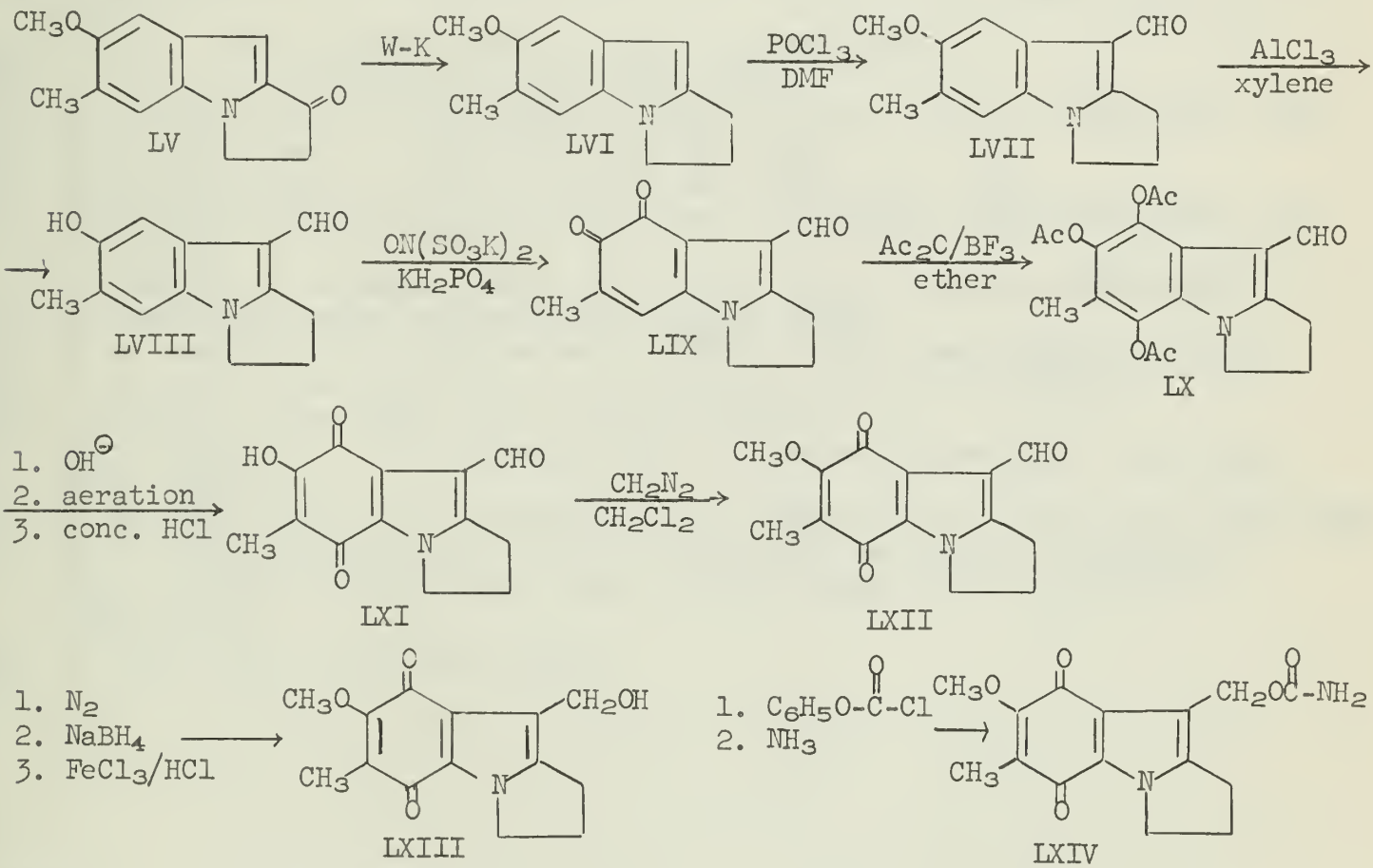
Now that Allen, Poletto, and Weiss had techniques available for the preparation of the pyrrolo[1,2-a]indole ring system, for the preparation of the indoloquinone chromophore, and for the introduction of the 9-carbamoyloxymethyl substituent, they tested the compatibility of these techniques by synthesizing 7-methoxymitosene (LXIV).[26,27] The required indole was readily prepared by the Reissert method,[28] using 4-nitro-2,5-xylenol (XLIX) as the starting material. This starting material was best prepared by sulfonation of 2,5-xylenol (XLVIII), treatment of the sulfonic acid with nitrous acid, and oxidation of the crude nitroso derivative with nitric acid. O-methylation of XLIX was then accomplished readily with methyl sulfate. Condensation of L with diethyl oxalate followed by ester hydrolysis gave the phenylpyruvic acid LI. Reductive cyclization of LI with ferrous ammonium sulfate furnished the 5-methoxy-6-methyl-2-indolecarboxylic acid (LII). The pyrrolo[1,2-a]indole ring



system was prepared by condensation of the indole ester LIII with methyl acrylate (using an equivalent of t-butoxide) to give the β-keto ester LIV. The best procedure for removal of the carbomethoxy group was found to be treatment with boiling 95% acetic acid.



This pyrrolo[1,2-a]indole-1-one(LV) was then converted into its 1-deoxy derivative LX by Wolff-Kishner reduction. Vilsmeier-Haack formylation of the latter compound afforded the 9-carboxaldehyde LVII, which upon treatment with aluminum chloride in boiling xylene suffered de-O-methylation, giving LVIII. Treatment of the aldehyde LVIII with potassium nitrosodisulfonate gave the o-quinone. Thiele acetoxylation[29] of the o-quinone LIX gave the hydroxyhydroquinone triacetate LX which, upon treatment with base followed by aeration, furnished the hydroxy p-quinone LXI. Reaction of LXI with diazomethane readily gave the corresponding methoxy-p-quinone LXII. Reduction of the formyl group then presented some difficulties since the quinone function was also reduced and required regeneration. However, by reduction of the methoxyquinone aldehyde LXII with sodium borohydride and subsequent treatment <u>in situ</u> of the resulting hydroquinone with acidic ferric chloride solution, the quinone carbinol LXIII was received in good yield. The only step which remained at this point was the preparation of the carbamate side chain. For this step the use of phosgene proved to be unsuccessful and it was necessary to use phenyl chloroformate. Ammonolysis of the phenylcarbonate formed from reaction of the quinone carbinol LXIII with phenylchloroformate in pyridine gave 7-methoxymitosene (LXIV) in good yield.



SUMMARY

The synthesis of 7-methoxymitosene, which is a possible precursor for the mitomycin antibiotics, has been discussed. This synthesis involved the preparation of indoloquinone chromophores, the preparation of pyrrolo[1,2-a]indole ring systems, and the introduction of a hydroxymethyl group at C-9 of the ring system. Attempts to introduce a fused aziridine moiety into the pyrrolo[1,2-a]ring system have also been discussed.

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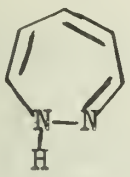
REARRANGEMENTS OF A NOVEL DIHYDRODIAZEPINONE

Reported by Steven A. Dombchik April 7, 1966

INTRODUCTION

Although there has been an increasing amount of work on heterocyclic systems, very little is known about the 1,2-diazepine ring system. The parent compound 1H-1,2-diazepine (I) has not yet been synthesized. Unlike other seven membered ring systems containing two nitrogen atoms there are few saturated 1,2-diazepines reported in the literature.[1] The most extensively studied 1,2-diazepine is 2,3-dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one (II), first reported by Moore in 1955.[2] The ensuing discussion is a result of the unusually large number of rearrangement products that can be formed from II. This has been attributed to the number of active electrophilic and nucleophilic centers which can react singly or in a concerted manner.[3] Although many of the transformations of II involve familiar and precedented reactions, the unique combination of functional groups on II allows a number of pathways into other ring systems. It will be the object of this seminar to cover the preparation and the chemistry of 2,3-dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one (DPO).

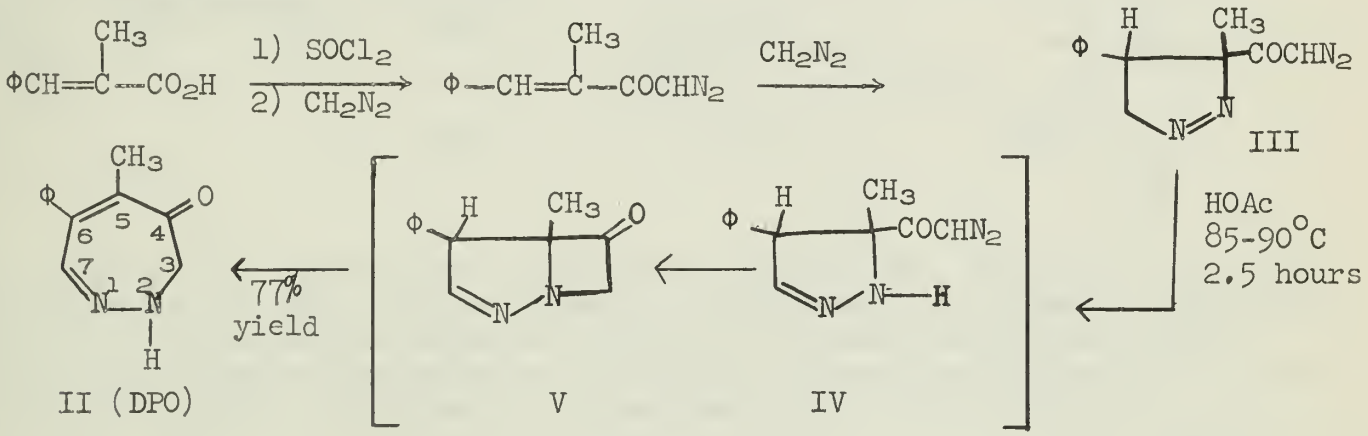


I

PREPARATION OF DPO

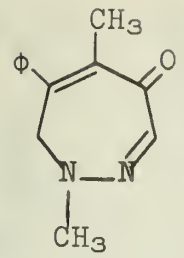
DPO can be prepared according to (1).[2,4] Although the reaction usually

(1)

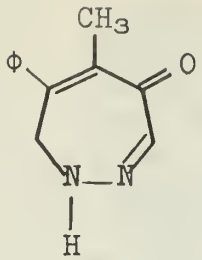


goes directly from III to II, both intermediates IV and V have been isolated by proper choice of conditions and have been shown to give DPO under the original reaction conditions.[5] The formation of a four-membered heterocyclic ketone analogous to V upon treatment of an α-hydroxydiazoketone with acetic acid has been described by Marshall and Walker.[6] Conversion of the strained bicyclo(3.2.0) system of V to DPO can be formulated readily as collapse of the N-1 → C-5 bond and loss of a proton at C-4. Dryden has demonstrated a similar fission of a carbocyclic(3.2.0) structure in his synthesis of cycloheptatriene.[7,8]

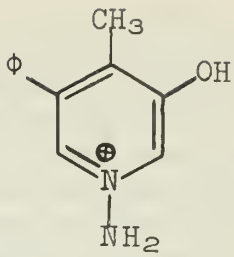
The diazepine structure II was first suggested on the basis of its spectral properties and is supported by chemical evidence. An extended chromophore is suggested by the visable spectrum (λ_{max}^{MeOH} 401 mu, ϵ 2960).[3] Compound VI has been prepared.[9] Its λ_{max} (357 mu) is found to be much smaller than DPO. This would seem to rule out VII as DPO. The infrared spectrum indicates both conjugated carbonyl and N-H adsorption. The nmr spectrum shows the expected peaks for $-\overset{|}{C}-CH_2-N$ (δ 3.87 ppm, J=2 due to N-H coupling), $CH_3-C=C$ (1.88 ppm), $\rangle CH=N$ (7.05 ppm), and C_6H_5 (mult., 7.2-7.4 ppm).[3] The presence of a carbonyl group in DPO is supported by the formation of a semicarbazone. The major evidence for the skeletal structure is the conversion of DPO to the quarternary 1-aminopyridine (VIII) with dilute HCl. This reaction will be discussed later in the abstract.



VI



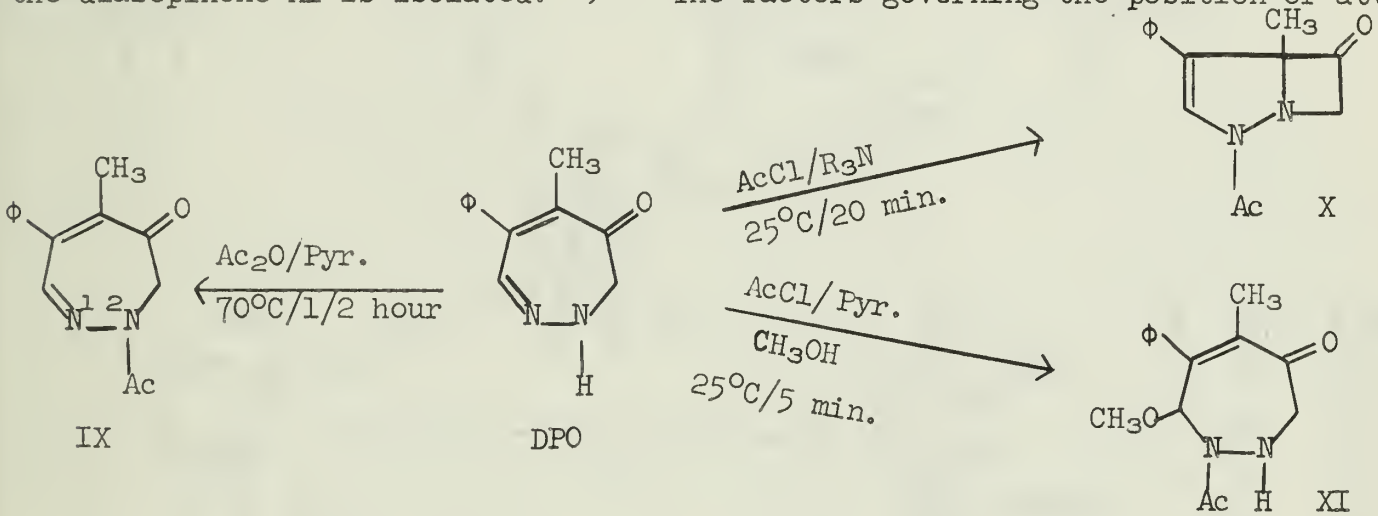
VII



VIII

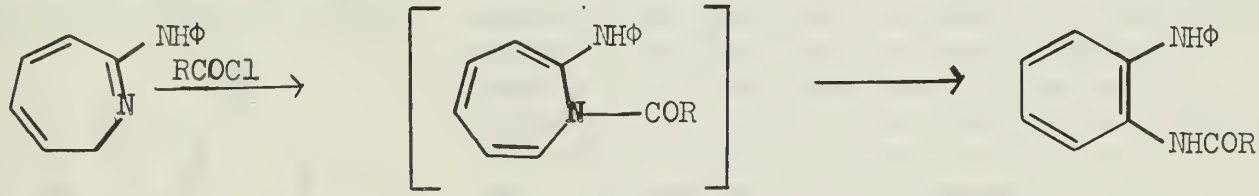
CHEMISTRY OF DPO

Both nitrogen atoms of DPO undergo electrophilic attack. Treatment of DPO with acetic anhydride and pyridine gives IX (69%).[10] When DPO reacts with acetyl chloride and pyridine (or dimethyl aniline) the bicyclo(3.2.0) compound X is obtained (65%).[11,12] However, if methanol is used with acetyl chloride and pyridine the diazepinone XI is isolated.[12,13] The factors governing the position of attack



on DPO with various reagents are not yet fully understood. While IX might be the expected product for acyl chloride attack, the bicyclo(3.2.0) product X probably results from electrophillic attack at N-1 with an ensuing tautomeric shift. This proposed mechanism resembles the acylation of 7-anilino-3H-azepine in which transannular bridging and subsequent aromatization are observed (2).[14]

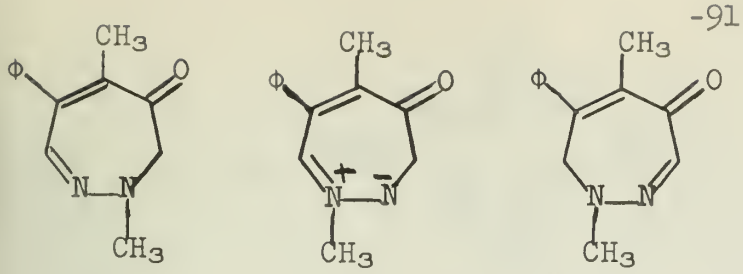
(2)



While a stable bicyclo(3.2.0)heptane derivative has not previously been isolated from such a transannular displacement, a process of this kind has been considered as a possible biosynthetic pathway to the penicillins from a 1,4-thiazepine precursor.[15] When DPO is treated with acetyl chloride and pyridine in methanol solution, the tautomeric shift and bridging are interrupted and the 1-acetyl-7-methoxytetrahydrodiazepinone XI is obtained. All three acylation products (IX, X, XI) can be converted back to DPO by warming with glacial acetic acid. These conditions suggest that the acyl group is removed by acetic acid, possibly in a concerted fashion. Similar acyl transfer to acetic acid with the formation of acetic anhydride has been observed with imidol acetates[16] and acetyl carbinolamine acetates.[17]

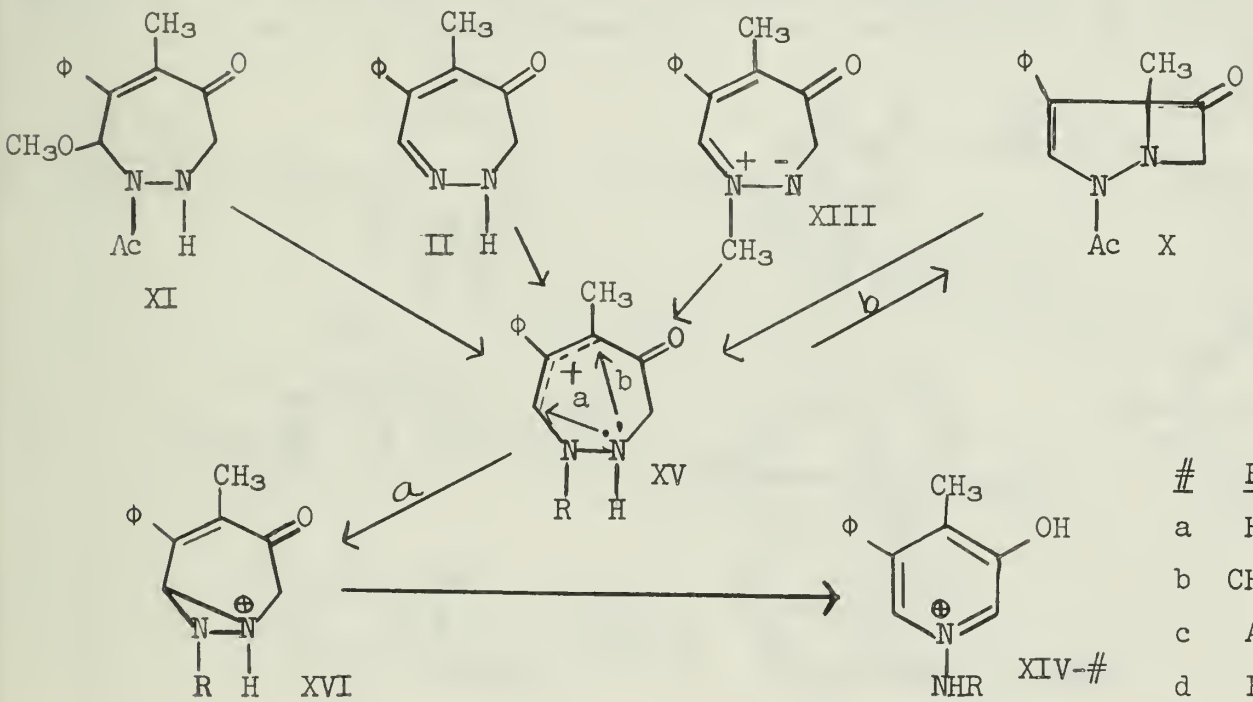
Methylation of DPO with dimethyl sulfate in base at 0°C gives approximately equal amounts of the 1- and 2-methyl derivatives (XII and XIII, 80% total yield). Upon standing for a day or upon warming XIII is isomerized to VI.

On treatment with acid DPO,[10,18] XIII,[9,10] XI,[12] and X[12] are converted to the 1-amino-3-hydroxy pyridinium compounds XIV. The driving force in this reaction is probably the formation of the six membered ring. The mechanism can be formulated,



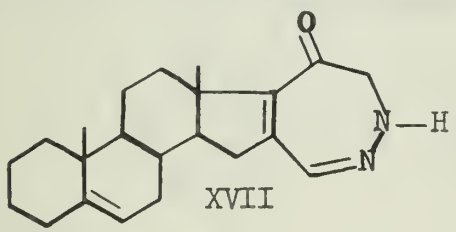
XII XIII VI

a priori, in either of two ways. The rearrangement of DPO is presumably initiated by protonation of the C=N bond as in the hydrolysis of a hydrazone. The reaction could then proceed through a ring opened carbinol-amine aldehyde with subsequent ring closure at N-2. Alternatively the reaction could go through an allylic cation (XV) which then collapses to the pyridinium cation via the bicyclo(4.1.0) intermediate XVI. There exists the possibility of a hydrogen shift from N-2 to N-1 in XVI



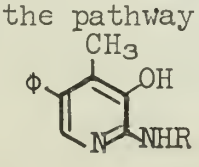
#	R	% yield
a	H	90%
b	CH_3	84%
c	Ac	30%
d	Bz	87%

before conversion to XIV. The analogous conversion of a cycloheptadienone system to a valence tautomeric bicyclo(4.1.0)heptene has been observed.[19] Although this mechanism has no direct support it is consistent with proposals for related ring contractions of other azepines.[20,21] The requirement of a hydrogen atom initially on N-2 is seen by the failure of XII to rearrange by mild acid treatment. Since XVII does not rearrange upon similar acid treatment,[22] the pathway is better formulated by way of the diazabicyclo(4.1.0) system rather than ring opening and reclosure sequence because XVII would probably lack conformation mobility needed for the (4.0.1) intermediate. Ring opening and reclosure should not hinder the reaction of XVII relative to the othe reactive compounds.

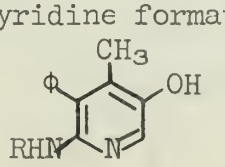


XVII

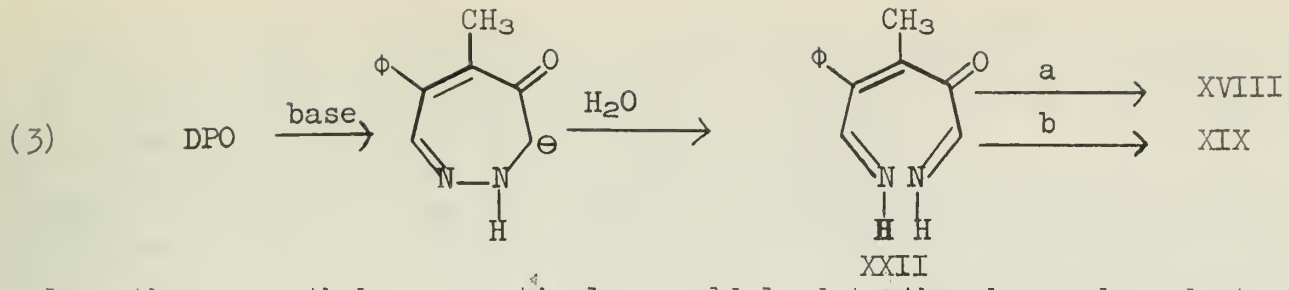
Deuterium exchange of DPO in basic solution was followed by nmr spectroscopy and was found to have occurred at C-3 and more slowly at C-7. Rearrangement of DPO occurs after a few days at room temperature in basic media to give 2- and 6-amino-3-hydroxyl-4-methyl-5-phenylpyridines (XVIII and XIX) in approximately equal amounts.[18] Furthermore 2-alkyl DPO (XII) gives only the 2-amino product (XX)[18] while VI exclusively leads to the 6-amino product (XXI).[9] Moore and coworkers favor (3) as the pathway leading to α-aminopyridine formation. Their mechanism entails initial enolate formation through C-3 followed by anion cleavage through β-elimination to give an acyclic precursor XXII. XXII could cyclize in two ways to give XVIII and XIX. In the cases of XII and VI



R	
H	XVIII
CH_3	XX

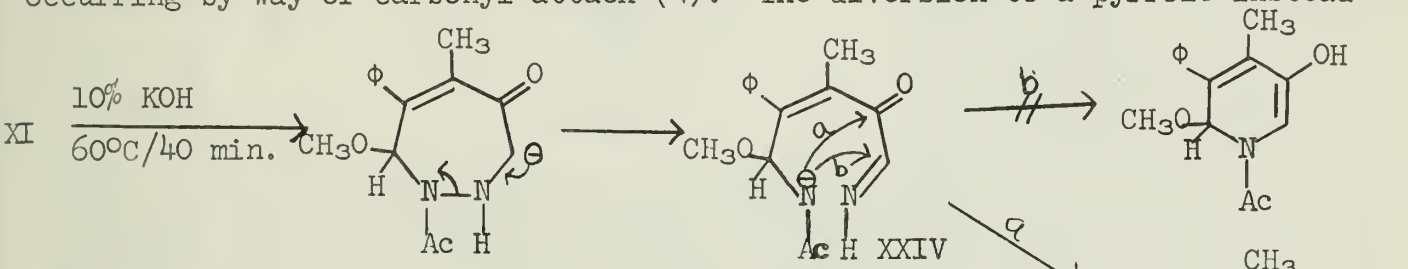


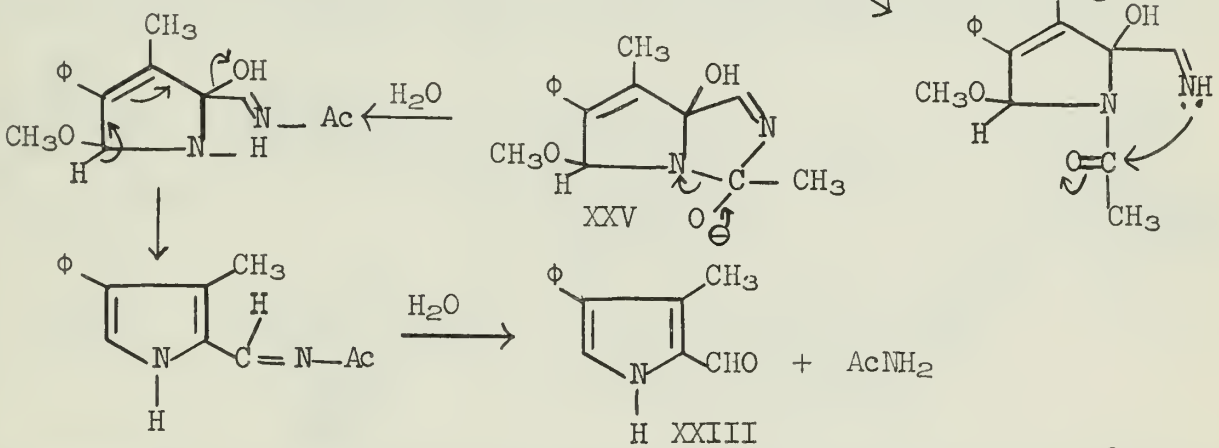
R	
H	XIX
CH_3	XXI

(3) 

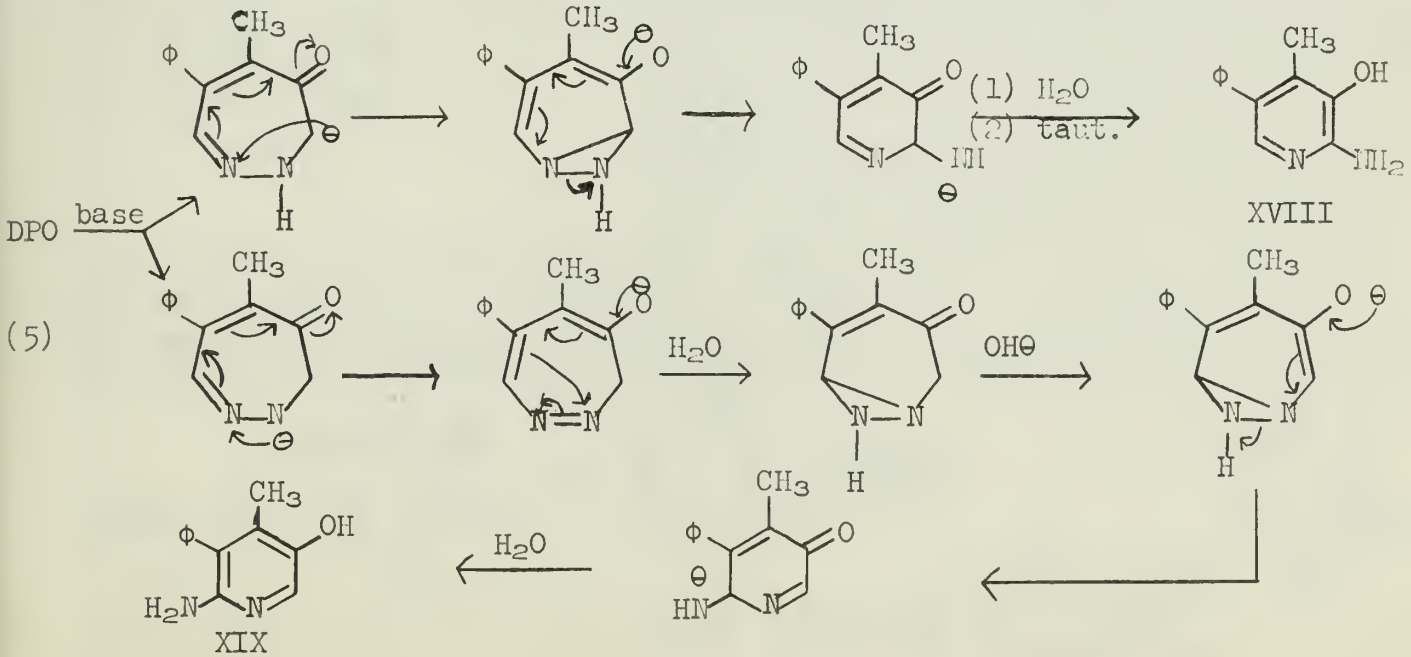
only path a or path b, respectively, could lead to the observed products.

When XI is warmed with aqueous KOH only 5-methoxy-3-methyl-4-phenyl-2-pyrrolealdehyde (XXIII) is obtained in 85% yield.[13] The formation of this pyrrole seems to be similar to (3) except that in this case cyclization would be pictured as occurring by way of carbonyl attack (4). The diversion to a pyrrole instead



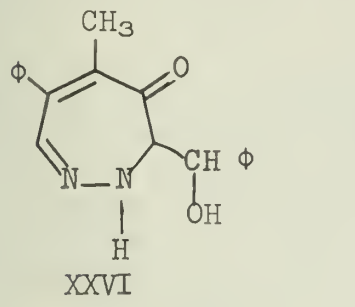
(4) 

of a pyridine was ascribed to the altered nucleophilic character of the $-\overset{\ominus}{N}COR$ group. This mechanism accounts for the observed product with acetyl migration occurring through a bicyclic intermediate (XXV) resembling the cyclols which are involved in amide-amine interactions of peptides.[23] It is also possible to account for the different ring system obtained here by suggesting an alternative mechanism for DPO rearrangement (5).

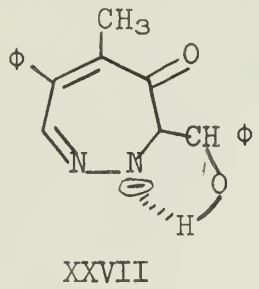
(5) 

While (5) could be invoked for the formation of XVIII-XXI, it could not lead to the pyrrole XXIII. It seems plausible to think that the presence of an electron-withdrawing acyl group might provide an explanation for the formation of the acyclic intermediate only in the case leading to pyrrole.

DPO undergoes aldol condensation with benzaldehyde only at C-3 to give XXVI (45% yield).[24] The aldol product is remarkably resistant to acid-catalyzed dehydration and is recovered unchanged from acid treatment sufficient to cause the rearrangement of DPO to the 1-aminopyridine (XV-a). The 2-N-methyl compound (XII) gives no aldol product. The failure of XII to undergo aldol condensation may simply be due to the loss of the enolate anion in the cleavage reaction, whose formation is readily reversible. The presence of an acidic proton at N-2 might lead to XXVII which could stabilize the aldol product by hydrogen bonding.[25] Treatment of the aldol (XXVI) with acetic anhydride at room temperature for several hours led to XXVIII which upon hydrolysis with methanolic HCl yielded XXIX (60% yield). The proposed mechanism (6) involves a heterocyclic counterpart of an aromatic tropone

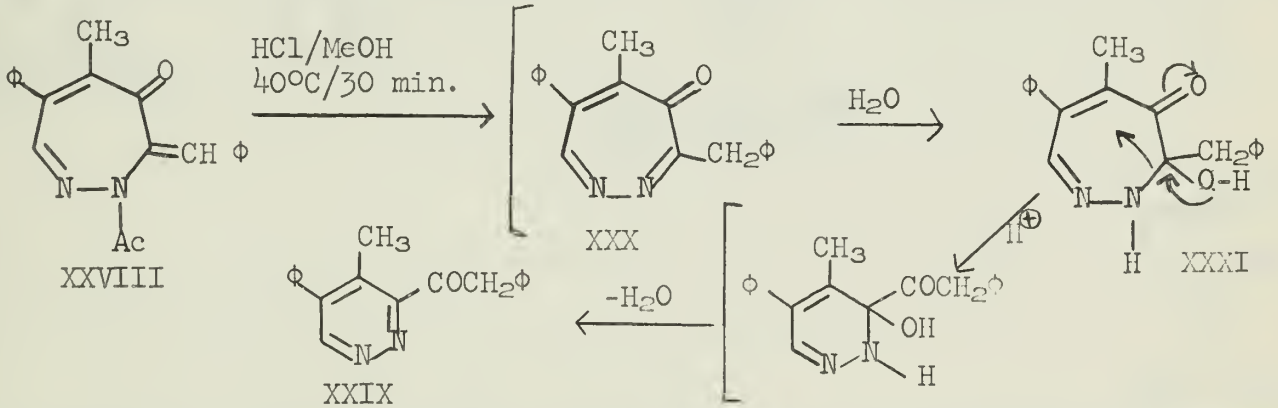


XXVI

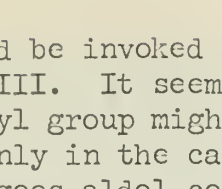


XXVII

(6)

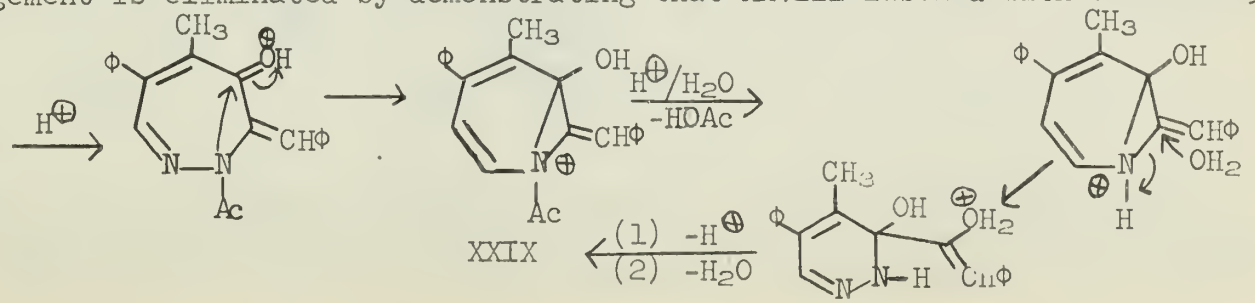


system (XXX).[26,27] It might be noted, however, that with the exception of a fused mono-nitrogen tropone (XXXII)[28,29] there is very little evidence of stabilization in these systems.[30-33] The carbinolamine (XXXI) could revert to the product by ring contraction by a pathway similar to the α-oxo alcohol rearrangement as shown above.[34] This rearrangement, although general for many different groups (alkyl, aryl, and hydrogen), has not been previously demonstrated for nitrogen. A further difficulty in this proposed mechanism is the mild conditions used for the amide hydrolysis of XXVIII. Another mechanism which could account for both the resulting product as well as the mild conditions can be pictured with initial protonation occurring at the C-4 carbonyl oxygen (7). A subsequent (4.1.0) intermediate could lead to the observed product. The possibility of C-5 --- N-2 rearrangement is eliminated by demonstrating that XXVIII labeled with C^{14} at C-3

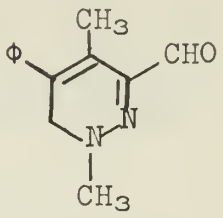


XXXII

(7)XXVII



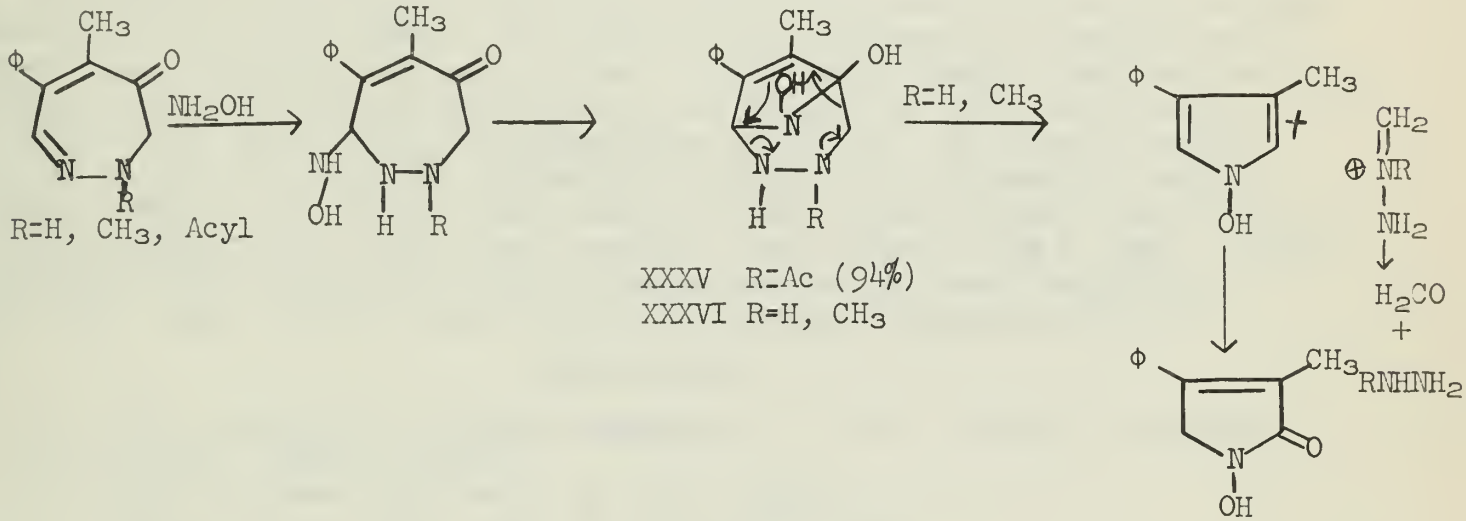
leads to XXIX with all of the C^{14} at the carbonyl carbon.[24] In a similar reaction VI gives XXXIII in 95% yield.[9]



XXXIII

While mixing semicarbazide with DPO or 2-methyl DPO (XII) leads to the expected semicarbazone,[10] mixing hydroxylamine and DPO or XII leads to a N-hydroxy-pyrrolone XXXIV. If there is an acyl group at the N-2 position a third product is obtained (XXXV). The postulation of attack at different positions of DPO by the two reagents seems to furnish the only explanation for the completely different reactions observed. It has been suggested by Moore that hydroxylamine attacks the C=N bond at C-7. Precedent for this attack is found in the cleavage of pyrrole with hydroxylamine to furnish succindialdoxime.[35] After initial attack transannular addition was postulated followed by ring opening and fragmentation to yield XXXIV (8). Fragmentation of XXXV might be effectively suppressed by an acyl substituent at N-2. While XXXV has not been conclusively shown to be the correct structure for

(8)



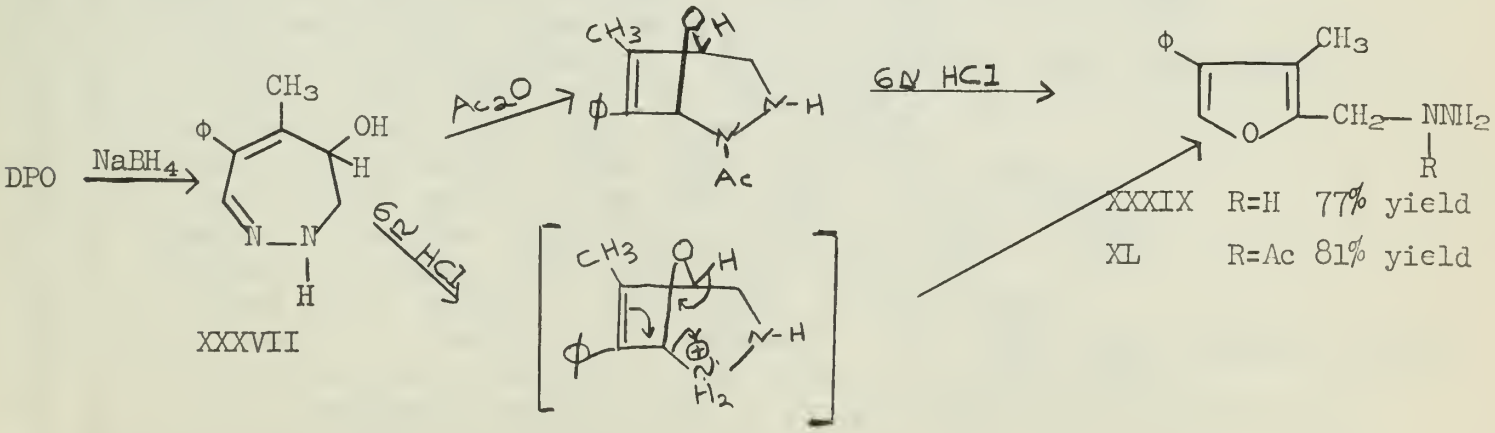
R=H, CH_3, Acyl

XXXV R=Ac (94%)
XXXVI R=H, CH_3

XXXIV (62%)

the acyl product, this probable structure fits into the general scheme. A similar transannular addition has been observed by Corey and Burke in the condensation of eucarvone with benzaldehyde.[19]

DPO can be reduced with sodium borohydride to give the diazepinol XXXVII in 68% yield.[36] Treatment of the diazepinol with acetic anhydride gives a bridged oxide (XXXVIII). Both the diazepinol and XXXVIII upon treatment with cold 6N hydrochloric acid are converted to the 3-methyl-4-phenyl-furfurylhydroazines XXXIX and XL respectfully. The similarity between structures such as XXXVIII



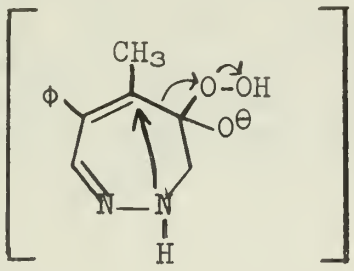
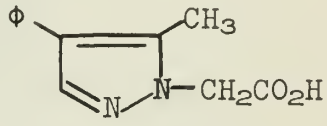
XXXVII

XXXIX R=H 77% yield
XL R=Ac 81% yield

and XXXVI tend to indicate a consistent pattern. In the case of DPO cleavage to the N-hydroxypyrrolones (8) a proton is not available at C-4 as in the diazepinol. The sequel to the C-4 ⟶ C-7 bridging is a fragmentation with complete

loss of the $-NH_2NRCH_2-$ bridge instead of the ring opening observed with XXXVII.

Oxidation of DPO with basic hydrogen peroxide gives 5-methyl-4-phenylpyrazole-1-acetic acid. (XLI).[37] This transformation has been formulated as an anionic Baeyer-Villiger oxidation with transannular participation of N-2 leading to fragmentation (9). This fragmentation is very similar to the base-induced cleavage of α-phenethyl t-butyl peroxide.[38]

(9) DPO $\xrightarrow[OH\ominus]{H_2O_2}$  $\longrightarrow$ 

XLI (50% yield)

CONCLUSION

Although the chemistry presented here is rather limited, there are several inferences which can be drawn. The potentialities presented by polyfunctional heterocyclic compounds with seven-membered and possibly larger rings can be seen. Although little mechanistic work has been carried out to date, DPO presents a possible tool in the study of transannular reactions. The diverse range of products encountered with DPO represents a multiplicity of specific reaction pathways. Nearly all of the ring contractions and valence isomerizations of DPO and its derivatives are very clean reactions with yields of 60% to 95%. However, extention of this chemistry to other systems has not yet been demonstrated. Finally DPO might provide a route into a heterocyclic tropone system.

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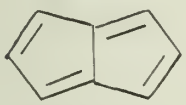
PENTALENE CHEMISTRY

Reported by Martin Dines April 18, 1966

INTRODUCTION

Nothing so much fascinates the organic chemist as the compound which consistently evades synthesis. And if the compound is ostensibly strain-free and simple in structure, the fascination increases. Such is the case with pentalene, first proposed as an interesting hypothetical model over fifty years ago, and sought ever since by numerous workers. This intense interest has attracted both theoretically and synthetically oriented chemists, and several reviews have been published prior to 1960 concerning both aspects of the involvement.[1,2,3]



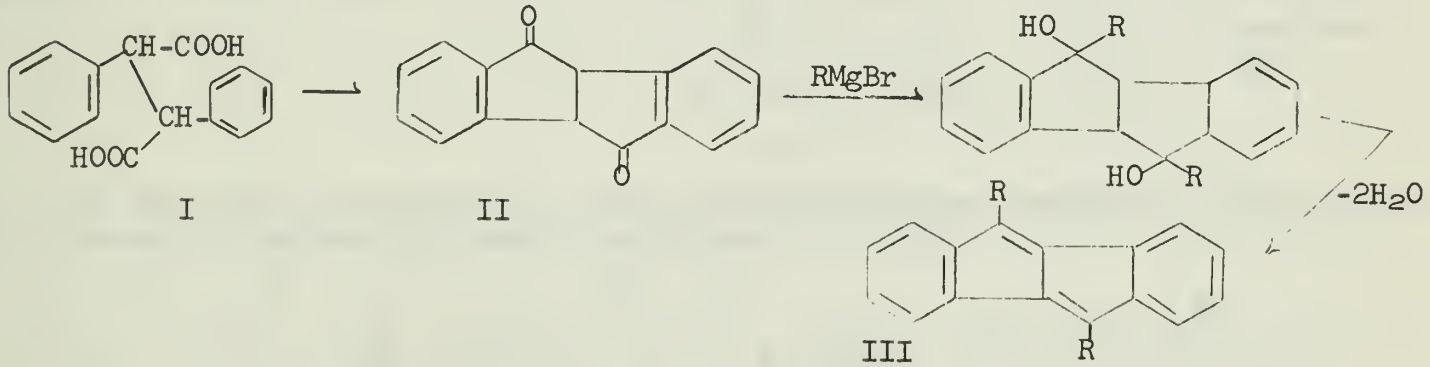
Pentalene

The purpose of this paper will be to review briefly past approaches and attempts toward parent pentalene and its derivatives, eventually bringing the reader up to date on the state of pentalene chemistry. Necessarily the theoretical questions of stability and structure will be discussed.

FUSED-RING PENTALENE DERIVATIVES

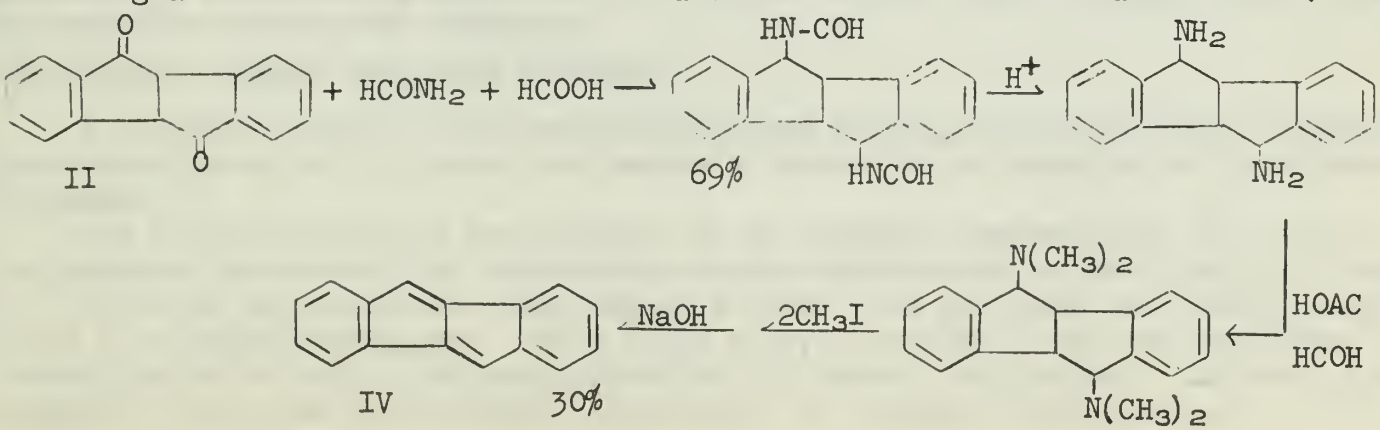
As is the case with most difficultly prepared (and even as yet unprepared) compounds, pentalene derivatives, especially those containing fused aromatic rings, are not hard to come by. The first was prepared and characterized by Brand ten years before Armit and Robinson first conjectured on the properties of the parent, which they named.[4]

Brand was able to prepare numerous 5,10-disubstituted dibenzopentalene derivatives, the first being the diphenyl derivative which he reported in 1912.[5] He treated the diketone formed from treatment of diphenylsuccinic acid with sulfuric acid with the appropriate Grignard reagent and subsequently dehydrated with acid.



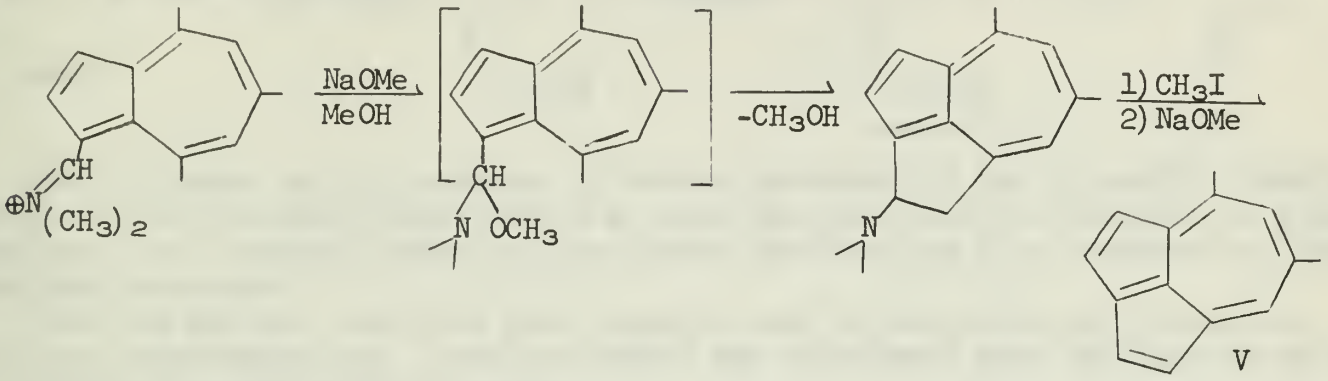
Brand never succeeded in preparing unsubstituted dibenzopentalene. Blood and Linstead first did so by brominating tetrahydrodibenzopentalene (prepared by a zinc amalgam and catalytic reduction of Brand's diketone II), then adding silver acetate.[6] An interesting observation mentioned in their article was that all attempts to dehydrogenate catalytically either dihydro- or tetrahydrodibenzopentalene failed.

Chuen and Fenton prepared dibenzopentalene six years after Blood and Linstead utilizing a Hofmann elimination of the diamine derived from the diketone II.[7] They

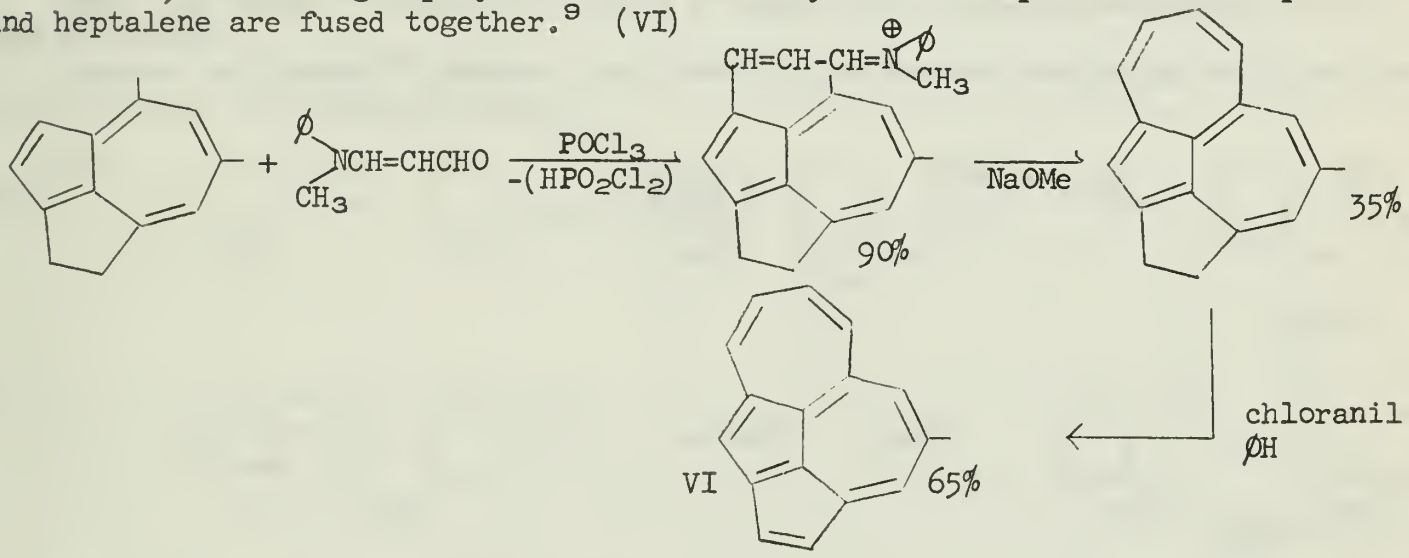


reported a tendency of dibenzopentalene to polymerize, an unexpected but common observation of pentalene workers.

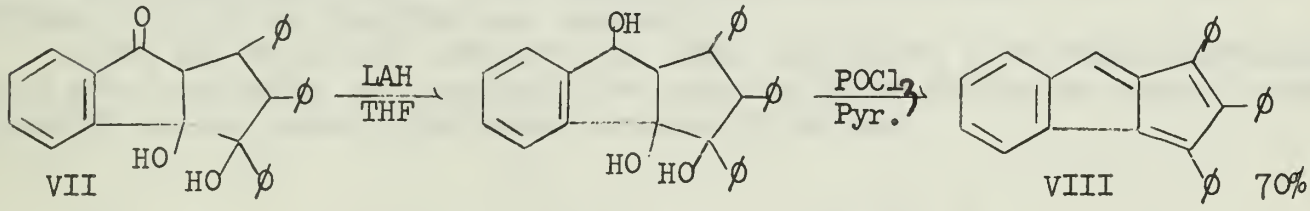
The first non-benzenoid fused-ring derivative was prepared by Hafner and Schneider a year later.[8] The synthesis involved formation of a cycloheptatriene fused ring derivative of pentalene from an azulene precursor.



Later, Hafner's group synthesized from dihydro-V a compound in which pentalene and heptalene are fused together.[9] (VI)



In 1962 LeGoff prepared the first monobenzopentalene derivative[10] from a keto-diol precursor reported by Ionescu and Popescu.[11] (VII)



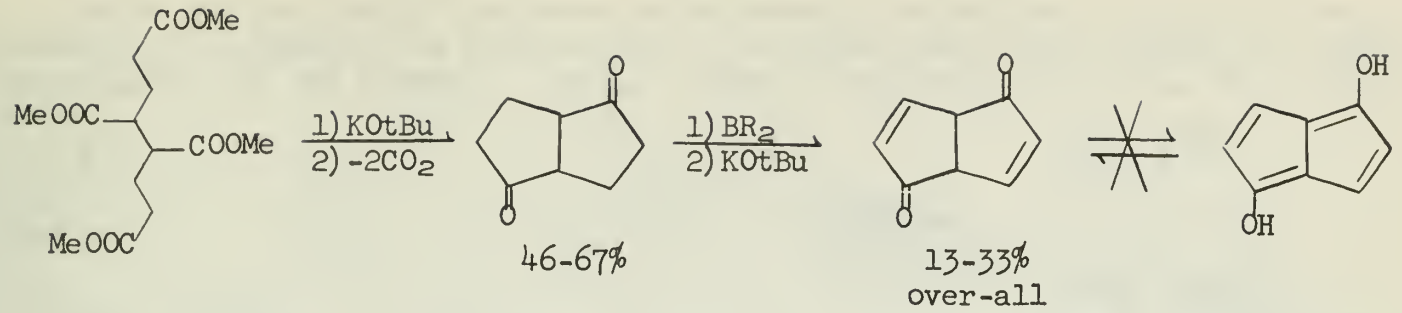
The n.m.r. of VIII consists of a multiplet at τ3.1 attributable to aromatic protons, and a singlet at τ3.75 due to a vinylic proton, the ratio being 19:1. It is air, heat, and acid stable, but readily reacts with weak nucleophiles, yielding products in which substitution has occurred across the open olefinic bond. Stronger nucleophiles destroy the compound.

UNSUCCESSFUL PARENT PENTALENE ATTEMPTS

A succinct example of the exasperation and futility which pentalene workers have encountered can be drawn from Dauben's report of the behavior of 1,4-diketo-pentalene.[12]

The diketo derivative was prepared by an internal condensation of 1,3,4,6-tetracarbomethoxyhexane and bromination-dehydrobromination of the bicyclic diketone.

Under no circumstances could Dauben's group coax the dione to enolize, and yield 1,4-dihydroxypentalene. They tried every conceivable type of base, from triethylamine to sodium triphenylcarbanide, to induce enolization. In every case reported, either an irreversible condensation or decomposition occurred.

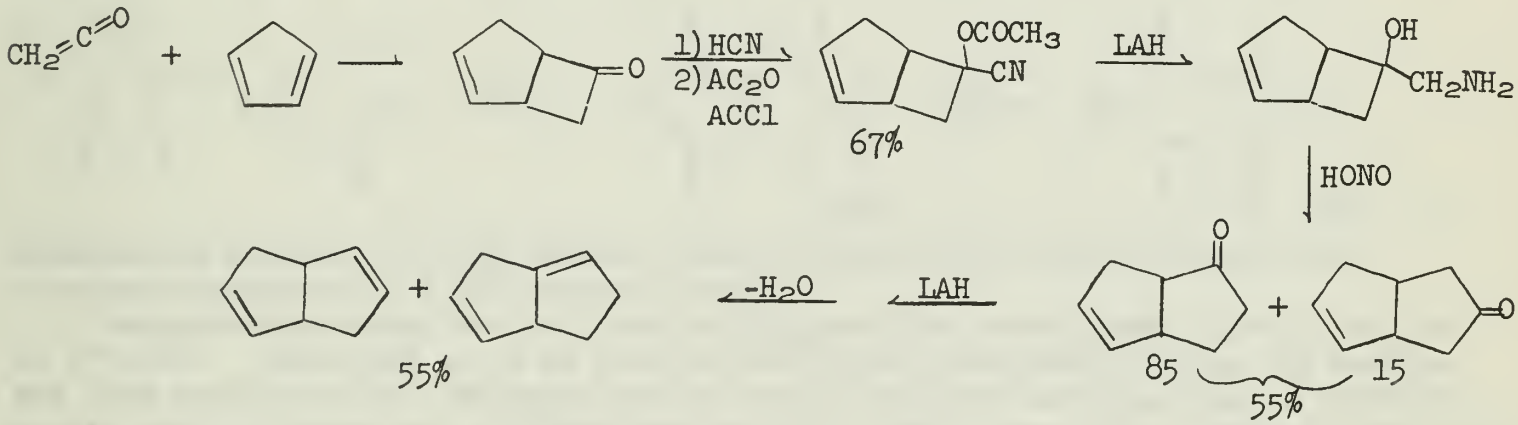


Every attempt at the synthesis of parent pentalene in the literature involves either a catalytic dehydrogenation of a pentalane (bicyclo[3,3,0]octane) or a hydropentalene, or a chemical means of introducing unsaturation in a pentalane or hydropentalene precursor.

Linstead and his coworkers have reported most of the early work involving catalytic dehydrogenation. Both platinum[13] and selenium[14] were utilized in attempts on cis-bicyclooctane with no success.

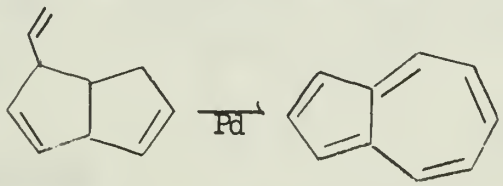
Mayer and Triebs[15] reported similar attempts with hexahydropentalene, also with no success.

Roberts and Gorham[16] prepared two tetrahydropentalenes beginning with the product of ketene and cyclopentadiene.



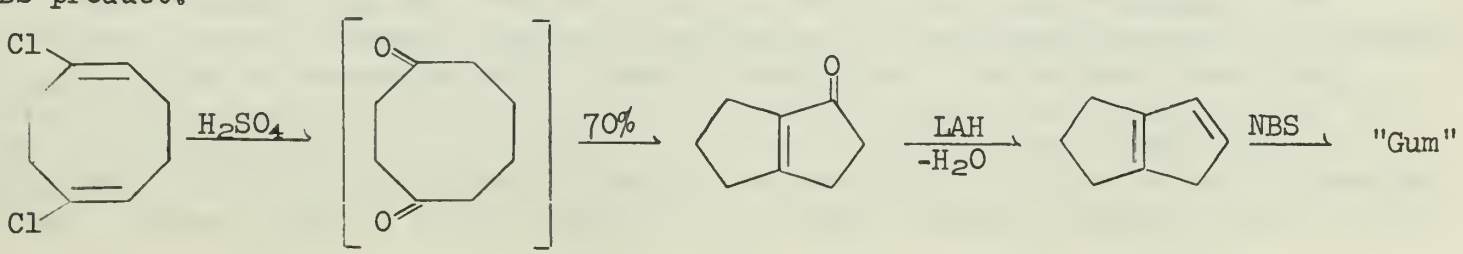
The two isomeric tetrahydropentalenes obtained were subjected to platinized asbestos, platinized carbon, and halogenation-dehydrohalogenation -- all of which failed to yield any identifiable products.

Gates and Malchick[17] prepared the vinyl derivative of tetrahydropentalene and upon dehydrogenation over pallidinized asbestos or palladium on charcoal could identify in the product only small amounts of azulene.

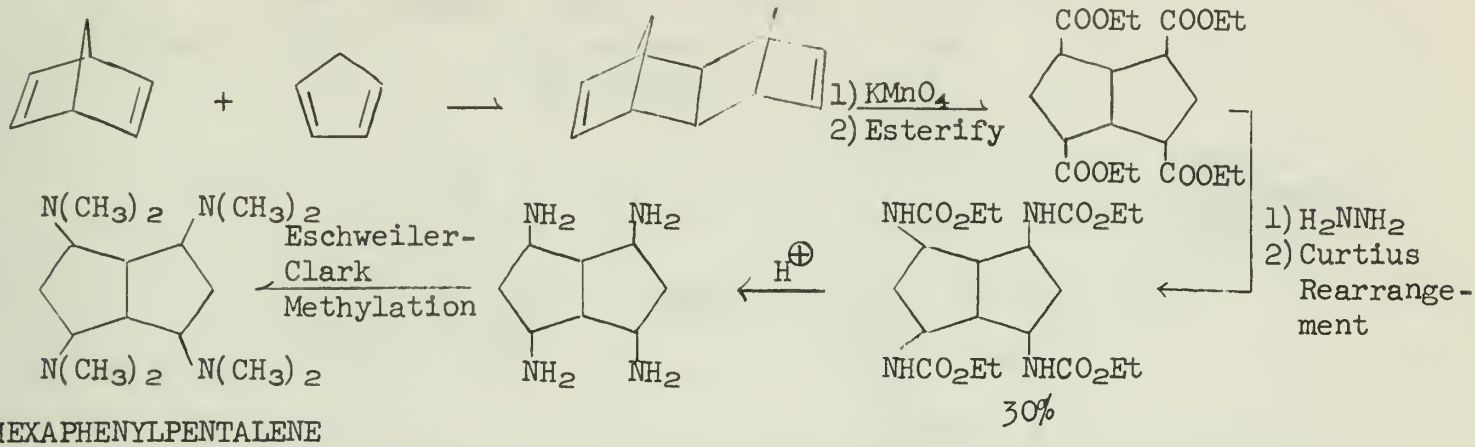


The chemical means of introducing unsaturation into the saturated or partially saturated bicyclooctane system have either been halogenation-dehydrohalogenation, or Cope-Hofmann type eliminations of the appropriate amine precursor.

Cope and Schmitz[18] prepared a third tetrahydropentalene isomer from cyclooctadienedichloride, and were left with only what they termed "polymers" from the NBS product.

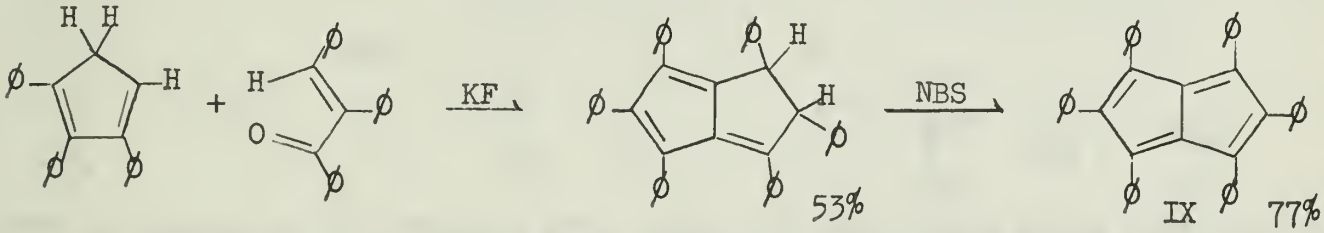


Hanna and his group[19] prepared the tetraamino derivative of pentalane and attempted to eliminate its amine-oxide in the traditional Cope fashion, but found only polymers in the product. Similar Hofmann eliminations were also to no avail.



HEXAPHENYLPENTALENE

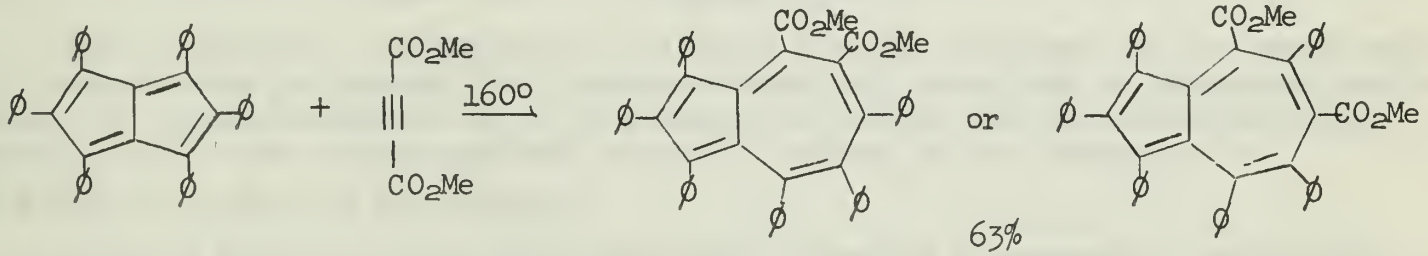
The closest any researcher has yet to come toward synthesis of pentalene has been LeGoff's preparation of hexaphenylpentalene (IX), reported in 1962.[20] 1,2,3-triphenylcyclopentadiene and 1,2,3-triphenylpropenone were condensed using potassium fluoride as a weak base (in accord with a Micheal-Knoevenagel sequence). NBS



bromination followed by a spontaneous loss of HBr in CCl_4 led to formation of hexaphenylpentalene in a 41% over-all yield.

Hexaphenylpentalene was isolated as air-sensitive brown-green crystals melting at 273-276°. Solutions of it as well as its dihydro precursor in CCl_4 and bromine are deep green in color, antimony pentachloride solutions are deep blue. Trifluoroacetic acid solutions are a fluorescent red, but other hydroxylic solvents immediately destroy the colors.

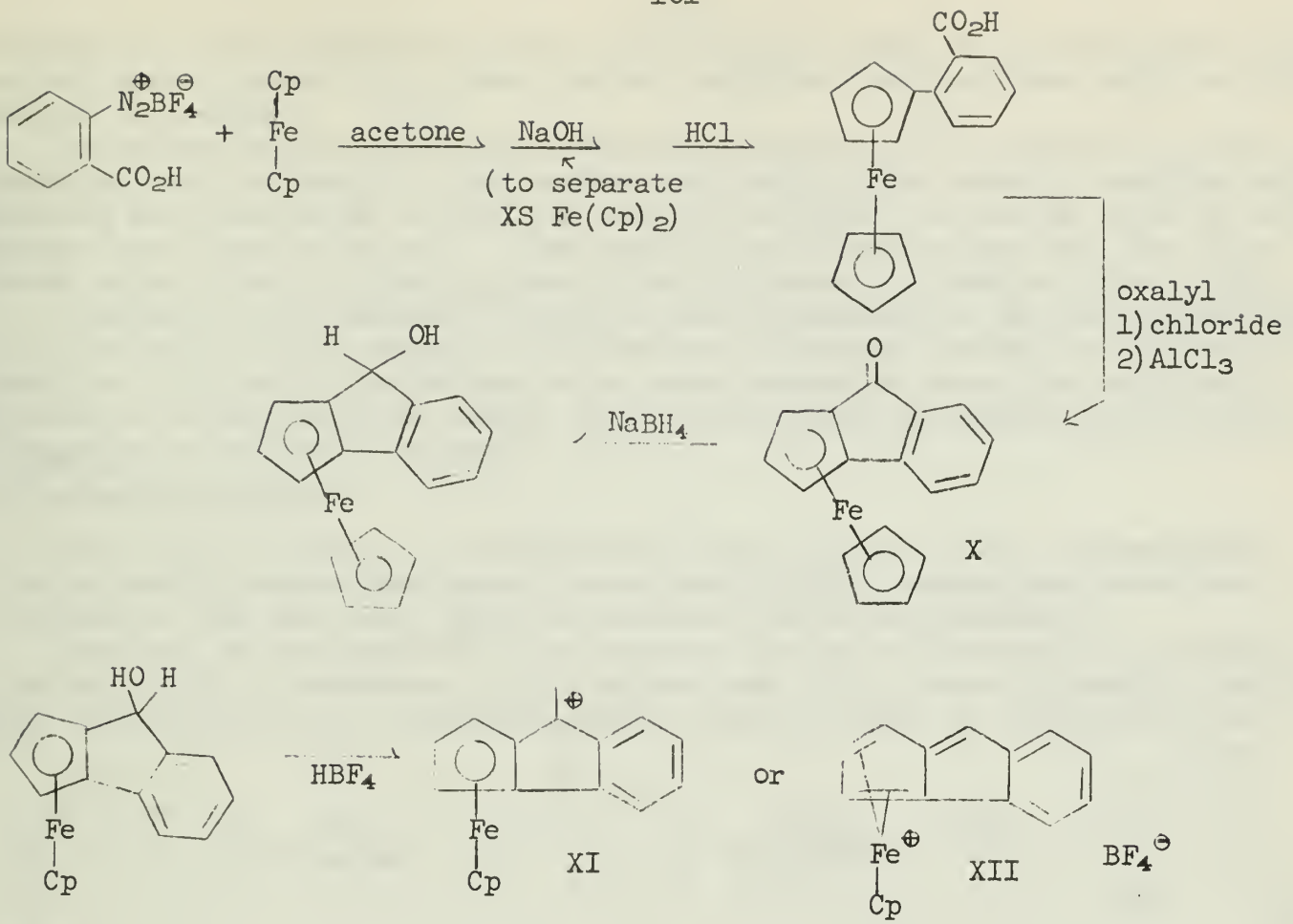
Hexaphenylpentalene undergoes an interesting Diels-Alder addition with dimethylacetylene dicarboxylate yielding an azulene derivative.



AN INORGANIC APPROACH TO PENTALENE

Recently, an entirely different approach to benzopentalene (and hopefully eventually to pentalene) has appeared in the literature. Comparing the pentalene problem to that of cyclobutadiene, Cais, Modiano, and Raveh decided to attempt a benzopentalene synthesis in a manner analogous to that of Pettit--that is, via the ferrocene derivative.[21]

Ferrocoindone (X) was prepared from the orthobenzoic acid derivative of ferrocene, which is formed from the diazonium salt of anthranilic acid and ferrocene. X was reduced to ferrocoindinol by sodium borohydride. The alcohol resulting solvolized in tertrafluoroboric acid to a green salt which analyzed as either XI or XII. Broadened signals in the n.m.r. spectrum of the green salt indicated the presence of a strong paramagnetic species, suggesting XII is the correct representation. However magnetic moment studies of the green salt were inconsistent with XII,



instead suggesting the presence of a dimer XIV which might arise from radicals XIII. XIII could conceivably arise from an internal oxidation-reduction of XI.

Mass spectrometry subsequently verified a dimeric structure for the green salt. The authors hope to surmount the problem of this salt's ability to internally reduce itself by either turning to Os or Ru analogs, or placing an electron-withdrawing substituent on the cyclopentadienyl ring not involved in the reactions.

THEORETICAL ASPECTS OF THE PROBLEM

Two main points concern those theoretical chemists attempting to explain the apparent maverick behavior of pentalene. The first pertains to the possible existence of large ring strains which prohibit its easy procurement, the second invokes a molecular-orbital-derived "destabilization energy".

Superficial inspection of models of pentalene will convince one that there is little or no strain above that present in any bicyclooctane system (which are relatively easily formed). A simple Dauben treatment of the pentalene ring system leads to a value of 0 strain energy.[22]

Many papers are in the literature in which pentalene is treated according to all of the known and accepted molecular-orbital and valence-bond methods.[23-28]

One of the most simple (yet harmonious with the more sophisticated) treatments was that of R. D. Brown[29] who employed a simple Hückel LCAO-MO approximation. Assuming D_{2h} symmetry, Brown calculated a resonance energy (DE_π) of 2.456β, or 37 kcal/mole. He suggested that pentalene would be "reasonably stable" (more so than fulvene, for example) yet very reactive chemically. It should undergo reactions of

substitution (like aromatics) rather then addition, based on the calculation that no bond orders exceed 1.7. Brown further predicted that pentalene would be colored, similar to azulene.

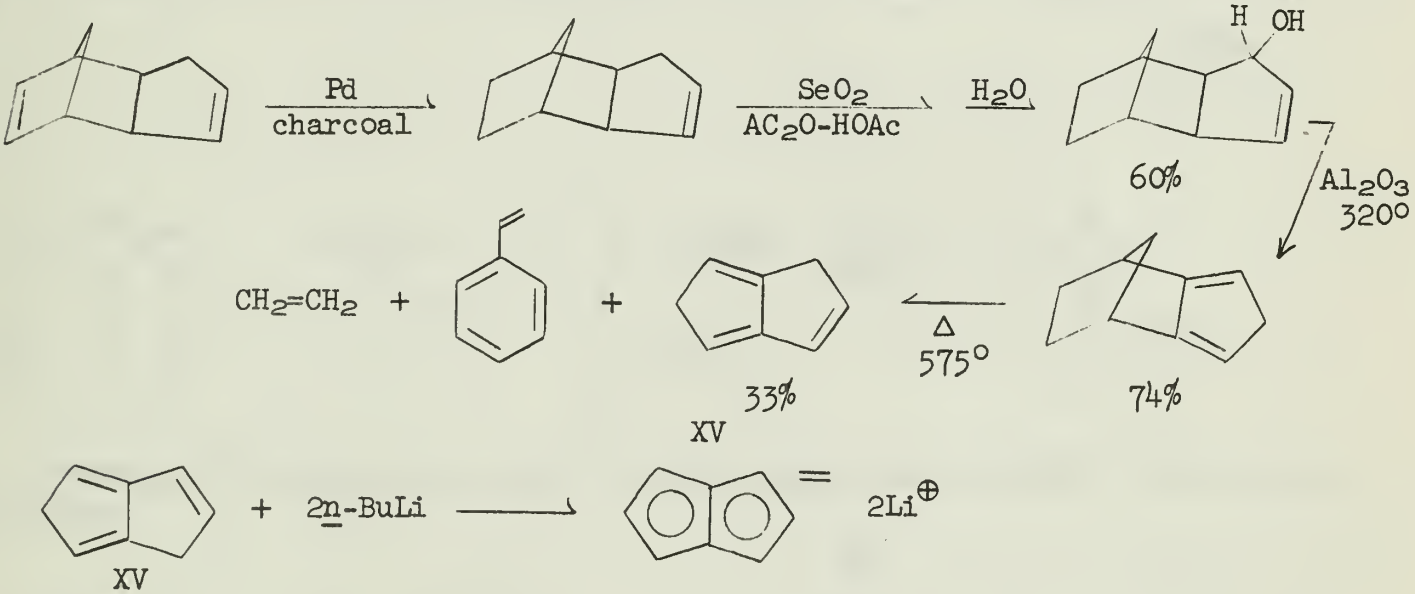
A more up-to-date and refined theoretical approach was carried out by den Boer-Veenendaal and den Boer.[30] They went a step further than Brown by carrying out an extended HMO calculation on both D_{2h} and C_{2h} pentalene (the latter being an alternating double bond structure). They conclude with little doubt that the lower energy ground state belongs to the C_{2h} model, the difference in energies being 0.322β.

Prominent in its absence from any of the discussions in the theoretical papers is the question of the source of the necessarily present destabilization energy of pentalene. For while the authors argue among themselves about the magnitude or presence of a stabilization energy, none has mentioned the possibility or source of a negative stabilization energy.

THE PENTALENE DIANION

One point on which all theoreticians seem to agree is that the pentalene dianion should possess considerably more stabilization energy than pentalene, since it satisfies the $4N+2$ rule, being isoelectronic with decapentaene.[31]

Katz and Rosenberger[32,33] first reported synthesis of dilithium pentadienyl dianion in 1962 by treatment of dihydropentalene with 2 moles of n-butyl lithium in THF. They prepared their dihydropentalene from the dimer of cyclopentadiene. The



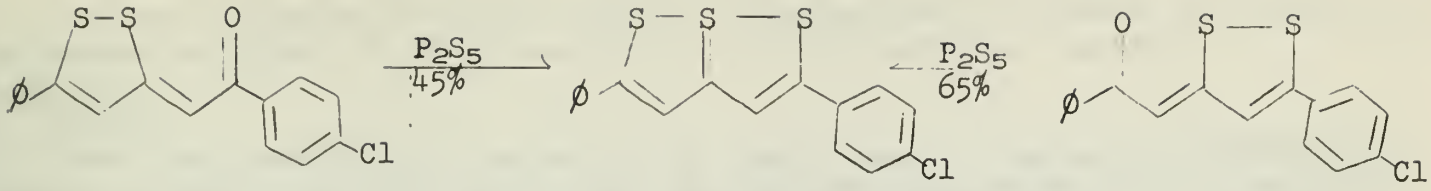
salt falls out as white crystals from pentane, and forms stable solutions in THF. The n.m.r. spectrum in THF shows a triplet at $\tau 4.27$ and a doublet at $\tau 5.02$. The splitting constant is 3.0 cps and the ratio of areas of the two multiplets is exactly 1:2.

The relative stability and ease of formation of the pentalene dianion seems to suggest that the instability of the parent compound is derived from electronic rather than ring-strain sources, as was surmised in the previous section.

HETEROCYCLIC PENTALENES

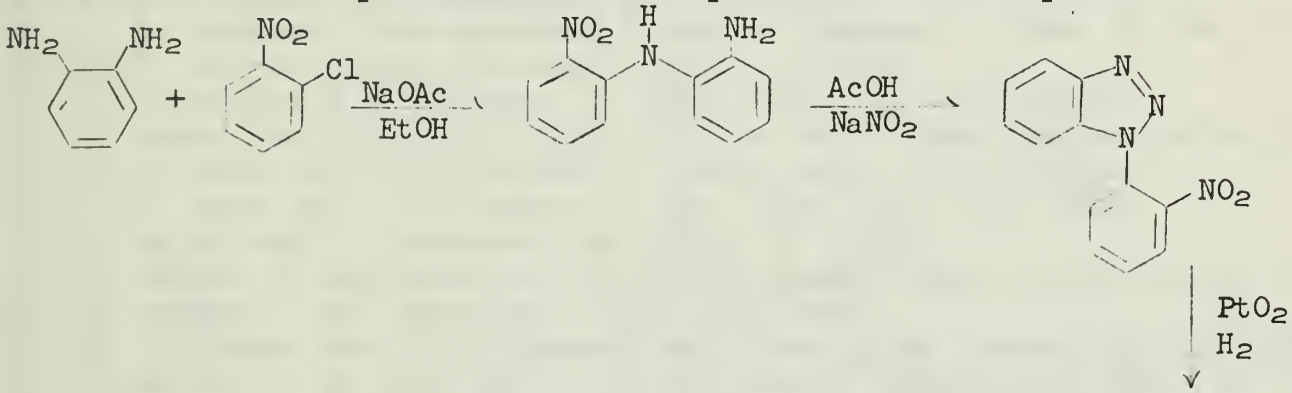
The relevance of heterocyclic pentalenes in this paper is analogous to that of the pentalene dianion. Like the pentalene dianion, heterocyclic pentalenes always contain an aromatic decet. And like the pentalene dianion, heterocyclic derivatives may serve as useful models for the study of possible ring-strain and electronic contributions to pentalene itself.

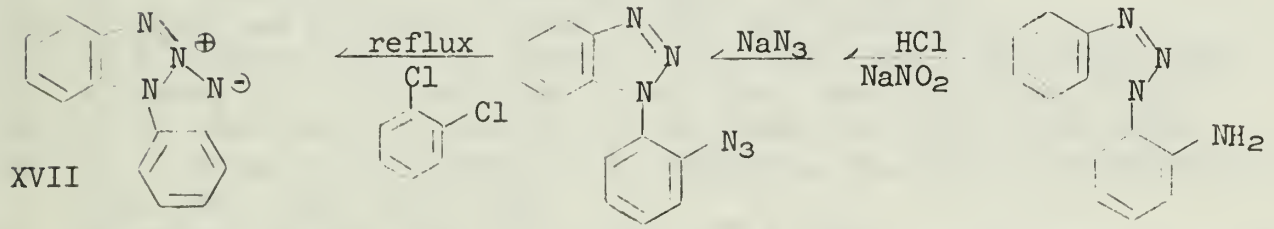
Both sulfur and nitrogen heterocycles have been reported. Pfister-Guillonzo and Lozac'h[34] have published the preparation of a trithio diarylpentalene. By treating either (phenyl-5 dithiole-1,2 ylidene-3)p-chloroacetophenone or (p-chlorophenyl-5 dithiole-1,2 ylidene-3) acetophenone with P_2S_5 (P_4S_{10}) they obtained the heterocycle 6aS IV-trithia-1,6,6a pentalene (XVI). If the central sulfur atom



contributes one pi electron to the pi system of the molecule, and the other two contribute two apiece, then, as with the pentalene dianion, ten pi electrons are present to satisfy the Hückel rule.

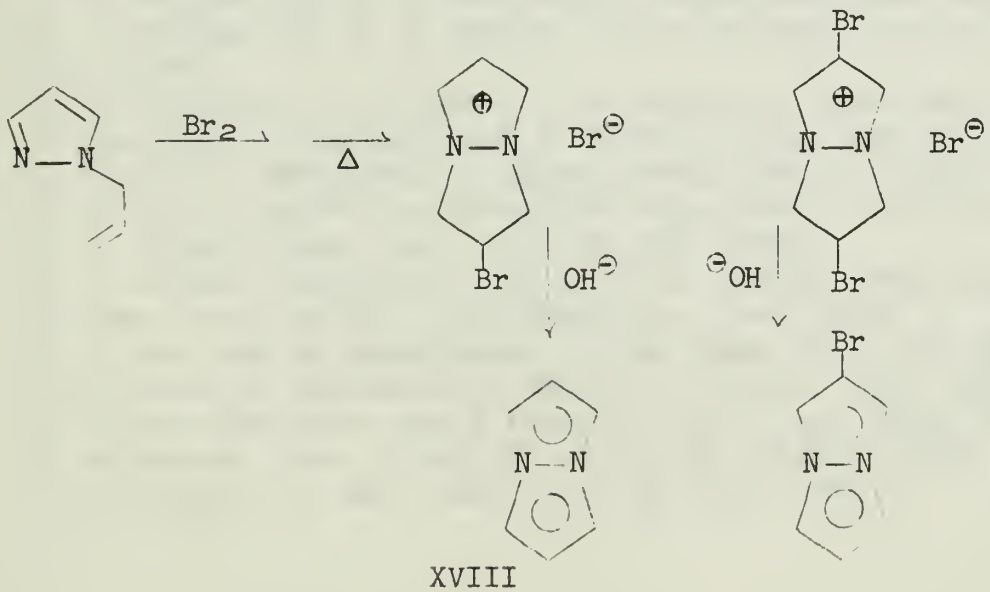
Both Trofimenko and Carboni of DuPont have published reports of nitrogen heterocycles of pentalene. Carboni[35] synthesized a dibenzo-tetraazapentalene (XVII) in a rather involved process which was reported as a DuPont patent.





XVII

Trofimenko[36] prepared the parent 3a,6a-diazapentalene (XVIII) from 1-allyl-pyrazoline.



XVIII

Diazapentalene exists as colorless crystals which immediately decompose in air, but are otherwise relatively stable. In accord with the other two heterocyclic pentalenes mentioned, it is isoelectronic with the pentalene dianion.

CONCLUSION

Pentalene remains today as one of the most simple of the as yet unsynthesized molecules. There is little doubt that its synthesis will eventually be realized, yet the enigma of its inherent stubbornness to exist appears to be the central problem to the modern pentalene chemist. Far more will be gained when we discover the source of the instability of pentalene than when we eventually trap and characterize it.

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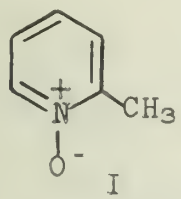
MECHANISTIC STUDIES OF THE REACTION OF 2-PICOLINE N-OXIDE WITH ACETIC ANHYDRIDE

Reported by James T. Lee, Jr. April 21, 1966

Reactions of heterocyclic amine oxides and acid anhydrides are of practical and theoretical interest.[1-3] Efforts to discern the mechanisms of these reactions have been directed to several picoline N-oxides. In this seminar attention is centered on the reaction of 2-picoline N-oxide and acetic anhydride. Analogous reactions in several other heterocyclic systems are considered where appropriate.

Treatment of 2-picoline N-oxide (I) with equimolar or excess acetic anhydride for 5 minutes to 1 hour at 140° gives in 70 to 90 per cent yield a mixture of isomeric esters whose major component is 2-pyridylmethyl acetate (II); 3-acetoxy-2-picoline (III) and 5-acetoxy-2-picoline (IV) are formed in smaller amounts. The identity and relative yields of these esters have been established by classical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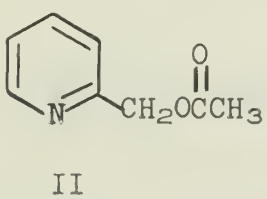
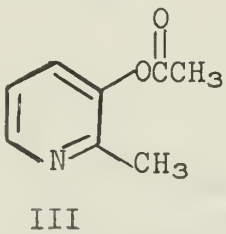
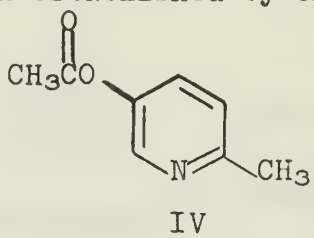
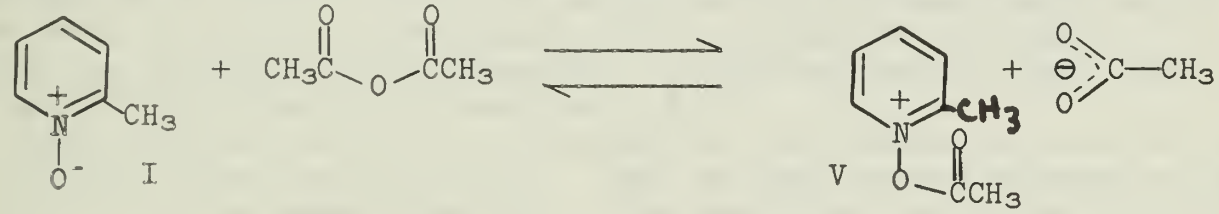

II


III

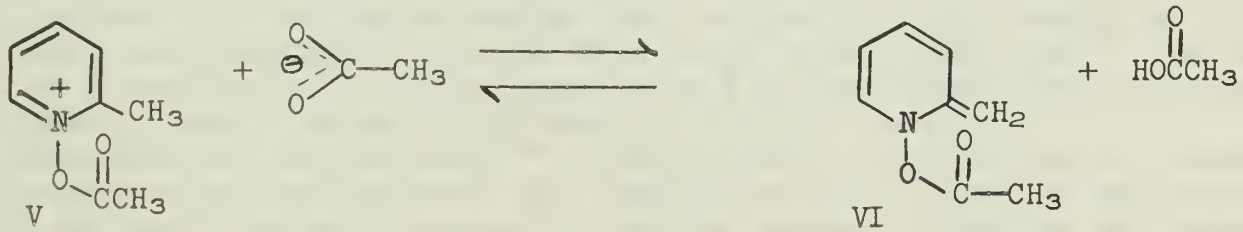

IV

chemical[4] and physical[12,13] methods. Many workers[5-9] have considered II the sole ester product. Other products of the reaction are carbon dioxide, 2-picoline, methane, acetic acid and methyl acetate. It has been reported that little change in rate[10] or product yield[5,11] is observed when the reaction is conducted in a variety of solvents. A complete material balance has never been obtained.

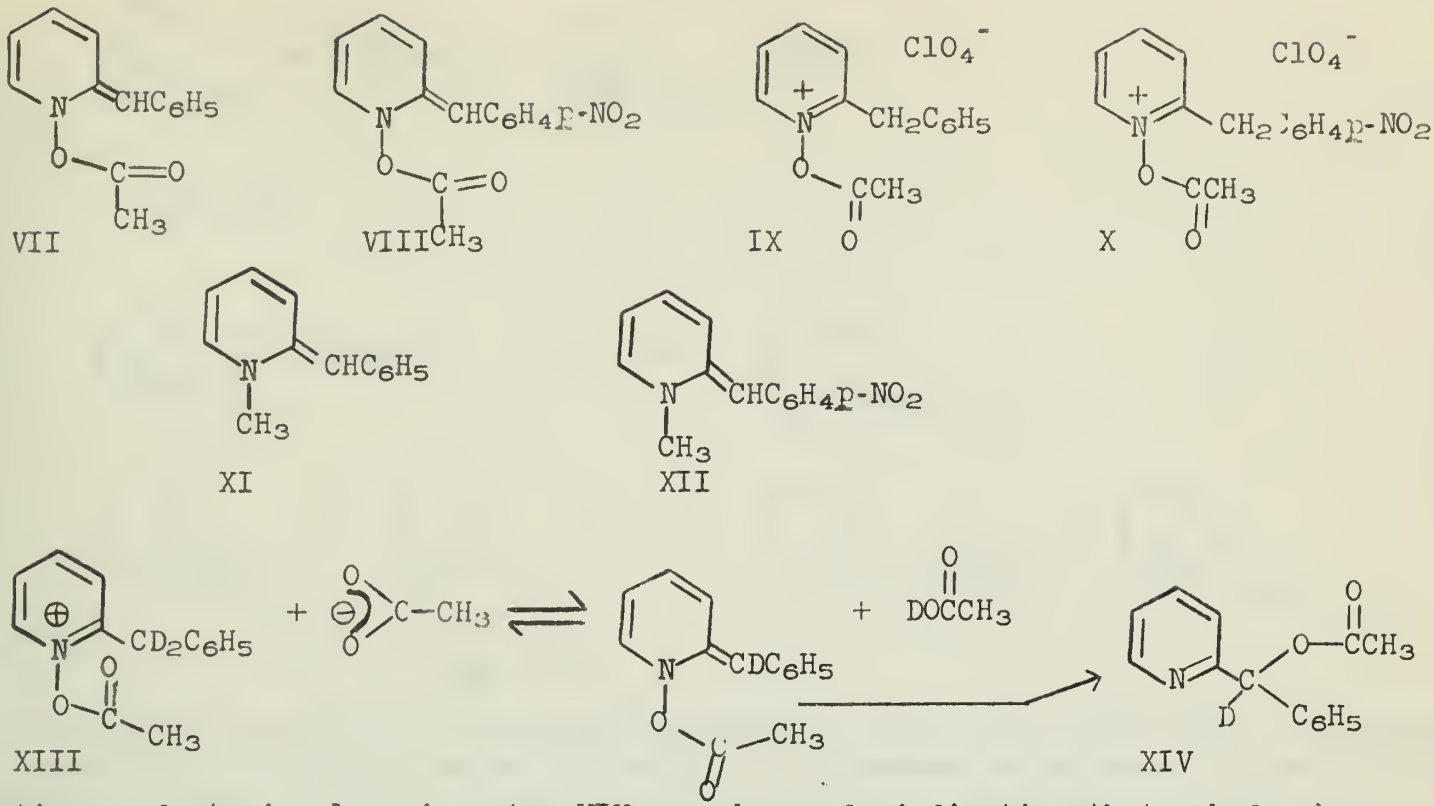
The reasonable postulate of nucleophilic attack of I on acetic anhydride to form N-acetoxy-2-picolinium ion (V) and acetate ion is included in most mechanisms proposed for the reaction. Evidence of this initial step has been obtained in the


I V

quinoline system. Muth and Darlak showed that the quinolinium ion analogous to V is an acceptable intermediate in the conversion of 2-methylquinoline N-oxide to the ester analogous to II. It was concluded by these workers that the formation of the quinolinium ion is reversible.[14] Traynelis has suggested that I is converted to V in a similar fashion.[15] Stable picrate[16] and perchlorate[14] salts of V have been isolated from the reaction mixture, characterized, and shown to lead rapidly to II upon treatment with acetate ion and other bases. It has not been established that III and IV arise similarly.


V VI

The role of acetate ion in the above is believed to be deprotonation of V to form anhydrobase intermediate VI which isomerizes to the esters. **Nevertheless, there is no direct evidence for the existence of VI. Attempts to detect intermediates VII** and VIII in the reactions of salts IX and X with triethylamine in acetonitrile proved unsuccessful.[15] Model compounds in this investigation were classical anhydrobases XI and XII. When the perchlorate of XIII was treated with sodium acetate in the presence of acetic acid and acetonitrile under conditions of 50 per cent

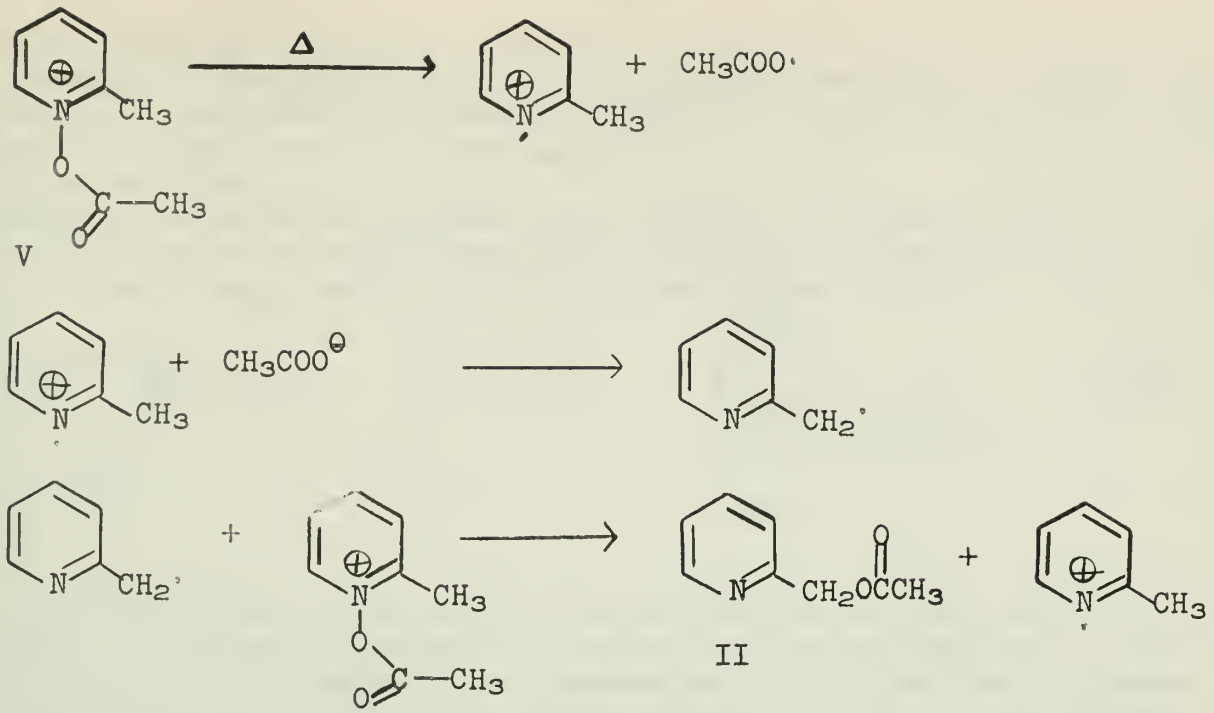


reaction no deuterium loss in ester XIV was observed, indicating that anhydro base intermediate does not revert to XIII under the conditions of the experiment.[15] Muth and Darlak suggested that reaction of N-acetoxy-2-methylquinolinium ion with acetate ion to form acetic anhydride and amine oxide is more rapid than the conversion of the cation to ester.[14] Reaction of N-acetoxy(carbonyl C^{14})-2-methylquinolinium perchlorate with sodium acetate in acetic anhydride produced ester in 71 per cent yield with 25 per cent retention of label. An initial rapid equilibration of amine oxide and cation is consistent with the postulated occurrence of the rate-determining step after cation formation. A thorough kinetic study should be made to test this postulate in the reaction of I.

When the perchlorate of V is treated with triethylamine in acetonitrile II is reportedly formed in low yield.[16] When the reaction is conducted at high dilution the yield of II increases three-fold. This result was interpreted as an indication that VI forms and is partitioned between isomerization to II and an unknown side reaction which is apparently at least bimolecular.[16] VI has been postulated in the reaction of acetyl chloride and I.[17]

The intermediacy of VI is a generally accepted postulate[5,6,7,9,11,12,14,15,16,20] in view of the possible mechanisms of conversion of V to II, III, and IV. In a direct conversion, concerted removal of a proton, rupture of the N-O bond, and recombination of fragments to form esters would involve extensive bond reorganization in the transition state. Intervention of VI appears to be reasonable.[15] Cohen and Fager reached this conclusion, noting that reaction of I with acetic anhydride was more rapid than reaction of pyridine N-oxide and acetic anhydride.[20] Oae suggested that the production of II in the reaction of I and substituted phenyl acetates[16] unequivocally demonstrated the presence of VI in the reaction.[5]

Shortly after the discovery[7-9] of the 2-picoline N-oxide reaction Boekelheide and Harrington obtained evidence that free radicals are formed in the reaction.[11] When I and acetic anhydride reacted in boiling benzene solvent in the presence of styrene, polymerization of the styrene occurred. Control experiments verified that radical initiators are present in the reaction. A radical chain mechanism for the formation of II was postulated. The observation of an induction period followed by an exothermic reaction, the apparent insensitivity of reaction rate to solvent polarity, and the fact that the dimethylaniline N-oxide-acetic anhydride reaction mixture initiates styrene polymerization were cited as support for the mechanism. However, none of these facts requires that the reaction occur by a radical chain mechanism.



V

II

Traynelis and Martello confirmed that radicals form in the reaction.[6] Treatment of I with acetic anhydride and acetic acid in the presence of styrene resulted in the formation of polystyrene in 60 per cent yield. Control experiments established that the initiating species is not I or acetic anhydride. It was further shown that styrene polymerization can be initiated under reaction conditions using benzoyl peroxide as initiator and that this polymerization is inhibited by p-benzoquinone. When the reaction of I and acetic anhydride was conducted in the presence of inhibitors and styrene the results in Table I were obtained. These results were interpreted as

Table I

The Effects of Inhibitors on Ester and Polystyrene Yields

Product	Per Cent Yield		
	No Inhibitor	5% p-Benzoquinone[a]	10% m-Dinitrobenzene[a]
Polystyrene	60	11	0
Styrene	15	83	89
II[b]	75	70	61

[a] Per cent, by weight, of I

[b] III and IV not separated from II

evidence that ester is not formed in a radical chain reaction. With varying levels of m-dinitrobenzene the results in Table II were obtained. The decrease in methane yield and invariance of ester yield with increasing inhibitor level were interpreted

Table II

Effect of Varying Inhibitor Level on Product Yields

Product	Per Cent Yield			
	No Inhibitor	2.2% m-DNB[a]	10% m-DNB[a]	20% m-DNB[a]
CH_4	0.93	0.59	0.40	0.31
CO_2	2.53	2.39	2.37	2.42
$CH_3CO_2CH_3$	0.16	0.26	0.25	0.98
II[b]	87	88	88	87

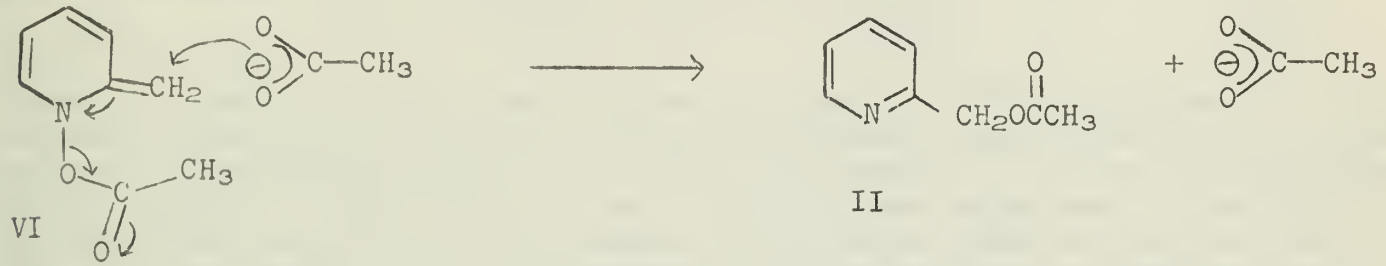
[a] Per cent, m-dinitrobenzene by weight, of I

[b] III and IV not separated from II

as evidence that two reactions occur, one giving rise to radicals and a major, non-radical path leading to II.[6] These results do not demand that radicals arise in a step other than the product-determining step.

Several modes of conversion of VI to II, III, and IV come under consideration if the presence of free radicals and radical-derived products are ascribed to a minor reaction. The question of how VI isomerizes to II, III, and IV is controversial and a variety of approaches has been employed in attempts to understand the final steps of the reaction.

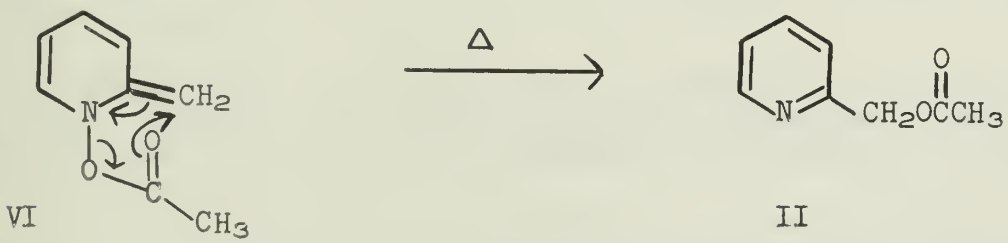
An addition-elimination sequence was suggested as a possibility by Oae[5] and Traynelis.[6] Attack of external acetate at the methylene group of VI with displacement of acetate from nitrogen leads to II in this mechanism. Attack at the 3- or 5-



VI II

positions of the pyridine ring followed by tautomerization would afford III or IV, respectively. Although the formation of esters can be rationalized by this mechanism evidence supporting an intramolecular rearrangement of VI has been reported. Traynelis and Martello found that reaction of I with butyric anhydride in the presence of sodium acetate produced only 2-pyridylmethyl butyrate in 69 per cent yield. I reacts with butyric anhydride under the same conditions to form this ester in 64 per cent yield. Negligible butyric anhydride--sodium acetate interchange[19] was assumed. It was concluded that the addition-elimination mechanism is not an acceptable postulate.[6] Oae suggested that sodium acetate may not dissociate in butyric anhydride to an extent allowing competition with butyrate ion.[5] However, Traynelis and his coworkers found that several phenyl acetates react with I in boiling xylene to form, among other products, II. In several cases where excellent material balances were obtained no aryl ethers were formed; intermolecular attack of acetate on I was thus abandoned as a possibility. Muth and Darlak found that treatment of N-acetoxy-2-methylquinolinium perchlorate with potassium cyanide in acetonitrile afforded 2-quinolymethyl acetate in 90 per cent yield. No nitrile was isolated.[14]

Concerted rearrangement of VI to form II was proposed by several workers[7,8] by analogy with Pachter's similar postulate in the reaction of quinaldine N-oxide with benzoyl chloride.[18] The postulate is reasonable in view of the favorable geometry



VI II

of VI and the precedents for such processes, but requires that III and IV arise in some other fashion.

If a cage effect is postulated, the presence of radicals in the reaction is rationalized by a mechanism in which II, III, and IV form by a radical-producing reaction. Such a postulate would accommodate the insensitivity of ester yield to radical inhibitor while avoiding the otherwise necessary multiple mechanisms which must be considered if radicals are viewed as arising in a minor reaction. Oae, Kitao, and Kitaoka presented arguments against the concerted rearrangement and the addition-elimination process and suggested instead a radical pair mechanism.[5]

When 0.08 mole of I and 0.10 mole of acetic anhydride equally enriched at each oxygen atom with O^{18} reacted II was obtained in 67 per cent yield. Isotopic analysis of the ester and the alcohol derived from it by basic hydrolysis gave the results in Table III. Control experiments establishing the isotopic stability of the ester under reaction conditions and hydrolysis conditions were reported. Unfortunately a crucial control experiment was omitted. It was not shown that I recovered after partial

Table III

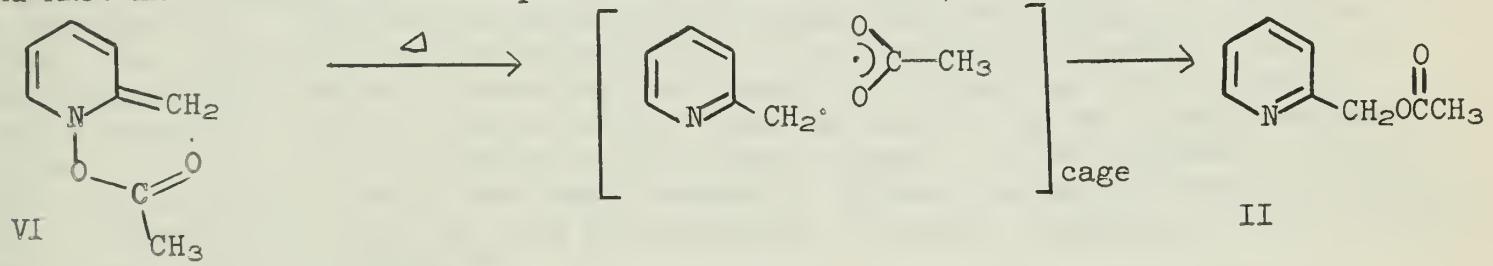
O^{18} Label Experiments of Oae, et al.

Compound	Observed Atom % O^{18}	Theoretical Atom % O^{18} Concerted Cyclic	Theoretical Atom % O^{18} Addition-Elimination
I	0.210	-----	-----
Acetic Anhydride	0.782	-----	-----
II	0.498	0.500	0.660
2-pyridylcarbinol	0.477	0.782	0.660

reaction contained no more than a natural abundance of O^{18} (0.210 atom %). Furthermore, III and IV were not separated from II before isotopic analysis and thus the value recorded in Table III for "II" is actually the average O^{18} content in the mixture of II, III, and IV. On the basis of the results of these experiments, the radical-pair mechanism was suggested for the formation of II; this mechanism requires that both "II" and the alcohol contain the average of one natural and one enriched oxygen atom or 0.496 atom % O^{18}.

The O^{18} content reported for the alcohol may be more meaningful than that of the esters since there is the possibility that alcohols from III and IV are lost during work-up of the hydrolysis mixture. Ford and Swan hydrolyzed the ester mixture under the conditions reported by Oae and his colleagues and apparently obtained only 2-pyridylcarbinol.[12] They concluded that Oae's failure to separate the three esters cannot affect the conclusion that the intramolecular cyclic and addition-elimination processes are ruled out since this conclusion is based on the O^{18} content of the alcohol alone. If there is equilibration of label in the acetoxy group in any manner other than that specified by the radical-pair mechanism the O^{18} content of the alcohol is also obviously inconclusive.

The radical pair mechanism, originally suggested as a possibility by Traynelis and Martello[6] accommodates the products of the reaction, the polymerization of styrene



by escaped radicals, and the apparent insensitivity of product yield to solvent polarity. Further, Oae, Kitao, and Kitaoka found that reaction of equally labelled acetic anhydride with I in chlorobenzene, nitrobenzene, or xylene gave the same O^{18} concentration in "II".[21]

The possibility of heterolysis of VI to form an ion pair which efficiently collapses to products is also consistent with available data.[6,12,20] Evidence supporting this alternative has been obtained from experiments with substituted acetic anhydrides. Cohen and Fager noted the instability of acetoxy radical[22] and reasoned that reaction of I and phenylacetic anhydride might serve as a test of the radical pair mechanism. Since phenylacetoxy radical is much less stable than acetoxy radical,[22,23] it was expected that no ester products should be formed. In a large scale isolation experiment equimolar I and phenylacetic anhydride reacted in boiling benzene to form trace amounts of toluene and an unidentified pyridinol (after work-up) in addition to the products listed in Table V. The formation of benzaldehyde, DPMA, and large quantities of 2-picoline was ascribed to oxidation-reduction reactions[24,25] involving I and phenylacetic anhydride. It is reported that I undergoes these reactions to a minor extent.[27] Evidence that process (A) occurs was found in the ratio of CO_2 yield to benzylpicolines yield, which greatly exceeds unity. The importance of this reaction was estimated by subtraction of the benzylpicolines

(A) $2C_6H_7NO + (\phi CH_2CO)_2O \longrightarrow \phi CH_2COOH + \phi CH{=}O + CO_2 + 2C_6H_7N$

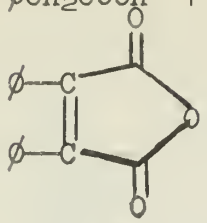
(B) $2C_6H_7NO + 3(\phi CH_2CO)_2O \longrightarrow$  $+ 2C_6H_7N + 4\phi CH_2COOH$

Table V

Products From Phenylacetic Anhydride And I

Product	Yield, moles per mole of I: No Inhibitor	10% m-dinitrobenzene[d]
2-pyridylmethyl phenylacetate	0.275[a]	0.281[b]
Benzylpicolines	0.183	0.176
CO_2	0.313	0.302
2-picoline	0.463	0.455
Benzaldehyde	0.081	0.089
DPMA[c]	0.002	0.004
Phenylacetic acid	1.02	1.01

[a] 80% 2(β-phenylethyl)pyridine
[b] 85% 2(β-phenylethyl)pyridine
[c] Diphenylmaleic anhydride
[d] Per cent, by weight, of I

yield from the total CO_2 yield. The extent of (B) was judged by the yield of DPMA. Material balances accounting for 92 per cent of I and 81 per cent of the benzyl groups as products were achieved. Benzaldehyde is consumed in the reaction, presumably by phenylacetic acid or phenylacetic anhydride. Oxidation-reduction reactions which do not form CO_2 or DPMA had to be postulated since the total yield of 2-picoline exceeds that expected from processes A and B. The constancy of product yields in the presence and absence of inhibitor was viewed as evidence against any radical chain character. The detection of only a trace of toluene and no diphenylmethane, biphenyl, or bipicolyl is consistent with this evidence. It was estimated that the latter three moieties would have been detected if present in greater than 0.5 per cent yield. Rüchardt has observed that acrylonitrile or styrene polymerizes only slightly when added to this reaction.[26]

Since pyridine N-oxide efficiently oxidizes phenylacetic anhydride[25] but is incapable of anhydrobase formation, the assumption that reactions (A) and (B) precede anhydrobase formation was found reasonable. It was concluded that the radical pair mechanism is an unacceptable postulate since high yields of ester were obtained. Ion pair formation from anhydrobase followed by efficient collapse to ester was suggested. Competing concerted cleavage of anhydrobase was suggested as the source of radical-derived products, CO_2, toluene, and benzylpicolines by analogy with the decomposition of t-butyl phenylperacetate.[30] Concerted rearrangement of anhydrobase to ester could not be ruled out. These suggestions were strongly favored in the case of acetic anhydride.[20]

Koenig has obtained further evidence favoring heterolytic cleavage of VI. When I and three substituted acetic anhydrides reacted the products in Table VI were obtained. It was reasoned that homolytic cleavage of VI is a possible step in the acetic anhydride reaction since recombination of acetoxy radical and picolyl radical can compete with decarboxylation. In the case of phenylacetoxy radical or trichloroacetoxy radical, however, it was predicted that the radical pair mechanism is not acceptable since both these radicals decompose with very low activation energy.[23,29] The model systems upon which this argument rests are the t-butyl peresters of the corresponding acids. It has been established that the decomposition of t-butyl phenylperacetate is a concerted process[29] and the decomposition of t-butyl trichloroperacetate is thought to occur similarly.[28] The decomposition of t-butyl

Table VI

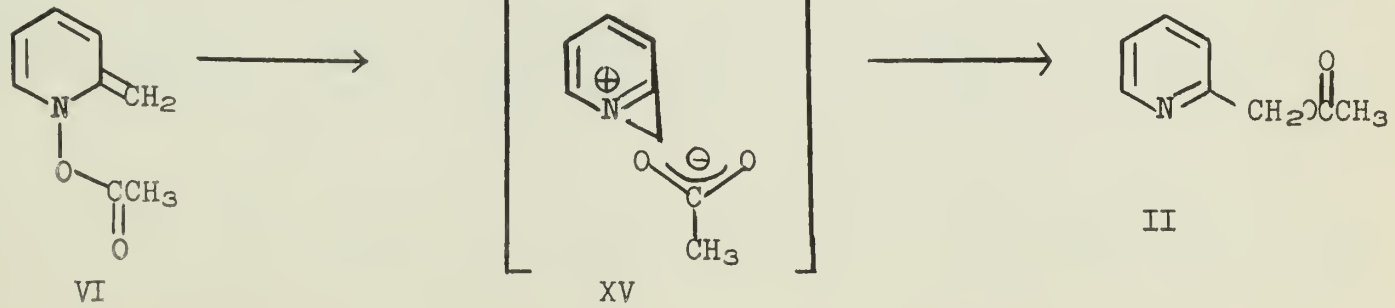
Product Yields (mole per mole of I) From I And $R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R$

R	Solvent	Esters	CO_2	Initial Acid	C_6H_5CHO	Other
$C_6H_5CH_2$	CH_3CN[a]	0.49[b]	0.36	0	0.25	0.06
"	"	0.56	0.28	0.05 M	0.16	c
"	"	0.62	0.25	0.49 M	0.13	c
CCl_3	$CHCl_3$[a]	0.74[e]	0.02	d	----	----
CF_3	CH_2Cl_2[f]	0.81	0	d	----	----

a Reflux
b NMR analysis: 65% 2-pyridylmethyl phenylacetate, 21% 5-phenylacetoxy-2-picoline, and 14% 3-phenylacetoxy-2- picoline
c Bibenzyl and picoline dimers present but not determined
d Reaction in excess anhydride containing some acid
e Yields of esters by NMR; isolated product after hydrolysis was 2-pyridylcarbinol
f 0°

trifluoroperacetate is not thought to be concerted.[28] The low yields of benzaldehyde were interpreted as an indication that competing oxidation-reduction is of minor importance. Addition of excess acid in several runs was expected to decrease the importance of competing oxidation-reduction; the magnitude of the changes in product composition were not as large as expected and it was suggested that benzaldehyde may form in more than one reaction. The rate of reaction was observed to be the same in the absence and presence of added acid.

Ester yields are comparable to those in the reaction of I and acetic anhydride when correction is made for the oxidation-reduction competition. The magnitude of increase in the importance of decarboxylated radical intermediate was considered more compatible with a dual mechanism than a radical pair mechanism. The high yield of ester and low yield of CO_2 in the trichloroacetic anhydride reaction were interpreted as evidence that a radical pair mechanism cannot be general for the reaction of I and acid anhydrides. It was proposed that ion pair formation can accomodate all experimental data.[28] The rate of reaction of trifluoroacetic anhydride compared to the other anhydrides was interpreted as support for the ion pair mechanism. Homolytic cleavage of the O-O bond in peresters is retarded by electron-withdrawing substituents; thus it might be expected that cleavage of the N-O bond of the anhydrobase intermediate in the trifluoroacetic anhydride reaction might no longer be rapid if homolytic cleavage were operative. An ion pair intermediate from VI was said to be more favorable than a radical pair on the basis of simple Hückel calculations. Rapid N-O bond cleavage could not be related to involvement of the pi electronic system of the pyridine ring. Instead, analogy with the Neber rearrangement was found in an intramolecular rearrangement involving nucleophilic attack at nitrogen. Intermediate XV was said to open rapidly to products in this mechanism. It was pointed out that XV may be alternately viewed as an approximation of the transition state in the rearrangement.



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RECENT ASPECTS OF ACYL NITRENE CHEMISTRY

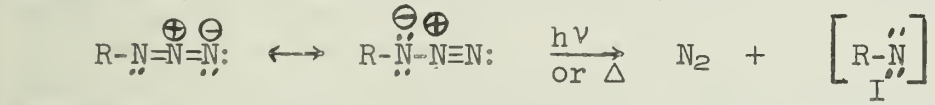
Reported by Kenneth C. Zahn April 25, 1966

Nitrenes, species with the general formula R-N:, where R may be aryl, alkyl, acyl, cyano, sulfonyl, carbonyl, hydrogen, etc., are formed or postulated as intermediates in a large number of reactions. Nitrene intermediates are similar in many respects to carbenes, with which they are isoelectronic. Two reviews on nitrene intermediates have appeared.[1,2] This seminar will consider, in general, only that work on acyl nitrene intermediates which has been reported since the later, more comprehensive review by Abramovitch and Davis.[2]

GENERAL METHODS FOR GENERATION OF NITRENE INTERMEDIATES

(A) Azide Decomposition

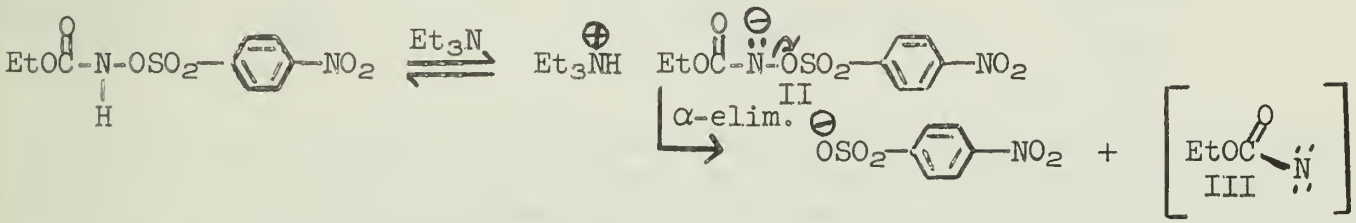
The most widely applicable method of generating nitrene intermediates (I) is by the photolytic or thermal decomposition of azides in solution:



These methods are not completely general, however, and many cases in which routes of decomposition of the azides other than those which lead to nitrene intermediates are known or postulated. Decomposition of gaseous azides,[3-6] liquid (neat) azides,[7,8] solid single azide crystals[9] and dilute frozen solutions (glasses) of azides[9-12] have also been described.

(B) α-Elimination

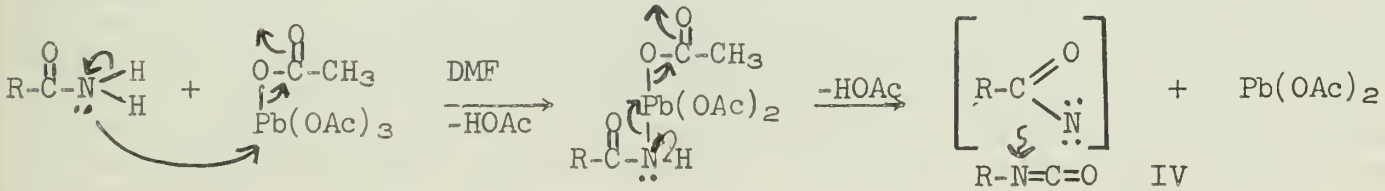
A less frequently encountered, but useful, method for generating the widely studied carbethoxy nitrene (III) is by α-elimination from the anion of N-p-nitrobenzenesulfonoxyurethan (II):[13,14]



This method has been used by Lwowski and coworkers to generate carbethoxy nitrene in order to compare its reactions with that prepared by azide decomposition (I, R=EtOC-). The more recent evidence for and reactions of acyl nitrene intermediates generated by azide decomposition or α-elimination will form the bulk of the material presented in this seminar.

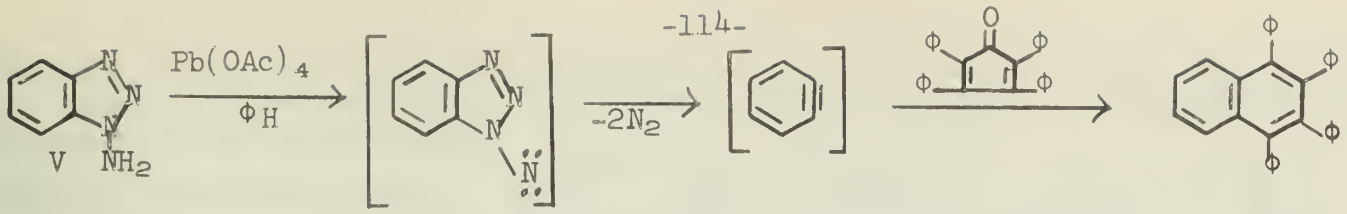
(C) Lead Tetraacetate Oxidation of Amines and Amides

Two recent communications have described interesting reactions which may involve nitrene intermediates.[15,16] Thus, some simple, unsubstituted aliphatic amides are found to undergo oxidative rearrangement, possibly through nitrene intermediates to isocyanates (IV):[15]



The mechanism and scope of this oxidative rearrangement are being investigated.[15]

Lead tetraacetate oxidation of 1-aminobenzotriazole (V) furnishes benzyne via an oxidative elimination that may also involve a nitrene intermediate.[16,21] The benzyne is trapped as tetraphenylnaphthalene by 2,3,4,5-cyclopentadienone:

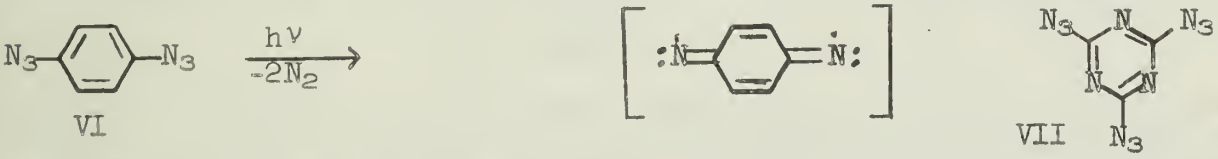


Preparation of nitrene intermediates by reduction of nitrocompounds and other miscellaneous methods are described by Abramovitch and Davis.[2]

DETECTION AND ELECTRONIC STATE OF NITRENE INTERMEDIATES

Since nitrene intermediates may exist in a singlet state (R-N̈:) or diradical, triplet state (R-Ṅ:) with two unpaired electrons, the question of whether they behave as one or the other in individual reactions has been widely discussed in the recent literature. Attempts to "detect" nitrenes directly and even to try to distinguish between the intermediates of different spin state have centered around several techniques: (A) observation of e.s.r. spectra from matrix-trapped triplet nitrenes generated photolytically at low temperatures,[9-11] (B) observation of ultraviolet spectra from nitrenes trapped in various matrices,[11,12,22,23] (C) flash photolysis of gaseous azides[3,20] followed by flash-kinetic spectroscopic study[19] of transient intermediates and products and (D) rationalization of products and product ratios in terms of the possible mechanisms of formation from nitrene intermediates (chemical trapping).

(A) The e.s.r. spectra of the following nitrene intermediates, generated by ultraviolet photolysis of dilute, frozen (77°K or 4°K) solutions of azides, have been detected and the signals assigned to the triplet ground state (or to a thermally accessible triplet state slightly above the ground state):[10,17] phenyl,[9,18] o-trifluoromethylphenyl,[18] benzenesulfonyl,[18] p-toluenesulfonyl,[18] cyano,[11,22-24] n-propyl,[10] 2-octyl,[10] cyclohexyl (4°K),[10] cyclopentyl,[10] α-carbethoxybenzyl,[10] t-butyl,[10] methanesulfonyl,[9] and the dinitrene derived from 1,4-diazidobenzene (VI).[17]



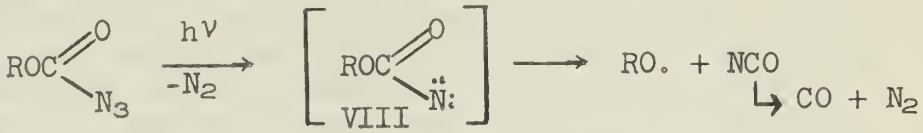
No signals were observed at 77°K from frozen Fluorolube (polychlorotrifluoroethylene) solutions of cyclohexyl azide, styryl azide, ethyl azidoformate or phenyl azidoformate.[18] Smolinsky and coworkers[2,18] rationalize these negative results by noting that the nitrenes derived from photolytic decomposition of these azides may undergo further reaction too quickly to permit buildup of a detectable stationary concentration. Photolysis of single crystals of p-fluorobenzenesulfonyl azide, triphenyltin azide, and cyanuric triazide (VII) at -160°C also furnished strong e.s.r. signals, which have been assigned to ground state triplet nitrenes.[9]

The observation of frozen matrix e.s.r. spectra attributable to stable nitrenes in a triplet ground state obviously does not imply that nitrene intermediates necessarily are generated or react as triplet species in liquid solution or gas phase reactions.

(B) The ultraviolet spectrum of nitrenes generated from photolysis of phenyl and α-naphthyl azides at 77°K in several frozen hydrocarbon and mixed solvent glasses have been reported,[12] as well as the ultraviolet and infrared spectra of the products of cyanoazide photolysis in frozen inert gas matrices at 4°K.[11,22-24] The spectra support the supposition that singlet, molecular nitrogen is lost from the photolytically excited cyanogen azide, resulting in production of excited singlet cyanonitrene (according to the Wigner spin conservation rule[25a]) which is then rapidly deactivated by the matrix to the relatively long-lived ground state triplet cyanonitrene.[22,28]

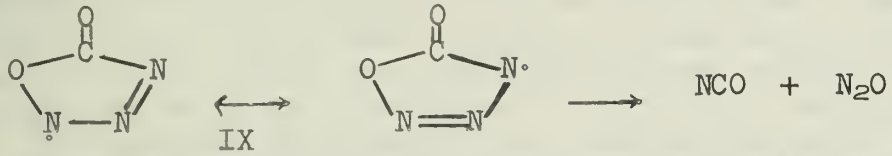
(C) Ethyl and methyl azidoformate have also been flash photolyzed in the vapor state using argon, nitrogen and CO_2 as moderating gases.[3] The flash-kinetic spectra showed the presence of both N_3 and NCO species. Product analysis showed N_2, H_2, CH_4, C_2H_6, C_2H_4, CO_2, CH_3CHO, CO and N_2O. From the flash-kinetic spectral data, it is apparent that azidoformates can be initially decomposed by at least two routes, one involving C-N bond cleavage to produce N_3 and a second route involving loss of nitrogen (N-N cleavage) and subsequent decomposition of the nitrene VIII to produce NCO radical

and other fragments. The C-N cleavage process was estimated to require more energy than that which produces NCO. Generalized schemes (1) and (2) were proposed to rationalize much of the data:[3]

Scheme (1) Low energy path: 

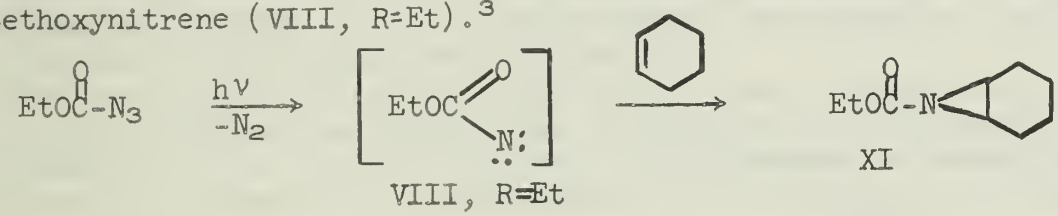
Scheme (2) Higher energy path: 

The formation of N_2O cannot be accounted for by these schemes, and may be the result of the decomposition (accompanied by the production of NCO) of a transitory fragment CO_2N_3 (IX), although this fragment was not observed in the flash-kinetic spectra.[3]



The formation of diethyl azodiformate ($EtO_2C-N{=}N-CO_2Et$, X) was not noted in this flash photolysis experiment,[3] but its formation had been alluded to in an earlier communication.[8]

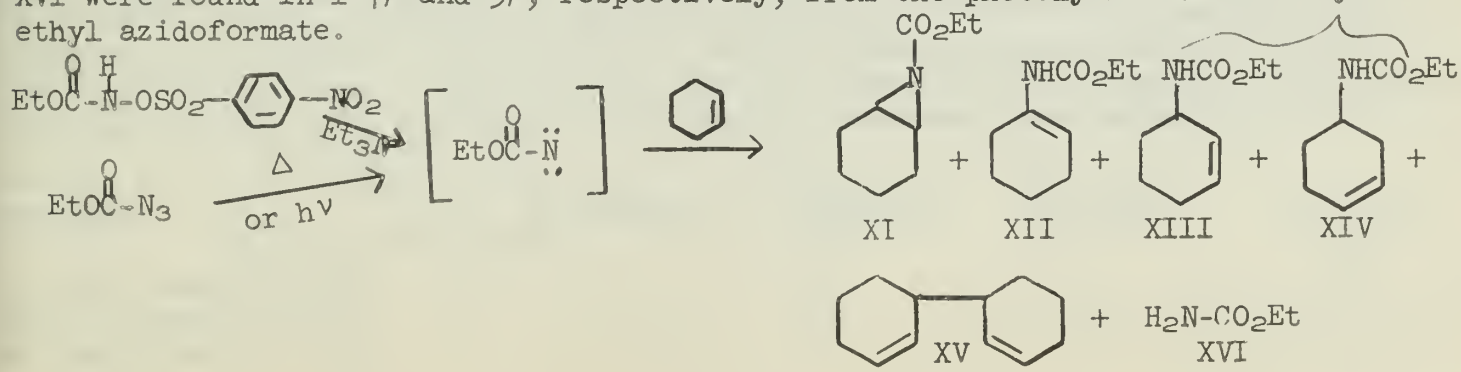
(D) When gaseous ethyl azidoformate was photolyzed in the presence of cyclohexene vapor in the experiment described in (C) above, condensation and vapor phase chromatographic (v.p.c.) analysis of the reaction products showed the main product to be 7-carbethoxy-7-azabicyclo(4.1.0)heptane (XI), indicative of the "trapping" of carbethoxynitrene (VIII, R=Et).[3]



From an estimate of the collisional frequency of cyclohexene with nitrene at the minimum cyclohexene pressure required for formation of the aziridine XI, a lower limit on the nitrene lifetime of about 3×10^{-7} sec. was estimated by Cornell, Berry, and Lwowski.[3] A rough estimate of the upper limit of nitrene lifetime was given as about 10 μsec (10^{-5} sec.) from the appearance time for intense NCO spectral bands after photolysis. Thus the reactive carbethoxynitrene can be "trapped" if it collides with cyclohexene before it undergoes C-O bond cleavage with subsequent formation of NCO and other products.

REACTIONS OF ACYL NITRENE INTERMEDIATES

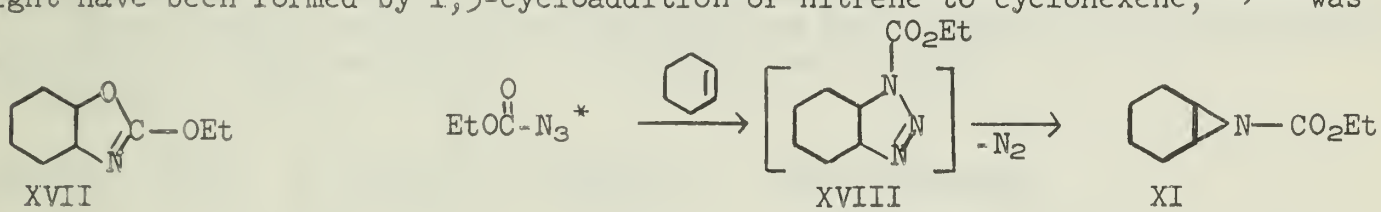
Lwowski and coworkers have found that carbethoxynitrene, generated from ethyl azidoformate photolytically (room temperature), thermally or by base-induced α-elimination of II gave similar ratios of products resulting from intermolecular reactions with a variety of substrates (solvents).[13,27] Thus from dilute cyclohexene solutions of ethyl azidoformate, products of addition of nitrene to the double bond (XI) and of its insertion into the three types of C-H bonds (XII-XIV) in relative yields of approximately 1.00: 0.02: 0.16 respectively, were isolated. Compounds XV and XVI were found in 1-7% and 3%, respectively, from the photolysis or thermolysis of ethyl azidoformate.



In the photolytically induced reaction, the small yield of hydrogen abstraction product, urethan XVI, could be reduced to nearly zero by exclusion of oxygen or lowering the reaction temperature to -75°. The relative ratios of isomeric cyclohexylurethans XII-XIV and aziridine XI were not significantly affected by introduction of peroxide, exclusion of oxygen or lowering the reaction temperature. The small, variable yield of 3,3'-bis-cyclohexene (XV) was apparently unaffected by these same variations of reaction conditions. It was also shown that aziridine XI did not rearrange to the 1- and 3-cyclohexylurethans under photolysis and v.p.c. analysis conditions and that continued photolysis of the reaction mixture did not alter the relative amounts of the isomeric urethans.[27] When this reaction was photosensitized[27,28] with acetophenone, the yields of products XI-XVI were sharply altered; aziridine XI: 1%; cyclohexylurethans XII-XIV: 4%, 3%, and 3.5%, respectively; 3,3'-bis-cyclohexene, XV: 63%; and the hydrogen abstraction product, urethan XVI: 74%. Some acetpinacol, from decomposition of sensitizer, was also isolated from the reaction mixture. That triplet state nitrene is involved in the photosensitized decomposition could not be concluded from these data alone, however, since the possibility of reaction through excited azide intermediates could not be excluded.[27]

The thermal decomposition of ethyl azidoformate in refluxing cyclohexene furnished the same products XI-XVI. The ratios of isomeric urethans varied with reaction conditions, the amount of 1-cyclohexylurethan XII increasing and the yield of aziridine XI decreasing with increasing reflux time after disappearance of all starting azide. A rearrangement of XI → XII is implied but cannot be purely thermal in nature since refluxing pure aziridine under the reaction conditions gave only 5% of 1-cyclohexylurethan XII. In the presence of atmospheric oxygen, yields of 16% of urethan XVI and 24% of 3,3'-bis-cyclohexene were obtained, but the yields dropped to 2% and zero % when oxygen was excluded.[27]

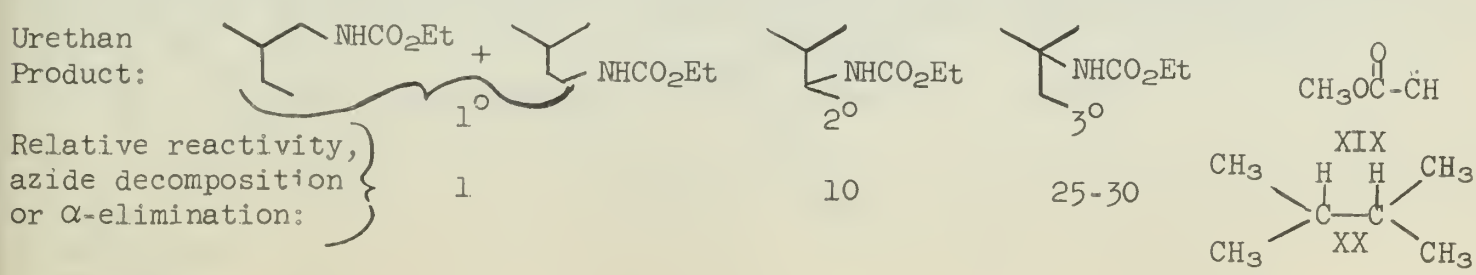
The absolute yields of products XI-XIV in the α-elimination reaction were lower than in the photolysis or thermolysis experiments but the product ratios remained quite similar.[13] No trace of 2-ethoxy-4,5-cyclohexano-Δ^2-oxazoline (XVII), which might have been formed by 1,3-cycloaddition of nitrene to cyclohexene,[13,38] was detected.



XVII XVIII XI

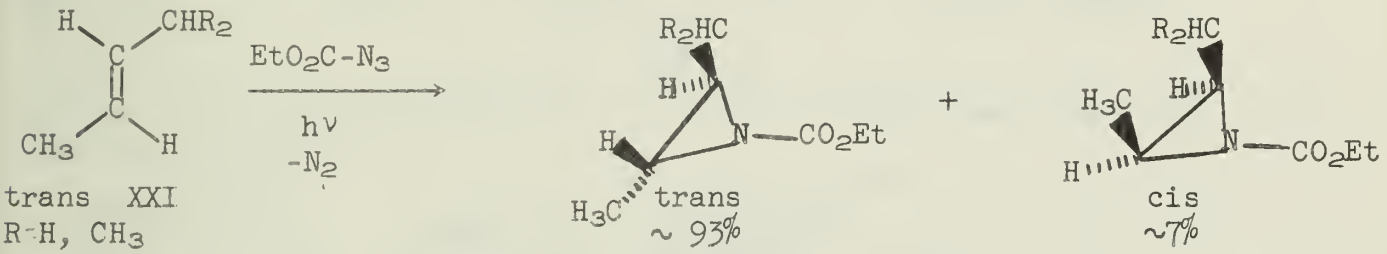
The addition of excited ethyl azidoformate to cyclohexene to yield a triazoline (XVIII, which would then decompose to nitrogen and the observed aziridine (XI) could not be rigorously ruled out in these azide reactions, even though the presence of triazolines was never observed and the rate of evolution of nitrogen equalled the rate of disappearance of azide, indicating that nitrogen loss from azide (to form the nitrene) is the rate-controlling step in the decomposition reaction.[27,44,45,56] (Triazolines have been isolated or postulated as intermediates in the decomposition of many azides, neat[29] or in the presence of norbornene,[30-32,34b,46-48,50] perfluorinated olefins,[33] unsaturated esters,[34,35] unsaturated ketones and some nitriles,[35] acetylenes,[36-38] enol ethers,[39] benzyne,[40] and Schiff's bases.[41,42])

The photolytic and thermal decomposition of ethyl azidoformate and α-elimination from urethan II all yielded the same C-H insertion (urethan) products and product ratios with several saturated hydrocarbon substrates.[43-45,13] For example, with isopentane as substrate, either neat or as an isopentane/dichloromethane mixture (44.5%/55.5% by volume), the following relative reactivities of primary (1°), secondary (2°) and tertiary (3°) C-H bonds toward carbethoxynitrene were observed:[13,43-45]



These results were significant in that a common intermediate was indicated for both the azide decomposition and α-elimination processes, ie., carbethoxynitrene. Carbomethoxycarbene (XIX), by comparison, showed a reactivity ratio of only 3:1 for reaction with the tertiary over the primary C-H bonds of 2,3-dimethylbutane (XX).[46] Thus carbethoxynitrene appears to be roughly ten times more selective in the C-H insertion than the closely analogous carbomethoxycarbene.

The stereochemistry of the addition of carbethoxynitrene (generated by azide photolysis and α-elimination) to olefins has been investigated by both Lwowski[14,49,51] and Hafner[52] and their respective coworkers. Preliminary results indicate that addition is partially sterospecific. Thus, carbethoxynitrene with pure trans-~~dimethyl~~-2-butene[52] or trans-4-methyl-2-pentene (XXI)[49] furnished approximately 93% of trans- and 7% of cis-disubstituted aziridine, while reaction of the nitrene with the cis-olefin yielded 13-26% of trans- and 87-74% of cis-disubstituted aziridine.



trans XXI
R=H, CH_3

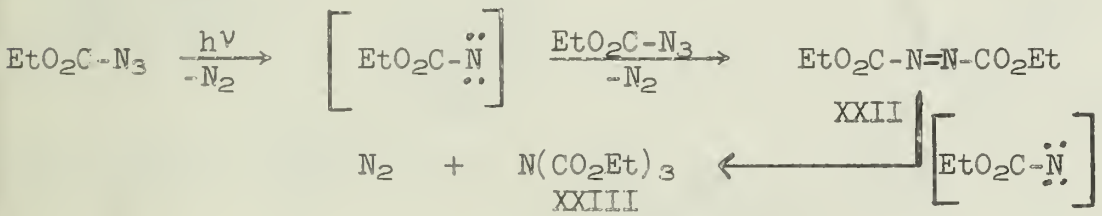
trans ~ 93%

cis ~7%

The postulate that sterospecific cis-addition of nitrene in the singlet state is occurring in these reactions[14,49,51,52] is in direct analogy to the postulates of Skell and coworkers to explain similar stereospecificity observed in carbene-olefin additions.[53] The validity and utility of Skell's postulates are being actively discussed in the literature.[54,55] The variation (decrease in stereospecificity) in the relative yields of cis- and trans-disubstituted aziridines with decreasing olefin concentration[14,49] in dichloromethane and neopentane solutions is being further investigated at this time by Lwowski and coworkers.[51]

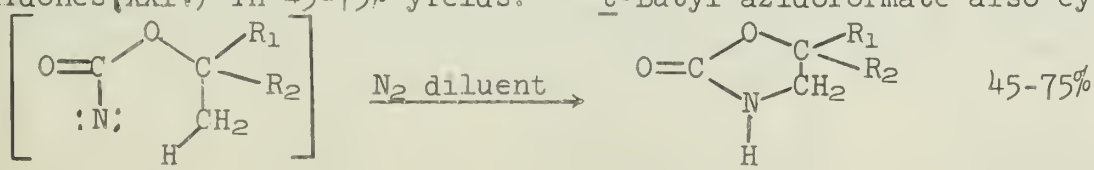
Irradiation of neat ethyl azidoformate has been reported[7] to yield diethyl azodiformate (XXII) and triethyl nitrilotriformate (XXIII).[7,8]

Proposed reaction path:[7]



The nature of intermediates or transition states leading to the formation of XXIII are not known[8] but the mechanism may not involve nitrene intermediates as originally proposed[7] since nitrene generated by α-elimination in pure azodiformate (XXII) does not lead to production of any nitrilotriformate even with a tenfold excess of N-p-nitrosulfonoxyurethan II for generation of the nitrene. Similarly, nitrene from α-elimination does not attack pure ethyl azidoformate to produce the azo compound XXII.[8] Compound XXII has also been produced by thermolysis of ethyl azidoformate in halogenated hydrocarbon solvents.[6a]

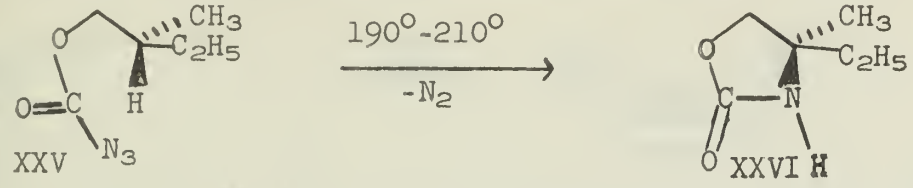
Intramolecular cyclization of carbalkoxynitrene intermediates in the gas phase and in solution has been reported.[6a,8,44,58,59] The resulting oxazolidone is presumably formed by insertion of the nitrene at C-H bonds in close proximity to the nitrogen atom. For example, at 300°, ethyl, isopropyl and t-butyl azidoformate form oxazolidones (XXIV) in 45-75% yields.[6a] t-Butyl azidoformate also cyclized photolytically.[58]



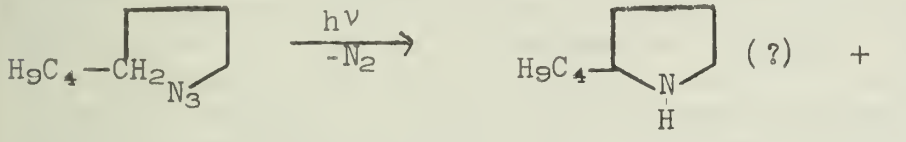
XXIV

$R_1=R_2=H$
$R_1=H$, $R_2=CH_3$
$R_1=R_2=CH_3$

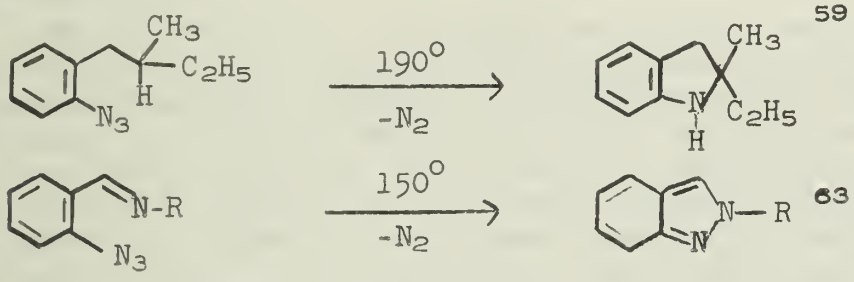
Similarly, optically octive[60] 2-methylbutyl azidoformate (XXV) can be thermolyzed in the gas phase to yield 4-ethyl-4-methyl-2-oxazolidone (XXVI)[59] with complete retention of absolute configuration at the asymmetric carbon atom.[59,60]



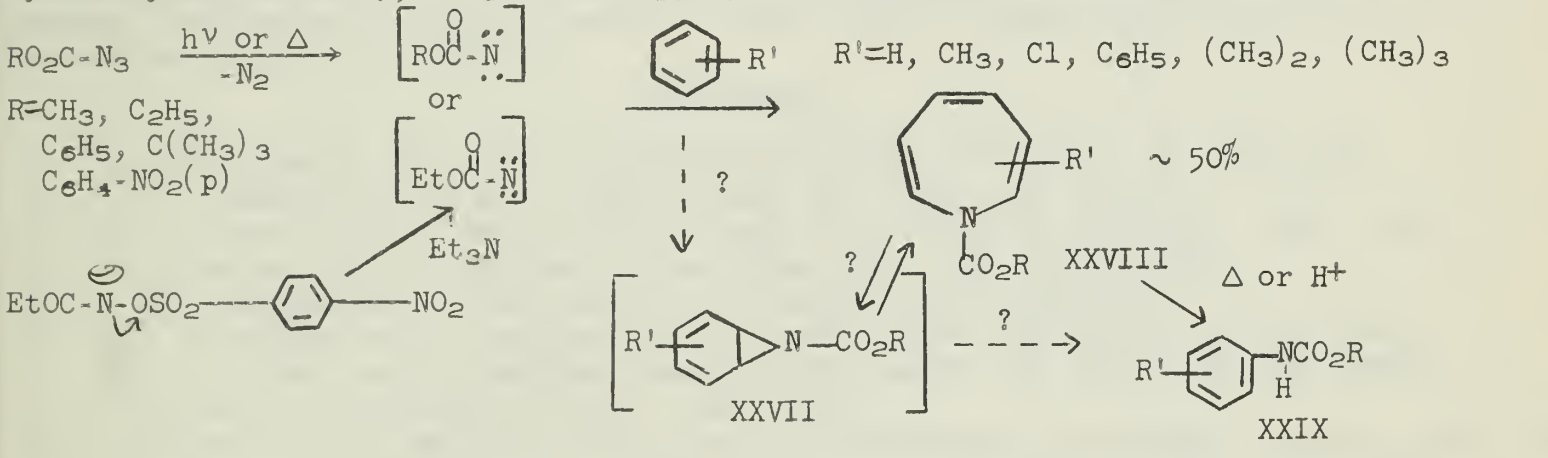
Two early reports[25b,61,62] of the photochemical decomposition of n-octyl azide to nitrogen and 2-n-butylpyrrolidine have been noted to be irreproducible,[59,62] although



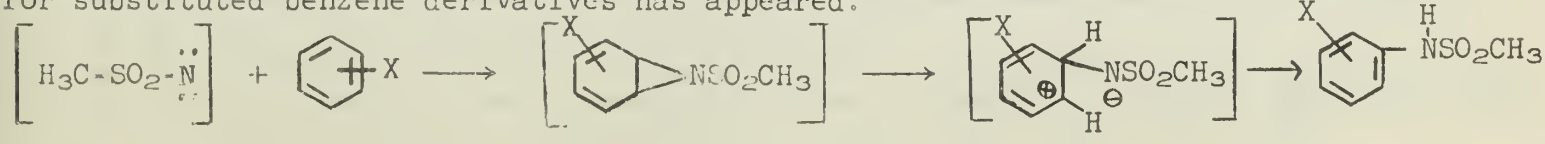
several apparently successful cyclizations of ortho-substituted aryl azides have been described:[59,63]



Alkyl azidoformates react readily with benzene and benzene derivatives, photolytically or thermally, to give the appropriate azepine derivatives (XXVIII):[64-67,13]



The intermediacy of 7-carbalkoxy-7-azabicyclo[4.1.0]heptadiene (XXVII) in the formation of azepines XXVIII or their thermal isomerization to phenylurethans XXIX has not been established.[13] On the basis of azepine isomer distribution, Hafner and coworkers have concluded that there is little difference in the selectivity of the carbethoxynitrene for various methyl substituted benzene derivatives[66] over that of carbethoxycarbene in its reaction with substituted benzene compounds. However, carbomethoxynitrene seems to be more selective than its analogous carbene toward chlorobenzene[65,67] (furnishing primarily 4-chloro-1-carbomethoxy-azepine rather than a 1:1 mixture of 3- and 4-chloro derivatives as in the carbene series),[67] in consonance with the relative selectivity of C-H insertion reactions described earlier. These disparities in substituent effects are currently being investigated by Baldwin and Smith.[67] A study of the relative selectivity of the methanesulfonylnitrene intermediate (XXX) for substituted benzene derivatives has appeared.[68]

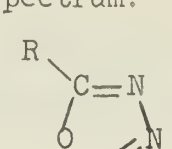


Carbethoxynitrene has been reported to react with cyclooctatetraene to form 9-azabicyclo[6.1.0]nonatriene (XXXI), which rearranges to an isomer postulated as XXXII on the basis of its nuclear magnetic resonance (n.m.r.) spectrum.[69,57]

XXXI

$\xrightarrow{80^\circ}$

XXXII



XXXIII

The reactions of acyl nitrenes with pyrrole, thiophene and 2,5-dimethylthiophene, furan,[70] naphthalene,[66] aliphatic alcohols,[58,72,73] amines,[66,71,72] dimethyl sulfoxide[71] and nitriles (to give 1,3,4-oxadiazoles (XXXIII)[74-76] have been reported.

Additional references to cyanonitrene,[75-77] aryl nitrenes,[78-82] triarylmethyl nitrenes,[83] sulfonyl nitrenes,[84,85] carbamidonitrene,[86] carbonyl nitrenes,[87] and benzylnitrene[88] may also be found in the recent literature.

SUMMARY

Recent references to the intermediacy and reactions of acyl nitrenes have been reviewed. Acyl nitrene intermediates appear to be ten times more selective than their corresponding carbene intermediates in C-H insertion reactions although possible discrepencies in expected selectivity of acyl nitrene intermediates toward substituted benzene derivatives have been observed. Studies of the stereochemistry and solvent concentration dependencies of nitrene addition to olefins have generally been interpreted in terms the different "behavior" of singlet versus triplet nitrene in analogy to Skell's much-discussed postulates in the related carbene reaction series.

The capability of generating a reactive species with (unambiguously) only one nitrogen atom by α-elimination from the anion of N-p-nitrobenzenesulfonoxyurethan has greatly facilitated the interpretation of many azide decomposition reactions in terms of a nitrene intermediate.

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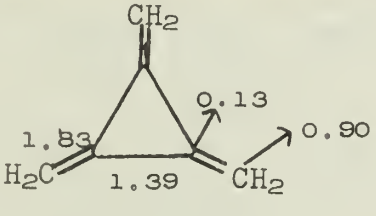
RADIALENE CHEMISTRY

Reported by Roy A. Swaringen, Jr. May 5, 1966

INTRODUCTION

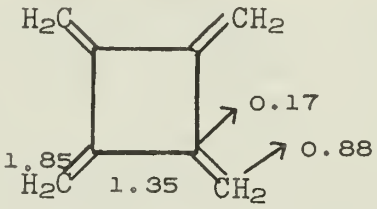
The [n]-radialenes are a class of cyclic hydrocarbons, $C_{2n}H_{2n}$, containing the maximum number of exocyclic double bonds. These compounds represent completely cross-conjugated systems and are thus of theoretical interest. Simple Hückel molecular orbital calculations by Roberts, Streitwieser, and Regan predicted singlet ground states and substantial delocalization energies for trimethylenecyclopropane (I) and tetramethylenecyclobutane (II).[1]

Figure I



D.E. = 1.30β

I



D.E. = 1.66β

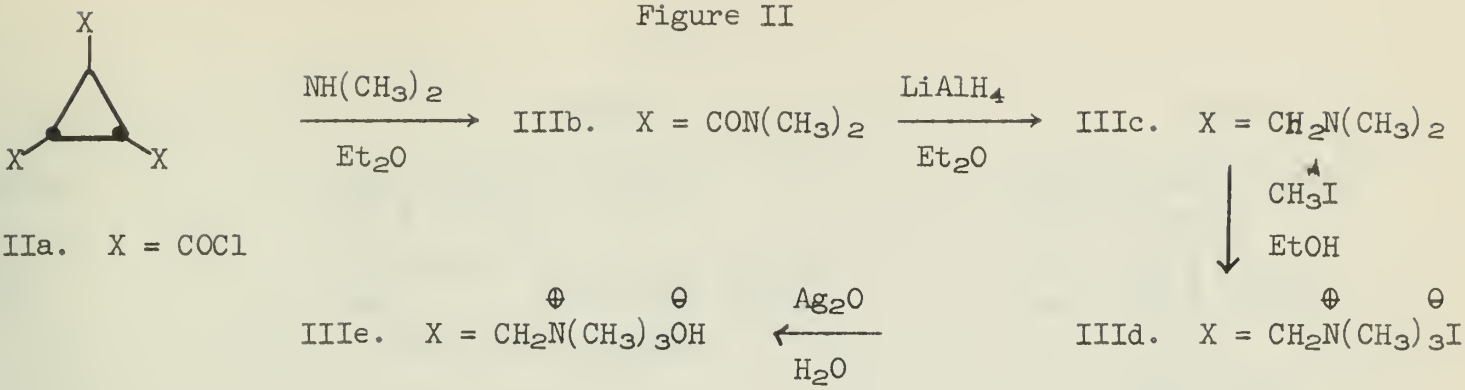
II

The calculated bond orders are shown by each bond, and the free-valence indices are shown for each position by the arrow points. The high free-valence indices for the terminal methylene groups suggest a high reactivity and a tendency to polymerize. Dewar and Gleicher have applied a SCF-LCAO-MO method to the radialenes, and their results suggest that bond energies are additive in these compounds since the π-contributions to the "single" bonds may be absorbed into the empirical C-C bond energy. Radialenes are therefore quite adequately represented by "localized" single and double bonds.[2] In opposition to the predicted delocalization energy is the obvious factor of strain. Cyclopropane and cyclobutane have strain energies of 27.6 kcal. and 26.2 kcal respectively,[3] and the introduction of trigonal centers increases the strain by varying amounts. There appears to be no reliable way to estimate the total strain in the corresponding radialenes either from theory or from the limited thermochemical data on related systems.[4] As these compounds become more available for calorimetric hydrogenation studies they may yield valuable data for assessing the strain in small ring compounds. Due to their high symmetry (D_{nh} for planar molecule) the radialenes are also of theoretical interest for spectroscopic studies. Heilbronner has applied Simpson's "Independent Systems Approach" to the [n]-radialenes to obtain predictions for their electronic spectra that are in good qualitative agreement with observation.[5]

[3]-RADIALENES

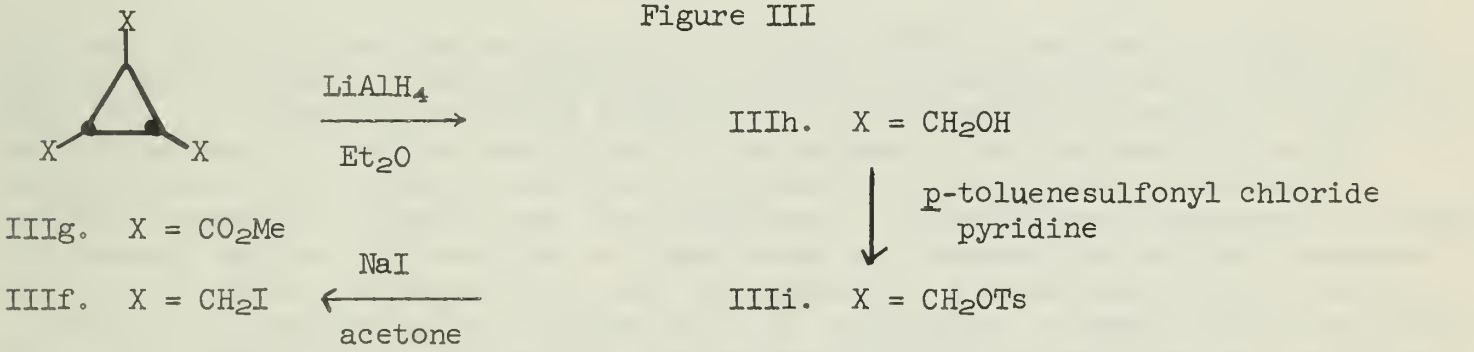
Trimethylenecyclopropane (I) was first observed spectroscopically by Blomquist and coworkers who obtained trace amounts of the compound by pyrolysis of 1-methylene-trans-2,3-bis(trimethylammoniummethyl)cyclopropane dihydroxide and the related amine oxide.[6] However, the compound was prepared in weighable quantities only recently by the independent efforts of Griffin[7] and Dorko.[8] Griffin favors the pyrolysis of trans-1,2,3-tris(trimethylammoniummethyl)cyclopropane trihydroxide (IIIe) as a route to I since contamination is minimized and the product may be easily collected in a suitable solvent. The Hofmann base precursor IIIe is prepared by the following scheme:

Figure II



The aqueous solution of IIIe is concentrated by lyophilization (1.0 mm) to a clear, colorless viscous solution (about 30% IIIe) which is pyrolized at 170° (4.5 mm Hg under nitrogen) to yield I collected at -78° in carbon disulfide, isopentane, or carbon tetrachloride. The product may be purified by a short-path distillation under conditions chosen to prevent codistillation of polymers with solvent and I, and is sufficiently stable to be washed with dilute hydrochloric acid and aqueous sodium bicarbonate at 0°. Precursor IIIe may alternatively be made by treating trans-1,2,3-triiodomethylcyclopropane (IIIf) (vide infra) with trimethylamine in ethanol to give IIId and then forming the quaternary hydroxide by use of silver oxide. Griffin has also generated I in dilute ethanolic solution by dehydrohalogenation of IIIf using sodium ethoxide. The route to IIIf is as follows:

Figure III



Dorko has prepared trimethylenecyclopropane by the dehydrohalogenation of trans-2,3-bis(bromomethyl)-1-methylenecyclopropane (IVa) which is obtained by the following sequence:

Figure IV

IVb. IVc. IVa.

The dibromide IVa is added dropwise to a U-tube containing potassium hydroxide at 150° while a stream of helium is passed through the tube. The effluent vapors pass through a series of cold traps (-40°, -78°, -196°), the trimethylenecyclopropane condensing in the -78° trap. The yield is 47% based on the amount of IVa passed through the U-tube. The structural evidence for I as the product of these reactions is summarized in the following table:

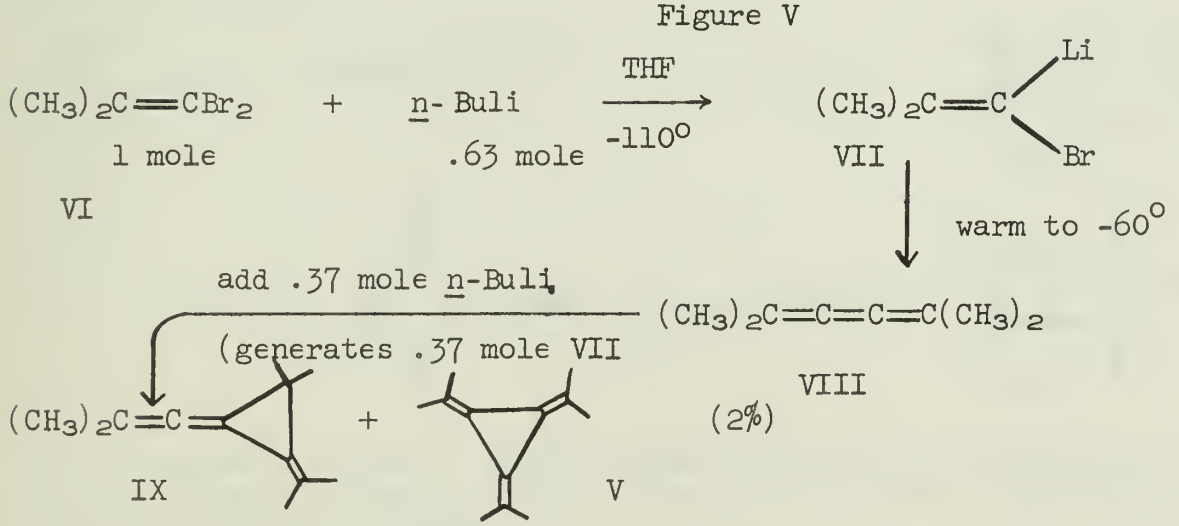
Table I

	Griffin	Dorko
n.m.r.	single peak at τ4.86 for I in CS_2	single peak at τ4.98 for I in CCl_4
UV	$\lambda_{max}^{isopentane}$ = 295 and 305 mμ shoulder at 322 mμ	λ_{max} 213, 289 } vapor; 213, 295 } EtOH
IR	(in CCl_4) 881 cm.$^{-1}$ $C{=}CH_2$	874 cm.$^{-1}$ (S) $C{=}CH_2$; 1773 cm.$^{-1}$ (W)
Molecular Weight	mass spectrum: m/e 78	mass spectrum m/e 78; mass spectral effusion 75
Hydrogenation	I $\xrightarrow[H_2]{Pd\ on\ C\ (5\%)}$ cmpd. m/e 84	

The mass spectral cracking pattern of the triene differs from that of other known C_6H_6 isomers (benzene, ethyl diacetylene, dimethyl diacetylene, divinyl acetylene).[9] This fact in conjunction with the finding of only one proton resonance in the n.m.r. and the presence of strong absorption in the infrared spectrum near the region characteristic of hydrogen out-of-plane deformations in terminal disubstituted olefins[10] presents a strong case for structure I. Trimethylenecyclopropane is stable for several days at -78° and can be transferred on a vacuum line at low pressures. However, the vapor polymerizes at room temperature to a colorless liquid, then to a viscous oil and finally to a yellow solid.[8] This yellow polymer is also deposited from a solution of I in CCl_4 at 0°. The nature of this polymer[8] and the reactions of I with dienophiles[7] are currently being investigated.

The report of a stable derivative of I, tri(isopropylidene)cyclopropane (V) has appeared recently.[11]

Figure V

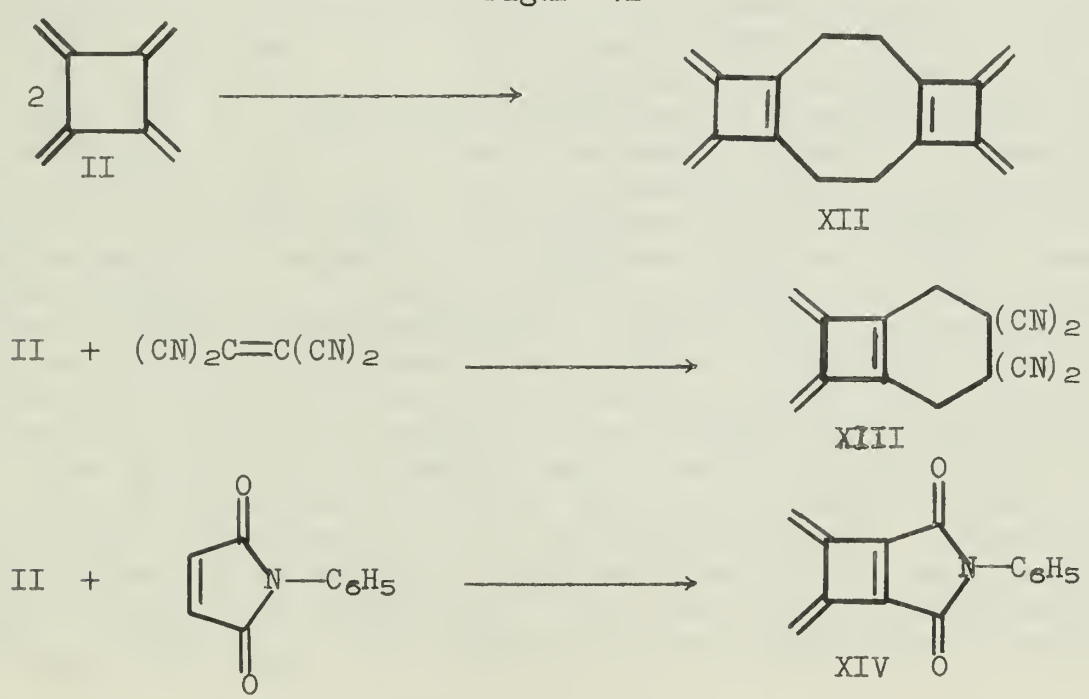


V was characterized by the following data: molecular formula of $C_{12}H_{18}$ by elemental analysis and mass spectrum, single sharp peak at -2.01 p.p.m. in n.m.r. spectrum, ultraviolet spectrum λ_{max}^{hexane} of 309.5 mμ (log ε = 4.26), catalytic hydrogenation using Raney nickel catalyst shows an uptake of 2.94 moles of hydrogen.

[4]-RADIALENES

Tetramethylenecyclobutane (II) has been prepared by Griffin using two independent routes.[12] The initial synthesis of II (in 1-2% yields) involved pyrolysis of cis, trans, cis-1,2,3,4-tetra-(dimethylaminomethyl)-cyclobutane tetraoxide (Xa) at 250° under nitrogen at reduced pressure. The effluent gases were trapped in hexane at -78°. The product was purified by washing the hexane solution with dilute hydrochloric acid and then codistillation at 0° under vacuum. In a similar manner II was produced (in 1% yield) from pyrolysis of cis, trans, cis-1,2,3,4,-tetra-(trimethylammoniummethyl)-cyclobutane tetrahydroxide (Xb) at 115°. Precursors Xa and Xb are obtained from cis, trans, cis-1,2,3,4-tetracarbomethoxycyclobutane (Xc), the photodimer of dimethyl fumarate.[13] Alternatively and more conveniently II is prepared by the dehydrohalogenation of a number of 1,2,3,4-tetrahalomethylcyclobutanes of different stereochemistry. For example the reaction of trans, trans, trans,-1,2,3,4-tetrabromomethylcyclobutane (XI) with sodium ethoxide in ethanol at 0° gives II in greater than 50% yield. Thermal dimerization of 1,2,3-butatriene was also attempted as a route to II; however, the passage of butatriene through a tube of Pyrex helices at temperatures from 150-550° failed to afford even traces of II. The following evidence may be cited in favor of structure II: (1) the mass spectrum in hexane solution shows a peak at m/e 104 (2) the infrared spectrum shows strong absorption at 880 cm.$^{-1}$ for $>C=CH_2$ (3) the n.m.r. spectrum in chloroform consists of a single peak at τ4.81 (4) catalytic hydrogenation using platinum-on-charcoal catalyst gives cis, cis, cis-1,2,3,4-tetramethylcyclobutane. Tetramethylenecyclobutane (II) is stable in dilute solution at -78° but dimerizes on standing at room temperature. Ethanolic solutions of II react with tetracyanoethylene and with N-phenylmaleimide to form mono-Diels-Alder adducts identified by their n.m.r. and UV spectra.

Figure VI



II is remarkably stable to dilute mineral acids and to strong bases; however, it is very sensitive to oxygen, forming intractable products containing up to 40% oxygen upon brief exposure to air.

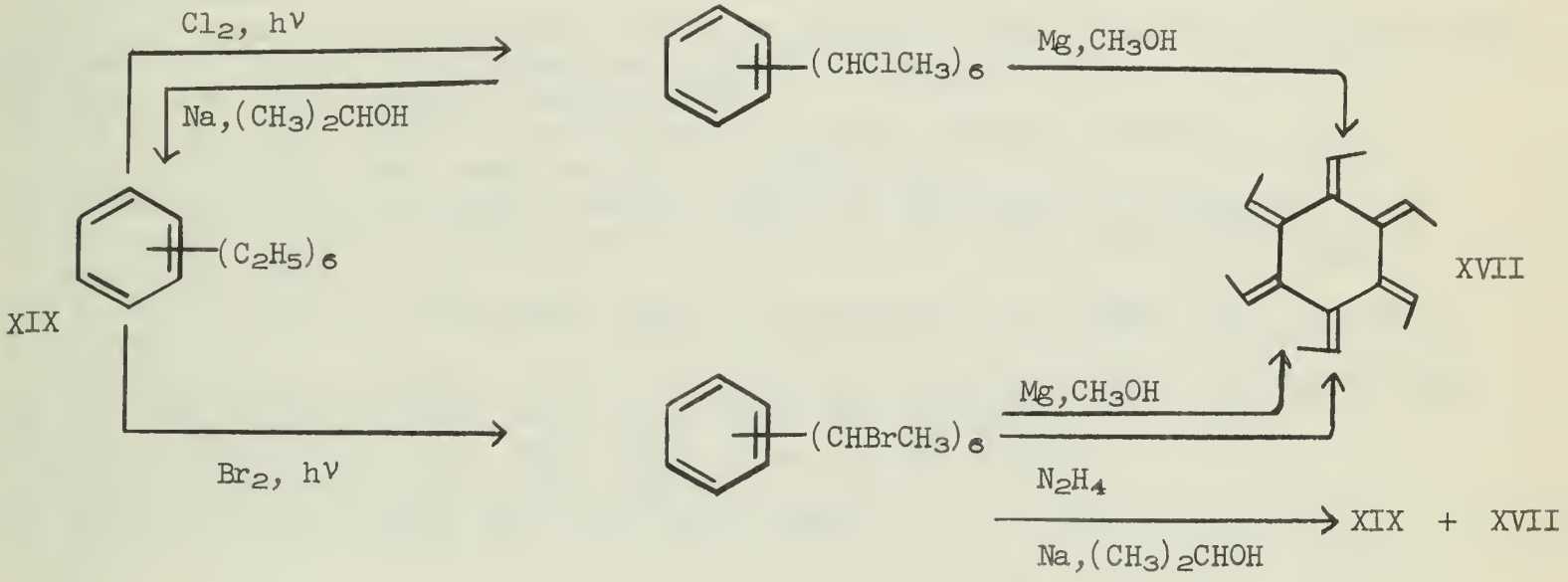
One stable derivative of II, octaphenyl-[4]-radialene (XV) has been reported.[14] XV is prepared by the photodimerization of tetraphenylbutatriene and is characterized by the following data: acceptable elemental analysis and molecular weight determination for $C_{56}H_{40}$, no absorptions attributable to allenic, acetylenic, or polysubstituted phenyl groups in the IR spectrum, single absorption for phenyl groups at

τ3.0 in the n.m.r. spectrum, and degradative studies (oxonolysis and diozonolysis).

[6]-RADIALENES

[6]-Radialene (XVI) is unknown; however, two substituted [6]-radialenes, hexamethyl-[6]-radialene (XVII) and hexaethyl-[6]-radialene (XVIII) have been reported. Hexaethylbenzene (XIX) may be halogenated under radical conditions to yield hexakis (α-haloethyl) benzenes[15] which may be dehalogenated to XVII.[15,16]

Figure VII



XVII is identified by the following data: (1) elemental analysis for $C_{18}H_{24}$, (2) IR: ═CH— at 830 cm.$^{-1}$ (s) and conjugated C═C at 1655 cm.$^{-1}$ (w) and 1620 cm.$^{-1}$ (s), (3) n.m.r.: τ4.7 (quartet) and τ8.2 (doublet) as expected for ═CH—CH_3, and (4) catalytic hydrogenation to hexaethylbenzene (XIX). XVII gives an orange color with tetranitromethane (indicative of unsaturation) and a fugitive red-violet color with a trace of mineral acid in a polar solvent. It does not form a Diels-Alder adduct with p-quinone, maleic anhydride, or diethyl acetylenedicarboxylate. Hexaethyl-[6]-radialene XVIII is the title compound of a French patent awarded to J. R. Geigy A.-G.[17] It (similar to XVII) is prepared by the reaction of hexakis (α-halohalopropyl) benzenes with dehalogenating and reducing agents such as alkalis in the presence of alcohol or hydrazine. Gerson has examined the e.s.r. spectra of the radical anions of XVII and XVIII by adding sodium or potassium metal to a solution of the compound in 1,2-dimethoxyethane at -70°.[18] The spectrum of the radical anion from XVII consists of 21 lines in accordance with 24 equivalent protons and $a_H \simeq a_{CH_3} = 3.82 \pm .15$ gauss (theory predicts 25 lines, but outermost 4 are too weak to be seen). The spectrum of the radical anion from XVII is much more complicated and is seemingly consistent with one set of 6 equivalent α-protons ($a_H = 3.64$), two sets of 6 each equivalent β-protons ($a'_{CH_2} = 4.68$, $a''_{CH_2} = 3.12$), and one set of 18 equivalent γ-protons ($a_{CH_3} < 0.2$).

SUMMARY

[3]-Radialene and [4]-radialene have been prepared by straightforward chemical reactions (pyrolysis of N-oxides and Hofmann bases and dehydrohalogenations) when used in conjunction with clever, careful isolation procedures. Much of the chemistry of these reactive compounds remains to be investigated.

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LOW TEMPERATURE MATRIX PHOTOLYSIS

Reported by James Billet May 9, 1966

The nature of excited states in photochemical systems is often governed by factors such as electronic and molecular structure, nature of the environment, pressure, temperature and excitation wave length. Furthermore, the kinetics, mechanisms and subsequent products yielded by the radicals, ions, carbenes or small molecules often produced in primary photochemical processes, have very obvious physical phase dependence, a fact frequently exploited by contemporary chemists. The recent literature on vapor and solution studies is voluminous, and the subject of organic solid state chemistry has been extensively reviewed.[1-3]

Advances in low temperature techniques have stimulated significant studies in the stabilization of photochemically generated reactive species.[4-8] Subsequent chemical reactions having appreciable activation energies are extremely slow at these temperatures (20°K and lower), thereby permitting the isolation of usually reactive intermediates in a frozen solvent matrix. Phosphorescence and fluorescence spectrometry, UV, visible and IR absorption spectroscopy, and electron spin resonance may then be enlisted to characterize these species and to establish the nature of the primary photochemical processes.[4]

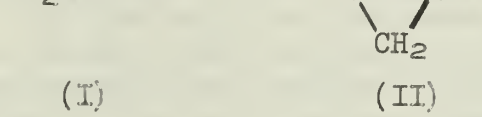
Solvent matrix isolation techniques were thus first developed for analytical use. Recently however, several investigations have disclosed some specific effects of the solvent matrix as a unique physical state, upon the mechanisms and products of the photochemical reactions. The latter is the subject of this seminar.

GENERAL CONSIDERATIONS[4]

The solvent matrix may exist as a rigid environmental cage which inhibits both formation and subsequent reaction of species photochemically generated in situ. If appreciable excitation energy is efficiently removed from an absorbing molecule, and dissipated through thermal cage vibrations, the probability of subsequent reaction may be drastically reduced. Furthermore, the matrix cage may impose severe orientational and translational restrictions upon the radicals, carbenes or other species that are generated. Germinate recombination of such species may subsequently be considerably more likely than in viscous solution. Once outside the parent cage, diffusion within the matrix is expected to be limiting. Finally, although the matrix solvent may be relatively unreactive in the gas or liquid phase, there is no guarantee that reaction will not occur in the condensed phase if highly excited species are generated in relatively isolated solvent cages where local heating effects may be substantial. Specific examples illustrating these general principles are presented in the text following.

METHYLENE

Moore and Pimentel[9] have performed IR spectral analysis on the products of the photolysis of diazomethane (I) and its cyclic isomer diazirine (II) in solid nitrogen matrices at 20°K.

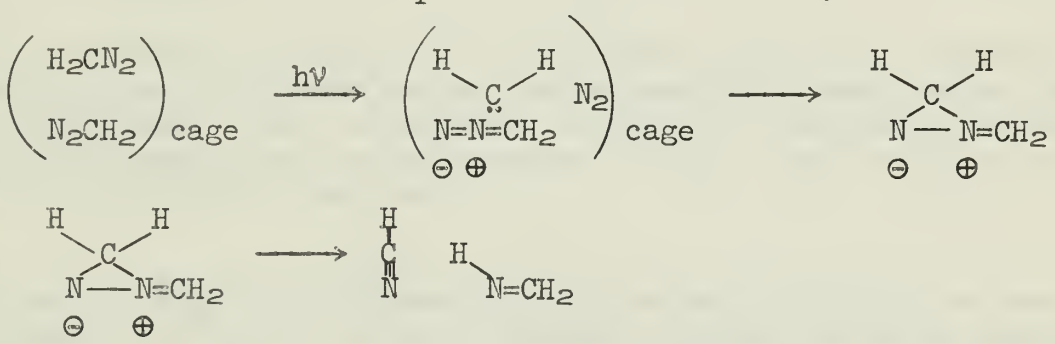


(I) (II)

Isotopic labeling with N^{15} and deuterium provides compelling evidence that the primary photochemical process is production of methylene which subsequently reacts with N_2^{14} in the matrix to form diazomethane $CH_2N_2^{14}$, methyleneimine $CH_2{=}NH$ and HCN. The formation of $CH_2N_2^{14}$ suggests why earlier attempts to detect spectroscopically, matrix isolated CH_2 had been unsuccessful.[10-15] These previous in situ photolyses of ketene, diazomethane, and diazirine had been based upon the expectation that CH_2 would not recombine at very low temperatures with the CO or

N_2 of the matrices. The difficulty in obtaining matrix isolated CH_2 from the photolysis of ketene is thus interpreted as the result of reaction of CH_2 with CO of the matrix to reform ketene. This is consistent with the formation of ketene upon photolysis of diazomethane in mixtures of solid CO and N_2,[10] and also upon gas phase photolysis of ketene in the presence of ^{13}CO.[16,17] Attempts to produce similarly, $CH_2N_2^{14}$ by photolysis of gaseous $CH_2N^{15}N^{14}/N_2^{14}$ mixtures failed. The fact that CH_2 reacts with N_2 in the matrix but not in the gas phase may be attributed to the need for a third body, i.e., the deactivation of hot CH_2 by energy transfer to the matrix cage.

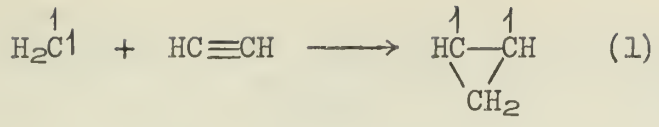
The methyleneimine and hydrogen cyanide products were quite unexpected, as gas phase photolysis of diazomethane gives primarily ethylene and nitrogen, together with a variety of other hydrocarbons.[18] Moore and Pimentel have subsequently invoked matrix orientational effects upon diazomethane dimers.



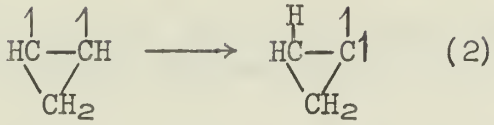
Such rearrangements following addition of CH_2 to double bonds are not uncommon,[17] ostensibly because of the high degree of vibrational excitation of the initial cyclic product. Decrease in C-H stretching frequencies and rise in the bending frequencies characteristic of H bonding further suggests the presence of both products in the same matrix cage.

Milligan and Jacox[19] have found that photolysis of diazomethane/acetylene mixtures in solid argon at $4^{o}K$ produced allene almost exclusively. Infrared spectra of the matrix films were identical with published spectra of allene and deuterated allenes. A small amount of ethylene is further evidence for drastically limited diffusion of methylene from its matrix cage. No cyclopropene or methylacetylene were found, although these may certainly have been the major addition and insertion products respectively. As it is well established that the primary photochemical process in the matrix decomposition of diazomethane is formation of CH_2 and N_2,[20] as in the gas phase, spin conservation requires that CH_2 be initially produced in a singlet state. Herzberg[21] however, has suggested that the ground state of CH_2 is a triplet. Gas phase studies[21-26] further suggest that collisional deactivation of singlet methylene to its ground triplet state may be effected before reaction. Thus one might expect at least comparable deactivation by the inert gas matrix. If the inert gas matrix is very effective in deactivation of singlet methylene, it should also be effective in stabilization of any vibrationally excited cyclopropene formed, before the latter could isomerize to allene. Gas phase studies[27] have again demonstrated that such collisional deactivation of vibrationally excited products can occur. At high ethylene pressures, the yield of propylene as the isomerization product of vibrationally excited cyclopropane formed in the gas phase photolysis of diazomethane/ethylene mixtures, decreases to zero.[28] In the corresponding matrix photolysis,[29] no propylene was found, indicating comparable deactivation, either of singlet methylene, or vibrationally excited cyclopropane.

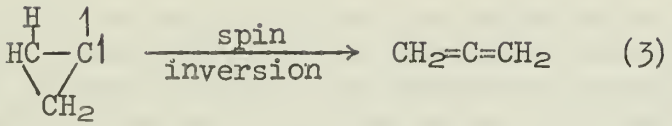
Jacox and Milligan[19] subsequently infer the following mechanism for the production of allene:



(1)



(2)

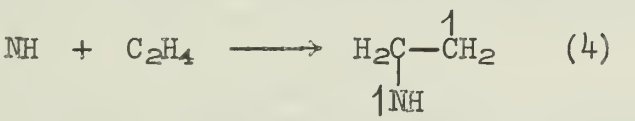


(3)

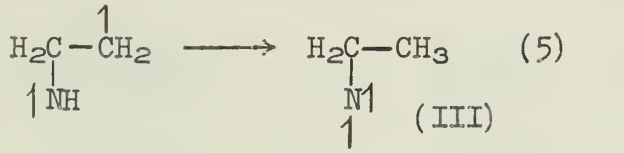
Spin inversion may actually accompany step (2) however, as strain considerations at least suggest cyclopropenylidene may be thermodynamically more stable than triplet cyclopropenylidene. This mechanistic rationale is suggestive at best, and adds to that already impressive list of attempts to infer spin states from the apparent chemical reactivity of carbenes.

NITRENES

The photolysis of HN_3/C_2H_4 mixtures in an argon matrix at 4^oK has been performed by Milligan and Jacox[30] with IR spectral analysis revealing exclusive ethyleneimine formation. These data may be compared to the gas phase results recently reported by Lwowski and coworkers,[31] who found that both flash and slow isothermal photolysis of HN_3/C_2H_4 mixtures yielded HCN, CH_3CN, H_2, CH_4, and undetermined polymeric products. An extensive search for ethyleneimine was unsuccessful. The well characterized band spectrum of triplet NH[32] was obtained by flash kinetic absorption spectroscopy. None of the short lived singlet NH was observed. The ratio of the amounts of HCN and CH_3CN was found to be insensitive to ethylene pressure over a range of 80-560 mm., suggestive that these two products arise from the same primary reaction of triplet NH with ethylene.

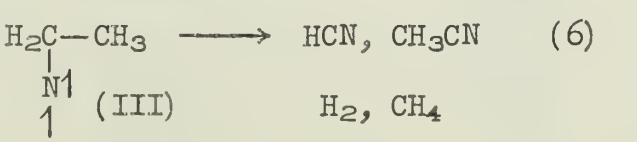


(4)



(5)

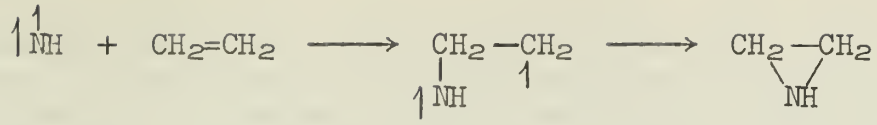
(III)



(6)

The presence of a well defined vibrationally stabilized nitrene such as (III) was suggested by isothermal gas phase photolysis of HN_3/1-butene mixtures. Addition of NH to the 2 position should give approximately equal amounts of CH_3CN and C_2H_5CN if the above mechanistic scheme, in which any two bonds to the α carbon are broken in a step analogous to (6), is sound. Such was found.

Subsequently, one could reason that in the earlier matrix photolysis of HN_3/C_2H_4 performed by Milligan and Jacox, ethyleneimine was probably formed by reaction of triplet NH with ethylene, followed by efficient spin inversion and vibrational deactivation before any hydrogen transfer from nitrogen to carbon.



Recent ESR evidence for the existence of other ground state triplet nitrenes photochemically generated in glasses may be found in the literature.[33-35]

RADICALS

Nelsen and Bartlett[36] recently studied the solution and matrix photolysis of azocumene. In solution, cumyl radicals are generated in a solvent cage, with subsequent competition between diffusion and geminate recombination. Cumyl radicals inside and outside the solvent cage can either combine to form dicumyl, or disproportionate to α-methyl styrene (AMS) and cumene. (Discussion of the cage effect in the thermal and photochemical decomposition of azo compounds has been quite recently reviewed.[37]) Thus for solution photolysis, the following mechanistic scheme is presented:

$$\phi(CH_3)_2C\text{-}N{=}N\text{-}C(CH_3)_2\phi \xrightarrow{k_{dec.}} [\phi(CH_3)_2C\cdot, N_2, \cdot C(CH_3)_2\phi] \text{ cage}$$

$$[\phi(CH_3)_2C\cdot, N_2, \cdot C(CH_3)_2\phi] \xrightarrow{k_{cage}} \text{Cage Products}$$

$$\xrightarrow{k_{diff.}} 2\phi(CH_3)_2C\cdot + N_2$$

$$2\phi(CH_3)_2C\cdot \xrightarrow{k_{comb.}} \phi(CH_3)_2C\text{-}C(CH_3)_2\phi$$

$$2\phi(CH_3)_2C\cdot \xrightarrow{k_{disp.}} \phi(CH_3)_2C{=}CH_2 + \phi(CH_3)_2CH$$

Vapor phase chromatographic product analysis was used to determine k_{disp}/k_{comb} ratios. No significant temperature dependence of the amounts of disproportionation and combination was observed, which was taken to indicate that the activation energies for the two processes must be very close or identical.

Disproportionation and Combination of Cumyl Radicals
Generated from Azocumene in Benzene Solution

Temp., °C.	Initial azocumene, mmole	$k_{disp}/k_{comb.}$	Cumene (AMS)
20.5	0.0436	0.054	0.80
		0.055	1.01
46.8	0.0436	0.056	1.31
		0.053	1.36
60.0	0.0413	0.056	1.30
		0.054	1.20

When azocumene was decomposed photolytically at about -8°C, in frozen benzene solution however, k_{disp}/k_{comb} ratios were found to be 0.93 and 1.05. NMR was used to determine when the photolyses were completed, with vpc product analysis as in the solution photolyses. The change in value of k_{disp}/k_{comb} cannot be a temperature effect, in view of the constancy of this ratio in all of the solution experiments.

At -8°C, frozen benzene solutions may have pockets of concentrated azocumene solution within the matrix.[38] High concentrations however might be expected to

affect both competing bimolecular reactions similarly. The experimental observations may be rationalized on the expectation that many more orientations of a cumyl radical pair are suitable for the disproportionation than for combination, and as the rigid matrix is expected to have considerable orientational effects, this may be significant. In the frozen matrix, rotational motion of cumyl radicals within their cage may persist, while diffusion out of the cage is limited. One might also consider the possibility of local heating effects. Within a matrix cage, radical generation may be accompanied by some microscopic "melting," which would allow the rotational freedom necessary for the disproportionation, while diffusion from the cage into the body of the matrix is still restricted.

Two quanta photolysis may also be invoked. As cumyl radicals undoubtedly have a longer lifetime in the matrix, secondary photoexcitation may generate some anomalously "hot" cumyl radicals which may subsequently undergo more disproportionation as a consequence of hydrogen abstraction from the solvent.

Stepwise decomposition of azocume to yield cumylazo radicals which would subsequently produce hot cumyl radicals upon second quantum photolysis could be involved. Such a rationale is not unprecedented.[39,40] As quantum yield data are not available for this system, this rationale cannot be excluded.

Aditya and Willard[41] have recently published an ESR study of radical formation upon photolysis of hydroiodic acid in hydrocarbon and olefin matrices at 77°K. They reasoned that matrix photolysis of hydroiodic acid should provide a sufficient number of cage-escaped hydrogen atoms, so that other radical reactions, more closely related to the gas and liquid phase studies, could be observed. The small size of hydrogen atoms should favor its escape, as does the fact that conservation of momentum provides that nearly all of the kinetic energy of the separating radical pair accompanies the hydrogen atoms.

Photolysis of 0.1 mole % HI in pure 3-methylpentane for 90 minutes yielded 3-methylpentyl radicals, ostensibly by hydrogen abstraction from the solvent. Prolonged photolysis of 3-methylpentane without HI present produced no detectable radicals.

In 3 mole % ethene and 2-methyl-1-propene/3-methylpentane solutions, ESR spectra also revealed ethyl and t-butyl radicals, respectively formed by addition of hydrogen atoms to the olefins. In 3 mole % 2-butene, and 1-pentene/3-methylpentane solutions, spectra attributable to allylic radicals gradually replaced the 3-methylpentyl radical spectra upon standing at 77°K.

Among the radicals observed, those with greater steric bulk decayed more slowly. Thus t 1/2 ethyl < t 1/2 3-methylpentyl < t 1/2 t-butyl radical. The latter's ESR spectrum persisted at about 1/4 its initial intensity after 30 hours at 77°K following irradiation. The decay order here is again strongly indicative of matrix orientational and/or limited diffusion effects. The intensity of the ESR spectrum due to the 3-methylpentyl radicals produced by 60-90 minute photolyses of 0.1 mole % HI in 3-methylpentane at 77°K, always showed an initially rapid decay of about 20% of the intensity followed by a much slower decay. Second order plots (1/peak intensity vs. time) did not give straight lines. If two consecutive rate processes were involved, the shorter lived process appeared to be first order, which would be consistent with radical pair recombination, i.e., 3-methylpentyl radicals and iodine atoms. The rate determining step may be diffusion controlled reorientation of the bulky 3-methylpentyl radical. The formation of the alkyl iodide would be consistent with the observed increase in absorbance at 2500 Å paralleling the decay of the 3-methylpentyl radical ESR spectrum.

More recently, Willard and coworkers[42] have reported the first order decay of ESR signals from radicals generated by the photoactivation of N,N,N',N'tetramethylphenylenediamine in 3-methylpentane solutions of methyl chloride, methyl bromide and methyl iodide. The methyl radical so obtained has a half life of 16 minutes at 77°K, and is independent of the halide precursor. Furthermore, d_3-methyl radicals decay at the same rate, which does not depend upon the absolute or relative concentrations of methyl halide and tetramethylphenylenediamine. When the

viscosity of the matrix was changed by using various concentrations of 2-methylpentane in 3-methylpentane, the half life of the methyl radicals at 77°K, decreases with decreasing viscosity. The 16 minute half life in pure 3-methylpentane (viscosity ca. 10^{12} poise) drops to 10 minutes at about 10^{11} poise. It remains nearly constant at about 10 minutes from 10^{11} to 10^{8} poise, and drops to about 2 minutes at 10^{6} poise. These data again suggest the importance of diffusion and orientational control of the rate of radical recombination in rigid matrices.

SUMMARY

Experimental observations revealing some specific matrix physical phase effects were herein presented. In the spirit of stimulating polite controversy, one might cautiously generalize that reactive species photochemically generated in situ are most frequently deactivated by the solvent matrix. Subsequent reactions are thus correspondingly considerably more selective than in the gas or solution phases. Anomalously "hot" species may in fact be the only species energetic enough to escape recombination reactions within their parent cage. Such is simply suggestive.

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BIMOLECULAR CIS ELIMINATIONS IN CYCLIC SYSTEMS

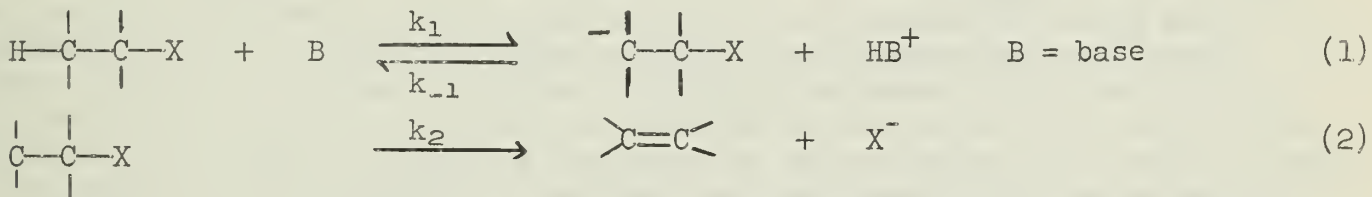
Reported by David J. W. Goon May 12, 1966

INTRODUCTION

Bimolecular eliminations appear to proceed most readily when the leaving groups, H and X, are situated in an antiperiplanar position (I). This is commonly denoted as trans elimination. The carbon atom bearing the substituent X is designated the α-carbon, and the carbon atom bearing the proton is the β-carbon. Several recent reviews of bimolecular eliminations present evidence for this stereospecificity.[1] A theoretical molecular orbital account has appeared recently.[2] However, cis eliminations or non-trans eliminations have been observed. These eliminations are usually found in cyclic systems in which rotation about the bond connecting the carbon atoms bearing the leaving groups is restricted. Evidence for cis elimination has been reviewed to 1962.[1a,b]

I

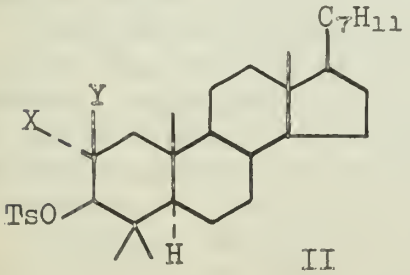
The observation of cis eliminations and rationalization thereof have initiated a controversy concerning the nature of the mechanism of such eliminations. Simply stated, the controversy concerns the extent of concertedness in cis eliminations. Presently, there appears to be a spectrum of possibilities. At one extreme is the E1 mechanism in which a carbonium ion is formed. This mechanism has little relevance to this seminar. A carbanion mechanism (E1CB) in which the H-Cβ bond is completely broken first (eq. 1-2) is at the other extreme. In the middle is the E2 mechanism where both the H-Cβ and X-Cα bonds are broken



simultaneously in the transition state. It is the prime purpose of this seminar to ascertain under what conditions cis elimination may become a predominant mode of elimination in cyclic systems and then to attempt to correlate the existing experimental evidence with the various mechanistic interpretations. In respect to the latter purpose, special consideration will be given to a theory recently postulated by DePuy[2b,2a] which emphasizes the conformation of the molecule in question. These problems will be approached by first considering the flexible cyclic systems, cyclopentyl and cyclohexyl, where the β-proton is rendered more acidic by the presence of a β-electron withdrawing group. This will provide background for the theory formulated by DePuy. Then, systems whose geometry prohibits trans elimination will be considered in light of the aforesaid theory.

CYCLOPENTYL AND CYCLOHEXYL SYSTEMS

It should be mentioned that there are a few reports of cis elimination as a predominant mode of elimination in a cyclohexyl ring in which the β-proton is not rendered more acidic by a β-electron withdrawing group. Levisalles, Ira and Pete have reported that the p-toluenesulfonates IIa and IIb give 91 and 73% of the cis elimination product, respectively, when treated with boiling collidine for five hours.[3] There is a possibility that the observed cis elimination is pyrolytic in nature. Brownlee and Saunders have reported that the trans tosylate and the trans trimethylammonium compound of 2-methylcyclohexane gave 52 and 94%, respectively, of 1-methylcyclohexene when refluxed in pyridine.[4] In one of the earliest observations of cis elimination in the cyclohexyl system, Stevens and



II

a. X = D, Y = H.

b. X = H, Y = D.

Grummitt reported that trans-1,2-dichlorocyclohexane reacted in three hours with refluxing quinoline to give 47% of cyclohexadiene-1,3 and 40% of 1-chlorocyclohexene.[5]

In a cyclohexyl system in which the leaving proton is activated, Arnold and Richardson observed that trimethyl-trans-2-phenylcyclohexylammonium hydroxide underwent Hofmann elimination to 1-phenylcyclohexene.[6] Weinstock and Bordwell showed that there was no tendency for the 3-phenylcyclohexene to rearrange to the 1-isomer under the reaction conditions or when heated with silver oxide.[7] Cristol, Stermitz, and Davies have also investigated elimination in trans- and cis-trimethyl-2-phenylcyclohexylammonium compounds along with the dimethylsulfonium analogues and observed rate ratios of trans elimination to cis elimination of 133 for the ammonium compounds and 383 for the sulfonium compounds.[8,9] An ylid intermediate is ruled out by the observation that no deuterium underwent exchange when deuterium was substituted on the α-carbon atom.

Bordwell and Pearson have published quite extensively on elimination reactions in general and also cis eliminations in the cyclopentyl and cyclohexyl systems. They observed that base-catalyzed elimination in trans- and cis-2-p-tolylsulfonylcyclohexyl p-toluenesulfonate and the corresponding trans and cis isomers in the cyclopentyl series yielded α,β-unsaturated sulfones.[10,11] The reactions were run in 50% aqueous dioxane and were first order in both tosylate and base concentration. Under reaction conditions, the 3-p-tolylsulfonyl-1-ene compound does not rearrange to the 2-p-tolylsulfonyl-1-ene compound in either system. As the dioxane content of the solvent is increased, the rate of elimination increases.[5] With sodium hydroxide in 50% dioxane and at 25°, the relative rates of reaction are 1 for the trans-cyclohexyl, 434 for the cis-cyclohexyl tosylates, and 62.6 and 1240 for the trans- and cis-cyclopentyl tosylates, respectively.[12] Thus, trans elimination is favored over cis elimination by a factor of 434 in the cyclohexyl series and 20 in the cyclopentyl series. With the trans- and cis-2-p-tolylsulfonyl cyclopentyl brosylates, trans elimination is favored over cis by a factor of 1.4 at 25° with trimethylamine as the base and 50% aqueous dioxane as the solvent.[14] General base catalysis was established by studying the rates of the tosylates with trimethylamine and triethylamine in the presence of varying concentrations of the corresponding salts. Although the concentration of hydroxide ion remains constant, the rates increase as amine concentration increases.[13] Eliminations with hydroxide ion as the base occur more rapidly than with trimethylamine which are in turn faster than with triethylamine. The ratio of the rate constants, k_{OH}/k_{Me_3N} and k_{Et_3N}/k_{Me_3N}, are smaller for cis elimination than for trans elimination.[10,13] In the cyclopentyl series, the rate of trans elimination to cis is 1.2 for trimethylamine, 6.5 for triethylamine, and 20 for hydroxide ion.

Bordwell and Pearson interpreted these observations as evidence that a "planar four-centered transition state is of very little importance in providing a favorable reaction path."[13] It was reasoned that since the presence of the electron-withdrawing β-sulfone group increases the acidity of the C_β-H bond, a difference in geometry from the preferred geometry plays a minor role in the cyclopentyl system. The observation of general base catalysis was interpreted to mean that a carbanion mechanism is very unlikely or that the carbanion had a half-life of less than 10^{-9} sec.[13] The dependence of rate on base, they attributed to steric and electrostatic repulsive forces. The greater rate of elimination in the cyclopentyl series over that in the cyclohexyl series was rationalized as due to partial relief of strain resulting from a reduction in the number of opposed hydrogens or other groups as the double bond is formed.[12]

The rates of base-catalyzed deuterium exchange of the cyclohexyl-1-d-p-tolysulfone and corresponding cyclopentyl sulfone were measured at several temperatures.[15] However, correlation of these rates with the rates of the tosylates is complicated by the fact that the inductive effect of the tosylate group must be estimated. Two different methods of estimation lead to contradictory interpretations as to whether a carbanion is consistent with the experimental observations.[16]

Goering, Relyea, and Howe have studied the rate of dehydrochlorination by sodium hydroxide of cis- and trans-2-chlorocyclohexyl arylsulfones and the corresponding cis-

and trans- cyclopentyl compounds in 80% aqueous ethanol. Trans elimination is 280 and 36 times faster than cis for the cyclohexyl and cyclopentyl sulfones, respectively.[17] A Hammett ρ-value of +1.42 is obtained for the trans-2-chlorocyclohexyl arylsulfones. The ρ-values of the other compounds are reported to be greater than zero. It was especially noted that the rate of elimination of trans-2-chlorocyclohexyl phenyl-sulfone was essentially the same as for the trans-2-tosyloxycyclohexyl phenyl-sulfone, 11.3×10^{-3} and 14.6×10^{-3} l. mole^{-1} sec.$^{-1}$, respectively. A two-step mechanism in which the first step leading to carbanion formation is rate-determining and irreversible was held to be consistent with these observations. Goering stated that the substituent effect and the similar reactivity of the tosylate and chloride were consistent with such a mechanism. It should be mentioned that his interpretation of the magnitude of their ρ-value is somewhat in question and will be discussed along with other observed ρ-values later.

Bordwell has found that with trans-acetoxy-2-nitro-1-phenylcyclohexane, acetic acid is eliminated 3.5 times faster than with the cis isomer with piperidine as the base and in 50% chloroform-ethanol at 35°.[18,19] He observed a relatively small dependence of relative rate on temperature and an increase in rate as solvent polarity increased. The energy of activation and entropy of activation are reported to be the same for both eliminations. Also, the rate increases on the addition of lithium bromide or tetrabutylammonium iodide. A deuterium isotope effect of 4.9 and a Hammett ρ-value of +1.49 are observed. Bordwell felt that these observations were "compelling evidence for a carbanion mechanism."[19] Also, since the response of both eliminations was identical in every instance, both cis and trans elimination involved a carbanion process. The primary factor was claimed to be steric hindrance to carbanion formation. This was supported by the fact that the rate ratio of cis elimination to trans elimination increases from 3.5 to 7.8 by the introduction of an axial methyl group on the 4-carbon atom. A conformational effect was ruled out on the basis that the nmr spectra of the trans isomer, the corresponding 4,4-dimethyl compound, and 1-acetoxy-cis-4-t-butyl-trans-2-nitro-1-phenylcyclohexane show that the H atom α to the nitro group was similarly situated in each. DePuy,[21] whose work will be presented next, seemed to agree with Bordwell's interpretation. However, although it is not stated by DePuy, there seems to be a disagreement on the interpretation of the magnitudes of the Hammett ρ-value and the isotope effect.

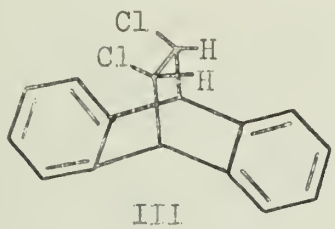
Using potassium t-butoxide and t-butyl alcohol, DePuy has studied the rates of elimination of 2-arylcyclopentyl and 2-arylcyclohexyl tosylates at 50°.[20,21] He observed that trans-2-phenylcyclohexyl tosylate was inert under reaction conditions. Cristol and Stermitz have made a similar observation except with potassium hydroxide as the base and ethanol as the solvent.[8] The ratio of trans elimination to cis is 9.1 in the cyclopentyl series and is greater than 10^4 in the cyclohexyl series. No isomerization of 3-phenylcyclopentene to the main product, 1-phenylcyclopentene, is observed. A deuterium isotope effect of 5.6 is observed with trans-2-phenylcyclopentyl-2-d tosylate at 50°. A Hammett ρ-value of +2.8 was obtained for the trans-2-arylcyclopentyl tosylates in potassium t-butoxide-t-butyl alcohol at 50° and +2.7 in sodium ethoxide-ethanol at 50°. For the corresponding cis-2-arylclopentyl tosylates, ρ-values of +1.5 and +1.0 in potassium t-butoxide-t-butyl alcohol and sodium ethoxide-ethanol, respectively, are obtained. The rate of reaction of trans-2-(m-chlorophenyl)cyclopentyl tosylate is 100 times slower in sodium ethoxide-ethanol than in potassium t-butoxide-t-butyl alcohol. It was noted that incorporation of the β-arylethyl system into a cyclopentyl ring reduces the rate of trans elimination by a factor of 2 in the t-butyl alcohol solution, but that the rate is increased by a factor of 6 in the ethanol solution.

DePuy felt that the ρ-values and relative rates were in accord with the view that eliminations in t-butyl alcohol have a transition state with less double-bond character than those in ethanol. Thus, trans elimination in the arylcyclopentyl series would be toward the E1 end of the E2 scale of eliminations in ethanol and back along the E2 scale in t-butyl alcohol. On the other hand, cis eliminations in the trans-2-arylcyclopentyl tosylates have a transition state in which breaking of the C-H bond is of greater importance. Based on the ρ-values and solvent effects, cis elimination in this cyclic system was thought to be similar to the open-chain

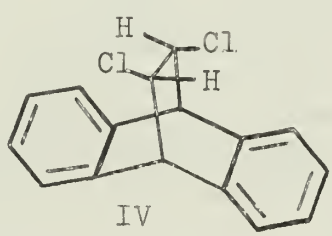
elimination observed in 2-arylethyl tosylates. For the 2-arylethyl tosylates, ρ-values of +3.4 and +2.3 at 50° in potassium t-butoxide-t-butyl alcohol and sodium ethoxide-ethanol, respectively, have been reported.[22] DePuy felt that there was no indication that cis elimination in the 2-arylcyclopentyl system proceeded by two steps although there appeared to be some E1CB character in these reactions. He substantiated this by stating that the ρ-value was too low and the isotope effect too high for a carbanion mechanism. Steric effects were ruled out on the basis that an axial proton is being removed in both cis and trans eliminations. He suggests that, since both cis and trans coplanar eliminations appear relatively favorable while non-coplanar eliminations are slow, a plot of rate of elimination versus the dihedral angle between the hydrogen and leaving group will show maxima at 0° and 180° and a minimum at 90°.

9,10-DIHYDRO-9,10-ETHANOANTHRACENE

The elimination of HCl has been studied in cis-(III) and trans-11,12-dichloro-9,10-ethanoanthracene (IV) by Cristol and Hause. The reaction was carried out with



III

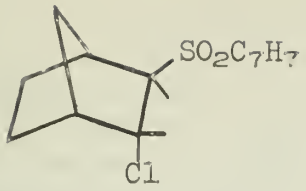


IV

a large excess of sodium hydroxide in 50% ethanol-dioxane. A yield of 83 and 85% of 11-dichloro-9,10-dihydro-9,10-ethenoanthracene was obtained from the cis and trans isomer, respectively.[23] The rate of elimination of the trans isomer is 7.8 times faster than the rate of the cis isomer. Cristol and Arganbright have also studied elimination in cis-(V) and trans-11-p-toluenesulfonyl-12-chloro-9,10-dihydro-9,10-ethanoanthracene (VI) using the same base and solvent as with the dichloro compounds. Both isomers V and VI dehydrochlorinate more rapidly than the corresponding dichloro isomers III and IV with the cis isomer (V) reacting three times faster than the trans isomer (VI).[24] It should be noted that the dehydrochlorination of III and IV was carried out at temperatures greater than 90° while the dehydrochlorination of V and VI was performed at 0° and 12°. The lack of stereospecificity of elimination and increase of reactivity caused by the replacement of the chlorine by the arenesulfonyl moiety were considered to be consistent with a carbanion mechanism. However, it should be noted that the dihedral angle between the chlorine and hydrogen atoms in the trans compounds of this ring system is 0° and that these experimental observations are completely consistent with conformational theory of DePuy. There does not appear to be any evidence for a carbanion mechanism other than that something unusual is occurring due to the geometry of the molecule.

NORBORNYL SYSTEM

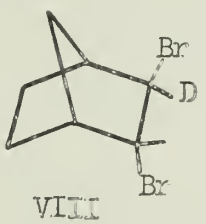
The bicyclic norbornyl system is another ring system in which the coplanarity necessary for the trans elimination is not possible. Roberts, Johnson, and Carboni have reported that while trans-2,3-dichloronorbornane did not undergo elimination after refluxing in quinoline for 2 hours, it did react with 20% conversion to 2-chloronorbornene after refluxing 30 hours with 20% potassium hydroxide-80% abs. ethanol.[25] Furthermore, the trans dichloride appears to dehydrochlorinate 2-3 times faster than the endo-cis-dichloride. No rationalization of these results was given. Cristol and Hoegger observed that trans-2,3-dichloronorbornane reacted 85 times faster than the endo-cis dichloride with sodium 1-pentoxide and 1-pentanol at 110°.[26] The exo-2-p-toluene-sulfonyl-endo-3-chloronorbornane (VII) dehydrohalogenates 70 times faster than the trans dichloride. However, the structure proof of VII does not rigorously exclude endo-2-p-toluenesulfonyl-exo-3-chloronorbornane as the possible



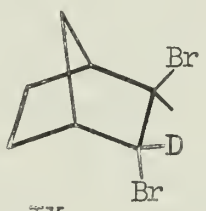
VII

starting material.[27] Cristol interpreted these observations as being consistent with a carbanion mechanism.[26,27]

Extensive studies of the kinetics and products of the elimination reactions of 2,3-dihalonorbornanes have been reported by LeBel. With ~~potassium t-butoxide~~ NaOAm in ~~t-butyl alcohol~~ AmOH at 110°, the rate of cis elimination is favored over trans elimination by factors of 31, 29, and 67 for the dibromides, chlorobromides, and dichlorides, respectively.[28] With potassium 2-methyl-2-butoxide and 2-methyl-2-butanol, the dehydrobromination of the endo-cis dibromo compounds is 71 times ~~faster~~ slower than that of the trans dibromo compound at 50° and 15 times ~~faster~~ slower at 110°. Product studies show that 2-bromo-2-norbornene is the only product from the elimination reaction of the dibromides while the chlorobromides eliminate hydrogen bromide to give greater than 95% 2-chloro-2-norbornene.[28,29] In a study of all possible 2-bromo-3-chloronorbornanes under varying conditions of base, solvent and temperature, LeBel observed that all except the endo-bromo-exo-chloronorbornane gave greater than 91% 2-chloro-2-norbornane after dehydrobromination.[30] The exception gives greater than 99% of 2-bromo-2-norbornene. Hydrogen-deuterium exchange experiments with the 2,3-d_2-endo-cis- and dideuterated trans-dibromonorbornanes indicated no exchange is occurring.[28] Isotope effects of 3.4 at 126.7° and 3.6 at 96.3° are obtained for the 2,3-d_2-endo-cis and trans-dibromonorbornanes, respectively. Monodeuterated endo-(VIII) and exo-trans-dibromonorbornanes (IX) were prepared and their rates of elimination were determined.



VIII

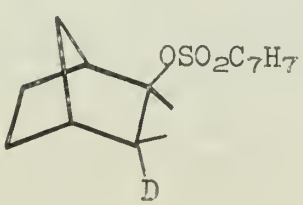


IX

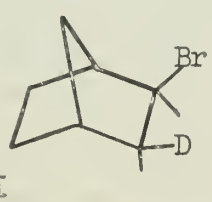
While a negligible isotope effect (for undeuterated VIII, $k = 8.12 \pm 0.12 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$; VIII, $k = 7.96 \pm 0.07 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, at 86.6°) is observed for VIII, a definite isotope effect ($k = 7.36 \pm 0.11 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ at 96.3°) is exhibited by IX.[30]

LeBel interpreted these results as indication that both cis and trans elimination occur by a very similar if not identical mechanism, a concerted one. He observed similar activation enthalpies and entropies for the 2,3-dibromo- and 2,3-dichloro-norbornanes and that the 2,3-dichlorides seemed to react more slowly because of enthalpy differences in spite of more favorable activation entropies.[28] The lack of deuterium exchange is a necessary but not sufficient criterion for a concerted process. It is claimed that the observed isotope effects are of the approximate magnitude necessary for a concerted process. The dependence of the products of dehydrohalogenation from the bromochlorides on the leaving group was considered to be consistent with the fact bromide ion is a better leaving group than chloride ion. Steric hindrance to endo-cis elimination was considered to be the only reasonable explanation for the prevalence of exo-cis elimination.

Kwart, Takeshito, and Nyce have studied elimination in 2-exo-p-toluenesulfonyl-3-endo-d-norbornane (X) and 2-exo-bromo-3-exo-d-norbornane (XI).[31] Thus, the



X



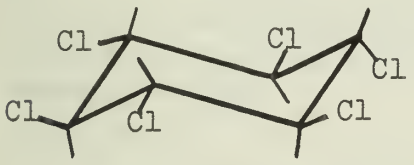
XI

influence of the β-electronegative group on the course of elimination would not have to

be considered in these cases. Potassium 3-methyl-3-pentoxide was employed as the base with 3-methyl-3-pentanol or p-cymene as solvent, and the reactions were run at 130°. In the more polar solvent, elimination in the tosylate yields 18% cis-elimination product, while in p-cymene, 65% of the cis-elimination and 30% of the trans elimination product are formed. The bromide gives 98% cis-elimination product in both solvents. These observations were interpreted to mean that cis elimination is concerted in nature. Elimination in the norbornyl system can be accommodated by the conformational considerations mentioned previously.

β-HEXACHLOROBENZENE

Cristol has studied the alkaline dehydrochlorination of β-hexachlorobenzene (XII), in which adjacent chlorine atoms are trans to one another and trans coplanar elimination of HCl is not possible. He observed that the rate of reaction of XII with sodium hydroxide in aqueous ethanol was 7,000 to 24,000 times slower than any of the other hexachlorobenzene isomers in which trans elimination was possible.[32,33] Product analyses show that 1,2,4-trichlorobenzene is the major product (>82%).[34,35]



XII

In independent studies, the loss of the first molecule of HCl is found to be rate determining.[33,34] Cristol ruled out repulsive forces as an important factor in influencing the elimination reaction in this system by estimating with use of Coulomb's law that the effect of electrostatic repulsion on the energy of activation was at most 3.6 kcal. mole.$^{-1}$ He felt this could not fully explain the 10-12 kcal. mole^{-1} difference in activation energy that was observed between the β and other isomers of hexachlorobenzene.[33] He further concluded that a carbanion mechanism was in effect in cis elimination of this system.

To test for the existence of a carbanion intermediate, Cristol and Fix studied the deuterium exchange of the β-isomer in sodium ethoxide in 70% deuterated ethanol-30% ethanol under conditions in which one-half of the starting material was dehydrochlorinated. Approximately 0.08 excess atom % of deuterium is observed in the unreacted hexachlorobenzene.[36] Hine investigated the trichlorobenzene mixture produced when the β-isomer was 70% dehydrochlorinated in 98% deuterated methanol-2% methanol. The mixture contains 88% of 1,2,4-trichlorobenzene and 3.1 ± 1.0% of 1,2,4-trichlorobenzene-3-d.[37] Cristol interpretated his results as confirmation of a carbanion mechanism in which approximately one out of every 150 carbanions formed was reprotonated with the others going to olefinic products. Hine felt that his results were indicative that carbanion formation was a major initiator of alkaline dehydrochlorination of β-hexachlorobenzene. He further argued that a concerted elimination which would require a conformation like a boat form would be unlikely since cis eliminations in general were slow and too great an energy would be needed to reach such a conformation.

Cristol and Barasch studied the rate of reaction of β-hexachlorobenzene as a function of temperature and solvent. A maximum in rate occurs as the water content of the aqueous ethanol used as solvent is changed.[38] Although Hughes, Ingold and Pasternak[34] observed the same phenomenon, their interpretation of it differed from that of Cristol and Barasch. The latter workers interpreted their results as a failure of the electrostatic theory of solvent effects. The former felt the anomalous behavior was due to a highly distorted transition state in which factors such as hydrogen bonding might arise which would introduce complications between theory and observation. They also felt that their own work and that of Cristol were indicative of a concerted process where the 10-12 kcal. mole^{-1} difference in activation energy observed between the β and other isomers of hexachlorobenzene was employed partly to force the molecule into a more desirable anti-configuration and partly to force the reaction against the still imperfect orientation of the bonds. In a concerted mechanism, it would seem that the charge of the base would be more dispersed in the transition state. The rate of reaction would be expected to decrease

as solvent polarity increases.[34] Hughes, Ingold and Pasternak interpreted their results as exhibiting a slight retardation in rate as the water content of the solvent was increased.

OTHER SYSTEMS

Bordwell has studied the effect of ring size on the elimination of acetic acid from 1-acetoxy-2-nitro-1-phenylcycloalkanes by amine bases in chloroform-ethanol. He found that in the heptyl compound cis elimination is 3.1 times faster than trans elimination.[19] He attributed this to steric hindrance to carbanion formation. Recently, Brown and Klimisch have reported that while trans-2-methylcyclopentyl tosylate and the corresponding cyclohexyl and cycloheptyl tosylates gave 99% of the 3-methylcycloalkene when treated with potassium t-butoxide in t-butyl alcohol at 50°, trans-2-methylcyclooctyl tosylate gave a 50-50 mixture of 1- and 3-methylcyclooctene.[39] The formation of the cis elimination product formed in the octyl system was attributed to the greater flexibility of the eight-membered ring.

CONCLUSION

It is apparent that cis elimination predominates over trans when the geometry of the molecule prohibits trans elimination. However, as was seen in the cyclohexyl systems, the presence of a β-aryl substituent, an electron withdrawing β-substituent, or a leaving group which is strongly electron withdrawing or appropriate combination thereof facilitates cis elimination over that of trans. From the evidence presented, it appears that dependence of cis elimination on solvent polarity is a function of the compound in question and the conditions of elimination. The effect of base strength is not readily apparent, but it does seem that the size of the base may have a significant role in determining the mode of elimination. The work of DePuy does present strong evidence that conformational effects are an important factor.

All the evidence presented in this seminar cannot be rationalized by one mechanism, i.e. a strictly E2 mechanism or E1CB mechanism. The rate dependences on solvent are especially conflicting. It should be noted that the effect of solvent on elimination reactions can be considered only in conjunction with the character of the reactants and of the transistion state.[1a,b] Recently, Breslow has pointed out that a carbanion mechanism should be distinguishable from an E2 mechanism by general versus specific base catalysis and by kinetic hydrogen isotope effects.[40] However, he also states ambiguities may occur which may obscure interpretation of experimental observations. It is generally accepted that in theory a maximum hydrogen isotope effect will occur for a completely concerted E2 reaction.[1c,41a] However, any theoretical calculation must ultimately be based on an absolute rate theory, none of which is completely rigorous or successful in predicting an absolute rate. Also dependence of the isotope effect on temperature has to be taken into account.[41b] The isotope effect of the leaving group X has been suggested as a means of determining the nature of the transition state in elimination reactions.[1c,42] Only studies with acyclic systems have been done, and the isotope effects observed have been interpreted as indication of some carbanion character in the transition state.[43] The interpretations of the magnitude of the Hammett ρ-value seem to be conflicting. However, DePuy's interpretation in which he draws an analogy with the ρ-values determined for the β-arylethyl system does seem to be the most persuasive. In conclusion, there does not appear to be one answer to what is the extent of concertedness in cis eliminations. There may never be, and in fact this problem is intimately related to whether trans eliminations are completely concerted. Depending upon the compound undergoing elimination and on the reaction conditions, cis bimolecular eliminations seem to be best rationalized in terms of the total spectrum of elimination reactions.

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LITHIUM DI-AND TRIALKOXYALUMINOHYDRIDES AS REDUCING AGENTS

Reported by Lennon H. McKendry May 19, 1966

Sodium borohydride[1,2] and lithium aluminum hydride[2,3,4] represent two extremes in their reducing ability. The former only reduces aldehydes, ketones and acid chlorides at a convenient rate, while the latter reduces numerous functional groups. The lithium di-and trialkoxyaluminohydrides have intermediate reducing powers, and have been found to be very selective in certain areas. Due to the ease of utilization of these intermediates and their apparently wide applicability, they should become very important reducing agents for the organic chemist.

PREPARATION

In a preliminary examination H. C. Brown and R. F. McFarlin[5,6] found that four equivalents of methanol, ethanol, or isopropanol react with one equivalent of lithium aluminum hydride in ethyl ether to yield the corresponding highly insoluble lithium tetraalkoxyaluminohydride. However, only three equivalents of t-butyl

$$LiAlH_4 + 4ROH \longrightarrow LiAl(OR)_4 + 4H_2$$

$$R = CH_3,\ CH_3CH_2,\ CH_3CHCH_3$$

alcohol react to give the tri-t-butoxy derivative as a stable insoluble white solid. This product can be sublimed at 280° at 2 mm. pressure and is soluble in both tetrahydrofuran (THF) and diglyme. When the same reaction is carried out in these solvents, identical results are obtained, and a clear solution remains. The fourth mole of t-butyl alcohol reacts only at elevated temperatures, thus, indicating that the tendency of the reaction to stop upon formation of the tri-t-butoxy derivative is not to be attributed to the formation of a precipitate. The reaction of t-amyl alcohol is analogous to that of t-butyl alcohol, but the tri-t-amyloxy derivative is soluble in ether. Three factors may be involved in preventing the fourth mole of tertiary alcohol from reacting with the lithium tri-t-alkoxyaluminohydride: steric effects due to the t-alkoxy groups, the decreased acidity of the tertiary alcohol compared to primary and secondary alcohols, and the lower reactivity of the remaining hydridic hydrogen in the anion.

Brown and McFarlin have also investigated the properties of the lithium tetraalkoxyaluminohydrides. Lithium tetramethoxyaluminohydride[7] had been previously prepared by the reaction of lithium methoxide with aluminum methoxide, and the ethoxy, isopropoxy and t-butoxy derivatives can be produced in the same manner.

$$LiOR + Al(OR)_3 \xrightarrow[\Delta]{} LiAl(OR)_4$$

The methoxy and ethoxy derivatives are soluble in methanol and ethanol respectively, but the other products are insoluble in their corresponding alcohols. All four products are insoluble in benzene, xylene, dioxane, acetone, ether, THF, and diglyme. Brown and Shoaf[8] investigated the reactivity of these compounds in a standardized lithium aluminum hydride solution using diglyme as the solvent. When three equivalents of lithium tetramethoxyaluminohydride are added, dissolution occurs resulting in a homogeneous solution of lithium trimethoxyaluminohydride. The tetraethoxy and tetraisopropoxy derivatives react at a much slower rate. After three days, some solid reactant still remains, and the aluminum to hydride ratio in the solvent is approximately 1:2.4. The insoluble t-butoxy derivative does not react at room temperature.

The reactions of isopropanol, sec-butanol, ethanol, and methanol have been investigated further in an attempt to find a convenient method of preparing the corresponding lithium di-and trialkoxyaluminohydrides.[8] A standardized solution of lithium aluminum hydride in ethyl ether, THF, or diglyme was treated with one, two, or three equivalents of the appropriate alcohol at room temperature. The amount of hydrogen evolved was measured, and the solution was analyzed for hydride and aluminum content. The composition of any solid that formed was determined by

difference. Since all of the tetraalkoxy derivatives are insoluble in the above solvents, the determination of the composition was made easier. The procedure was tested by using t-butyl alcohol which gave results identical to those previously discussed. It was also observed that in ether two equivalents of the alcohol caused an evolution of two moles of hydrogen, and the solution remained clear. Addition of slightly more than two equivalents caused the formation of a small quantity of white precipitate. The clear solution still consisted of only lithium di-t-butoxyaluminohydride.

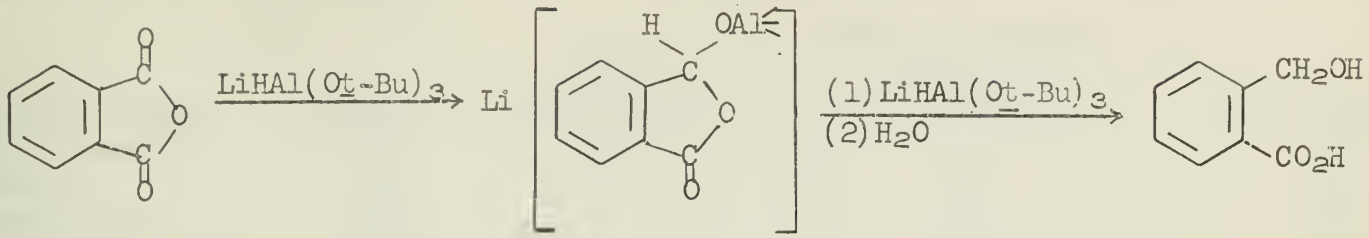
Unlike the above case, isopropyl alcohol reacts with lithium aluminum hydride to produce the tetraisopropoxy derivative as the major product. Thus when one equivalent of alcohol is utilized in ether, 22% of the available aluminum is precipitated, and the solution contains a hydride to aluminum ratio of 4:1. In diglyme or THF the quantity of precipitate decreases, but analysis of the solution indicates that more than one derivative has formed. Changes in reaction temperature from -80° to 65° and changes in the reactant from isopropyl alcohol to acetone have no significant effects. Sec-butyl alcohol reacts in a similar manner. Two equivalents of ethanol react with lithium aluminum hydride in ethyl ether to give a slight amount of white precipitate and an aluminum to hydride ratio of 1:2. Addition of a third equivalent produces a considerable quantity of precipitate believed to be the tetraethoxy derivative, and a solution with an aluminum to hydride ratio of 1:1.5. The solution is believed to be composed of the di-and triethoxy derivatives. In THF, no precipitation occurs when two equivalents of alcohol are added, but 30% of the available aluminum is precipitated when a 3:1 mole ratio is utilized. Diglyme causes even a greater degree of precipitation than does ethyl ether. The reaction of three equivalents of methanol with lithium aluminum hydride results in a clear solution. During the course of the dropwise addition, a white precipitate initially forms, but dissolves at a rate which decreases as the quantity of alcohol added increases. It is believed that the insoluble tetramethoxy derivative is immediately formed which then reacts with lithium aluminum hydride or its methoxy derivatives. In diethyl ether a 2:1 mole ratio of alcohol to lithium aluminum hydride causes complete precipitation of all the available aluminum. Addition of a third equivalent of methanol results in the evolution of a third mole of hydrogen. The resulting white solid is soluble in THF and diglyme and readily reacts with one equivalent of methanol in these solvents to produce the insoluble tetramethoxy derivative. Thus lithium trimethoxyaluminohydride appears to be insoluble in ether.

The fact that in ethyl ether two moles of t-butyl alcohol react with one mole of lithium aluminum hydride to yield lithium di-t-butoxyaluminohydride led Brown and Shoaf[8] to consider producing different mixed alkoxy derivatives. When one equivalent of methanol is added to an etheral solution of lithium di-t-butoxyaluminohydride, a mole of hydrogen is evolved. The resulting clear solution gives an aluminum to hydride ratio of 1: .99. Further addition of methanol causes the formation of a gelatinous precipitate. The reaction with ethanol is more complex causing some precipitation and yielding in the solvent an aluminum to hydride ratio of 1:1.47. Isopropyl alcohol reacts to give slightly soluble lithium isopropoxydi-t-butoxyaluminohydride.

REDUCTIONS WITH LITHIUM TRI-T-BUTOXYALUMINOHYDRIDE

The general reactivity of lithium tri-t-butoxyaluminohydride in THF was investigated by Brown and Weissman.[9] The procedure used is to add 10 mmoles of organic compound to 40 mmoles of reducing agent in enough THF to give 40 ml. of solution at 0°. The reaction takes place in the presence of a dry nitrogen atmosphere and any hydrogen evolved can be measured by means of an inverted gas buret. The progress of the reaction is studied periodically by hydrolyzing 5-ml. aliquots and measuring the amount of hydrogen evolved. Aldehydes and ketones such as cinnamaldehyde, benzaldehyde, and acetylphenone are rapidly reduced to give the corresponding alcohols upon hydrolysis. Acid chlorides and anhydrides rapidly react with two equivalents of reducing agent to give the corresponding alcohols.

In the latter case both molecules of reducing agent attack the same carbon atom as shown below. Carboxylic acids, esters, amines, amides, nitriles, sulfoxides,



and sulfones are usually unaffected under the above conditions while epoxides react very slowly. Brown and McFarlin[5] have investigated the reactivity of lithium tri-t-butoxyaluminohydride in ether and diglyme and obtained the same results as above. A summary of these results is given below.

REDUCING PROPERTIES OF LITHIUM TRI-T-BUTOXYALUMINOHYDRIDE

Compound	Utilization of Hydride in 0.5 hours (mmoles per mmole of compound) Ether	Diglyme	THF
Acetone	0.93	0.99	-
Acetophenone	-	.98	0.96
Chloral	.92	.99	-
Benzaldehyde	.90	.96	.86
Benzoyl chloride	1.91	1.93	1.88
p-Nitrobenzoyl chloride	1.83	1.89	-
Acetonitrile	0.0	0.0	-
Benzonitrile	0.0	0.0	0.0
Ethyl benzoate	0.0	0.0	0.0
Succinic anhydride	1.95	-	1.98
Phthalic anhydride	-	1.99	1.91
Benzyl chloride	-	0.0	-

Thus, lithium tri-t-butoxyaluminohydride approaches sodium borohydride in its reducing ability and is much less reactive than lithium aluminum hydride.[3]

Until recently, the most widely used method of reducing acid chlorides to the corresponding aldehydes has been the Rosenmund reduction.[10] In this process, the acid chloride is reduced with hydrogen over a palladium catalyst poisoned with a sulfur containing compound. Yields as high as 90% have been obtained. Two major difficulties with this procedure are reproduction of the precise poisoning to obtain

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl + H_2 \xrightarrow{Pd(S)} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + HCl$$

good yields, and the sensitivity of certain substituents to the reaction conditions.[11] Lithium aluminum hydride reduces the acid chloride completely to the alcohol stage in THF or diglyme while sodium borohydride does likewise in the latter solvent.[11,12] In both cases, the aldehyde appears to be more easily reduced than the acid chloride. In a preliminary investigation, Brown and McFarlin[5,6] have discovered that lithium tri-t-butoxyaluminohydride selectively reduces certain acid chlorides at low temperatures to give the corresponding aldehydes in high yields, while the trimethoxy, triethoxy, and triisopropoxy derivatives give only negligible yields. The procedure used is to precipitate lithium tri-t-butoxyaluminohydride from ether, dry

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl + Li(t\text{-}BuO)_3AlH \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + LiCl + Al(Ot\text{-}Bu)_3$$

it, and to dissolve it in diglyme. This solution is then added to the acid chloride over a period of one hour at -75°. The mixture is allowed to warm to 20°, poured onto crushed ice, filtered, and the solid is extracted several times with 90% ethanol. The solvent is evaporated, and the aldehyde remaining recrystallized from aqueous ethanol. A second procedure followed has been to generate the reducing agent in THF by adding three equivalents of t-butyl alcohol to a standardized

lithium aluminum hydride solution. This solution is then added to the acid chloride. However, this method produces lower yields, and thus the former procedure is preferred. The results are shown below.

Acid Chloride	Moles	Yield of Aldehyde THF By Analysis	Diglyme By Analysis	By Isolation
p-Nitrobenzoyl	0.244	-	-	80
Benzoyl	.256	65	78	73
Terphthalyl	.200	-	-	85
p-Toluyl	.056	-	61	-
m-Chlorobenzoyl	.074	-	63	-
o-Chlorobenzoyl	.174	-	36	20
Pivaloyl	.033	60	44	-

The analysis involves determining the quantity of the 2,4-dinitrophenylhydrazone obtained from a 5 ml. aliquot of the solution. The procedure could be greatly simplified if the isolation of lithium tri-t-butoxyaluminohydride could be eliminated, and Brown and Subba Rao[13] have investigated this possibility further. They have prepared the reducing agent by five different methods: A. The reagent is isolated from ether, dried, and dissolved in diglyme. B. The reagent is produced in ether followed by decantation of the solvent and dissolution in diglyme. C. The reducing agent is prepared as in B followed by addition of enough diglyme to dissolve the precipitate in the etheral solution. D. The reagent is prepared in diglyme. E. The reducing agent is prepared in THF. p-Nitrobenzoyl chloride is then reduced by the reagent, and the effects upon the yield of aldehyde are determined. Significant differences occur only when THF is used as the solvent.

Procedure	% Yield of p-Nitrobenzaldehyde As 2,4 Dinitrophenylhydrazone	Isolation Crude	Pure
A	-	81	67
B	-	80	67
C	-	78	63
D	84	80	66
E	70	65	53

Brown and Subba Rao[13] have studied the effects of temperature on the reaction and found that the yield of aldehyde decreases as the temperature increases as shown below.

EFFECT OF TEMPERATURE

Acid Chloride	% Yield of Aldehyde[a] -78°	-40°	-10°
Benzoyl	81	74	58
p-Nitrobenzoyl	84	66	53
o-Chlorobenzoyl	41	44	35
Cinnamoyl	71	67	64
Pivalyl	58	57	46

a. Analyzed as the 2,4-dinitrophenylhydrazone.

Two competitive reactions may be occurring with the latter having a higher transition state energy. Thus, it will be favored by an increase in temperature

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl + LiHAl(O\underline{t}\text{-}Bu)_3 \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + LiCl + Al(O\underline{t}\text{-}Bu)_3$$

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + LiHAl(O\underline{t}\text{-}Bu)_3 \longrightarrow LiHCH_2OAl(O\underline{t}\text{-}Bu)_3$$

causing the aldehyde yields to decrease. However, no experimentation has been done to verify this hypothesis. The selectivity of the reduction has been investigated by reducing acid chlorides containing other functional groups. Yields of 60-80%

are obtained with the aromatic acid chlorides comparable to those for the Rosenmund[10,11] process, and 40-60% yields are obtained for the aliphatic derivatives. The results indicate that nitro, cyano, carbethoxy and even aldehyde groups can be

Acid Chloride	% Yield of Aldehyde			
	As 2,4-Dinitrophenylhydrazone		Isolation	
	Crude	Pure	Crude	Pure
p-Tolyl	61	-	-	-
p-t-Butylbenzoyl	77	-	70	63
p-Nitrobenzoyl	84	-	81	67
m-Nitrobenzoyl	88	-	-	-
o-Nitrobenzoyl	77	64	74	61
p-Carbethoxybenzoyl	48	-	-	-
Terephthalyl	82	-	85	77
Isophthalyl	77	-	80	64
α-Naphthoyl	84	68	-	-
Cinnamoyl	71	-	65	50
Cyclopropanecarboxyl	42	-	52	-
p-Cyanobenzoyl	87	77	80	68

tolerated. Double bonds conjugated to the acyl group offer no difficulty. Thus due to the simplicity of the procedure, the wide applicability of the reaction, and the fairly good yields obtained, this process of producing aldehydes appears to have general applicability.

LITHIUM TRIETHOXYALUMINOHYDRIDE

In the past the Stephen reaction[14] has been the principle process used for converting nitriles to aldehydes. Stannous chloride is usually used as the reducing agent, and an imino-chloride is formed as an intermediate. This procedure works well

$$RCN + HCl \xrightarrow{Et_2O} R\text{-}\overset{\overset{N\text{-}H}{\|}}{C}\text{-}Cl$$

$$R\text{-}\overset{\overset{NH}{\|}}{C}\text{-}Cl + SnCl_2 + 2HCl \longrightarrow RCH{=}NH\cdot HCl + SnCl_4$$

$$RCH{=}NH\cdot HCl + H_2O \longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}H + NH_4Cl$$

for most aromatic compounds, but has proved unsatisfactory for many aliphatic nitriles.[15,16,17,18] Sodium triethoxyaluminohydride[17] has been found to be excellent for converting aromatic nitriles to the corresponding aldehydes. However, aliphatic compounds give very low yields in this process. Nitriles are reduced completely to the corresponding amines by catalytic hydrogenation[19,20,21] and are unaffected by sodium borohydride.[2,22] Brown and Shoaf[8] have investigated the reduction of n-butyronitrile at 25° using various lithium trialkoxyaluminohydrides prepared in situe. Lithium triethoxyaluminohydride appears to be the best reducing

$$R\text{-}C{\equiv}N + LiHAl(OR)_3 \longrightarrow Li\,\begin{matrix}R\\H\end{matrix}\!\!>\!C{=}N\text{-}Al(OR)_3$$

$$Li(RO)_3Al\text{-}N{=}C\!<\!\begin{matrix}R\\H\end{matrix} + 5H_2O \longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}H + LiOH + NH_3 + Al(OH)_3 + 3ROH$$

REDUCTION OF n-BUTYRONITRILE

Reagent	% Yield of Aldehyde Analyzed as 2,4-Dinitrophenylhydrazone		
	Ethyl Ether	THF	Diglyme
$LiAlH_4$	22	23	21
$Li(MeO)_3AlH$	31	15	19
$Li(EtO)_3AlH$	59	25	15
$Li(i\text{-}PrO)_3AlH$	30	25	15
$Li(t\text{-}BuO)_3AlH$	0	0	0

agent and ethyl ether the best solvent. Upon further investigation of the above reduction at 0°, Brown and Garg[23] find that lithium triethoxy-(69% yield), tri-n-propoxy-(69% yield) and tri-n-butoxyaluminohydride(77% yield) give the best results in ether. Again the reducing agents are prepared in situe by adding three equivalents of the appropriate alcohol to a standardized lithium aluminum hydride solution. It must be remembered that the lithium triethoxyaluminohydride solution is a complex mixture containing both the diethoxy and triethoxy derivatives. Further investigation on a series of nitriles has indicated that the lithium tri-n-butoxyaluminohydride solution must be warmed in certain cases so the triethoxy derivative has been chosen as the desired reducing agent. It is also much easier to remove ethanol than n-butyl alcohol after hydrolysis. Brown and Garg[23] then investigated the effects of reaction conditions on the reduction of n-butyronitrile with lithium triethoxyaluminohydride. Addition of the nitrile to the reducing agent or vice versa gives the same yields. The reagent is prepared at -80°, 0°, and 25° and brought to 0°. The nitrile is then added and after one hour the solution is analyzed. The aldehyde yield is greatest for the reagent synthesized at 0°. After the nitrile has been added to the reagent, the reaction mixture is allowed to stand for various lengths of time. The yield is 69% after .25 hour, 67% after 1 hour and 45% after 3 hours indicating the reaction should be limited to one hour. A 1:1 molar ratio of reactants also gives the best yield. The reduction of a series of nitriles with lithium triethoxyaluminohydride has been carried out and 70 to 90% yields[24] of aldehyde have been obtained. The above reagent was also compared to the Stephen[14] procedure and the results are shown below.

COMPARISON OF ALDEHYDE YIELDS

Nitriles	% Yield of Aldehyde Stephen Reduction	% Yield of Aldehyde $Li(EtO)_3AlH$ Reduction
Capro-	0	69
Isocapro-	31	-
Isobutyro-	-	81
γ-Phenoxybutyro-	79	66
Cinnamo-	40,65	61
Benzo-	97	96
o-Chlorobenzo-	Nearly quant.	87
p-Chlorobenzo-	Nearly quant.	92
o-Tolu-	9	87
α-Naphtho-	7	80

Thus, the simplicity of the procedure and the high yields obtained make this a very useful reduction process.

Lithium aluminum hydride reduces unsaturated N-acylcarbazoles,[25] 1-acyl-3,5-dimethylpyrazoles[26] and several N-methylanilides[27] to the corresponding aldehydes in satisfactory yields. However, in the above cases the power of the reducing agent is controlled by the steric and electronic characteristics of the tertiary amide. Brown and Tsukamoto[28] have investigated the selective reduction of N,N-dimethyl-n-butyramide with the lithium dialkoxy- and trialkoxyaluminohydrides. The reducing agent is prepared in situe in ether and the reaction is carried out at 0°. The

$$LiHAl(OR)_3 + R{-}\overset{O}{\overset{\|}{C}}{-}N{<}^{R'}_{R''} \longrightarrow Li\ R{-}\overset{OAl(OR)_3}{\overset{|}{\underset{H}{\underset{|}{C}}}}{-}NR'R''$$

$$Li\ R{-}\overset{OAl(OR)_3}{\overset{|}{\underset{H}{\underset{|}{C}}}}{-}NR'R'' + 4H_2O \longrightarrow R{-}\overset{O}{\overset{\|}{C}}{-}H + HNR'R'' + LiOH + Al(OH)_3 + 3HOR$$

aldehyde is analyzed as the 2,4-dinitrophenylhydrazone. Lithium di- and triethoxyaluminohydride give the best yields which are thrice that of lithium aluminum hydride. The effects of varying the structure of the tertiary amide group of n-butyric acid were then investigated since the reduction with lithium aluminum hydride[29] is very sensitive to this. The above procedure is again utilized. In general the reducing ability of the di- and triethoxy derivatives is only slightly

t-Amide of n-Butyric Acid	% Yield of n-Butyraldehyde $LiAlH_4$ in Ether	$Li(MeO)_3AlH$ in Diglyme	$Li(EtO)_3AlH$ in Ether	$Li(EtO)_2AlH_2$ in Ether
Dimethylamide	16-25	55-60	86-92	77-83
Diethylamide	22	5	59	47
Diisopropylamide	N.R.	N.R.	N.R.	N.R.
N-Methylanilide	58	47	69	82
Pyperidide	33	-	68	67
Pyrrolidide	16	36	70	50
Aziridide	88	-	87	83
Pyrrolide	30	-	46	39

dependent upon the structure of the amide. Brown and Tsukamoto also found that the yields are not effected when relatively hindered acyl amides[30] such as N,N-dimethylbenzoylamide are used. A series of aliphatic N,N-dimethylamides have been reduced, and the corresponding aldehydes are obtained in 60-80% yields by isolation. Chloro and thio groups and double bonds not conjugated to the carbonyl group can be tolerated. When the double bond is conjugated, it is selectively reduced. Thus, this procedure appears to offer a very easy method of converting acyl amides to the corresponding aldehydes.

LITHIUM TRIMETHOXYALUMINOHYDRIDE

Brown and Weissman[31] have investigated the reactivity of lithium trimethoxyaluminohydride[2] in THF at 0° and find that it approaches lithium aluminum hydride[3] in its reducing power. The reagent is prepared *in situe*. Aldehydes, ketones, oxides, acid chlorides, and esters are rapidly reduced to the alcohol stage, lactones to glycols, and nitriles to both the corresponding aldehydes and amines. Epoxides are reduced very slowly and selectively to yield the more hindered alcohol. It reduces disulfides to thiols and reacts with alcohols, phenols, thiols, and primary and secondary amines. Unlike lithium aluminum hydride it does not reduce cyclohexanone oxime, azobenzene and cyclohexyl tosylate. Epoxides are reduced much more rapidly by lithium aluminum hydride. The trimethoxy derivative has advantages over lithium aluminum hydride due to the fact that it has only one available hydrogen preventing cross linking and the formation of a number of intermediates of varying activities.

STEREOSPECIFIC REDUCTIONS

The alkoxy substituted lithium aluminum hydrides have been found to be much more stereoselective than either lithium aluminum hydride or sodium borohydride. Thus, lithium tri-t-butoxyaluminohydride has been used for the stereospecific reduction of the keto groups in steroids[32,33] to give the more hindered alcohols. Brown and Deck[34] have investigated the stereoselective reductions of cyclic and bicyclic ketones with lithium aluminum hydride and the trimethoxy, triethoxy, and tri-t-butoxy derivatives derived from it. With the monocyclic ketones the triethoxy and tri-t-butoxy derivatives give the same yields of the more sterically hindered cis alcohol as does lithium aluminum hydride. The trimethoxy derivative gives considerably higher yields, however. The reduction of the bicyclic ketones is stereoselective with all of the reagents yielding the more hindered alcohol in 80-98% yields. Again the triethoxy and tri-t-butoxy derivatives give about the same isomeric ratio as lithium aluminum hydride, but the trimethoxy derivative gives a much larger percentage of the cis isomer. In all cases, THF is used as the solvent.

REDUCTION OF NORCAMPHOR

Ketone	Mmoles	Reagent	Mmoles	Hydride used mmoles	Alcohol found mmoles	Product %endo
Norcamphor	20	$LiAlH_4$	20	21.9	19.2	89
	15	$LiAlH(OMe)_3$	20	17.9	15.1	98
	15	$LiAlH(OEt)_3$	20	16.4	15.3	85
	15	$LiAlH(O\text{-}t\text{-}Bu)_3$	20	13.5	14.5	93

The results of the trimethoxy derivative may be due to its greater steric effects compared to lithium aluminum hydride. The triethoxy reagent actually contains lithium diethoxy- and triethoxyaluminohydride which could cause it to be less stereoselective than the trimethoxy derivative. It is believed that the reduction with the tri-t-butoxy derivative does not involve a simple hydride transfer but this has not been investigated.

CONCLUSION

By placing alkoxy groups on lithium aluminum hydride, its reducing power can be decreased and its selectivity increased. New general procedures of producing aldehydes from various acid derivatives have been found using these substituted compounds. The simplicity of the procedures and the high yields obtained make them very desirable methods. Finally the stereospecificity of lithium trimethoxy-aluminohydride offers new methods of obtaining isomers of relatively high purity.

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THE MECHANISM OF THE BECKMANN REARRANGEMENT

Reported by Daniel B. Dixon May 26, 1966

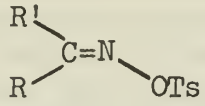
The Beckmann rearrangement was first discovered in 1886 when benzophenoneoxime was found to rearrange to benzanilide when treated with phosphorus pentachloride.[1] This carbon-to-nitrogen rearrangement of oximes to produce isomeric amides has been developed into a very useful method of synthesis and degradation and also has become an accepted method for oxime configuration determination. The rearrangement proceeds by Lewis acid catalysis with the catalyst usually being in equivalent quantities or greater. Some of the more common catalysts are phosphorus pentachloride in ether, concentrated sulfuric acid, polyphosphoric acid, hydrochloric acid in acetic acid/acetic anhydride, and arylsulfonyl chlorides, and solvents used vary from hydrocarbons to concentrated acids. Oxime sulfonates also rearrange with mild heating in the absence of acid catalysts. Many catalysts create, if possible, oxime esters or ethers which then spontaneously rearrange, while others react with the oxime to produce some type of rearranging species. In any event, all catalysts seem to act by causing the creation of a conjugate base of a strong acid during the migration. This is evidenced by the observation that the oxime esters derived from stronger acids rearrange faster. In general the rate of reaction increases in various solvents as the ionizing ability of the solvent increases.[2,3] This seminar will present evidence for the mechanism of the rearrangement and will contain only the pertinent references, as the Beckmann rearrangement has been well referenced in the most current reviews.[4,5]

MECHANISM OF THE REARRANGEMENT OF OXIME TOSYLATES IN AQUEOUS ETHANOL

The large variety of catalysts and solvents commonly used in the Beckmann rearrangement makes it impossible to assign one mechanism to the rearrangement. Each set of conditions can produce a different mechanism and certainly, each catalyst produces a different rearranging species. However all mechanisms should have three steps in common, conversion of the oxime to the rearranging species, rearrangement, and conversion of the intermediate to the isolated product.

Grob has proposed a mechanism for the Beckmann rearrangement of oximetosylates in 80% ethanol based upon a kinetic study.[6] The oxime toluenesulfonates were rearranged at various temperatures with a two molar equivalent of triethylamine added to neutralize the toluenesulfonic acid formed. The rate of reaction was followed conductometrically. All the reactions were determined to be first order in oxime toluenesulfonate concentration. It is seen from Table 1 that the rate increases with increased branching due to inductive stabilization, but the effect on the rate of rearrangement is much less than the effect on the rate of solvolysis of the corresponding alkyl chlorides. There is no relationship between the relative rates of rearrangement of the oxime tosylates and the corresponding alkyl chloride solvolyses. Of the compounds compared, the rearrangement rates are almost constant while the solvolysis rates increase rapidly with charge stabilization. These data point to an electron deficient species in the transition state but with less concentration of positive charge than of a carbonium ion. That the rates do not increase linearly with increased branching is attributed to a decrease in the solvation of the transition state caused by steric crowding. The appreciable rate of rearrangement of 1-bicyclo[2.2.2]octylmethylketoxime tosylate is further evidence for the lack of carbonium ion character in the rearrangement process. It is also observed that alkyl migration is faster versus stationary methyl than stationary phenyl and phenyl migration is faster versus stationary phenyl than methyl. This indicates that the transition state of phenyl migration has a different charge distribution than that of alkyl migration.

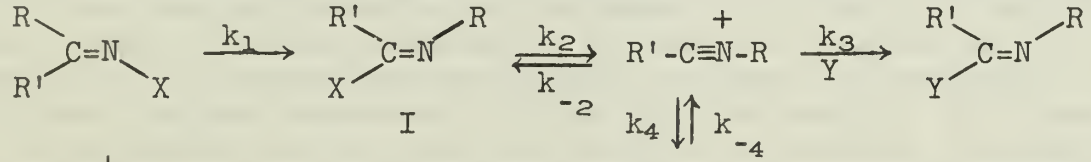
Table 1. Rate constants of some ketoxime tosylates in 80% ethanol at 23°



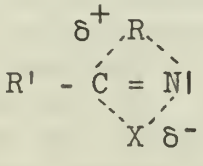
R=	R'=	kx10^5	$k_{rel.}$	R'Cl solvolysis, $k^{25°}$ x10^5
CH_3	CH_3	1.07	1	
"	C_2H_5	64.8	60	
"	$CH(CH_3)_2$	868	810	$<1x10^{-3}$
"	$CH(C_6H_5)_2$	43.1	40	172
"	1-bicyclo[2.2.2]octyl	510	480	
"	$C(CH_3)_3$	931	870	0.924
"	$C(CH_3)(C_2H_5)C_6H_5$	878	820	528
"	C_6H_5	106	100	
C_6H_5	$CH(CH_3)_2$	45.8	1	
"	$C(CH_3)_3$	55.3	1.2	
"	$C(CH_3)(C_2H_5)C_6H_5$	247	5.4	
"	C_6H_5	288	6.3	
cyclopentanoneoxime tosylate		78.5	1	
diethylketoxime tosylate		221	2.8	
cyclohexanoneoxime tosylate		1660	21	

To answer the question of whether the migration produces directly a linear nitrilium salt in the rate determining step or a trigonal intermediate, Grob examined the rate of rearrangement of cyclopentyl-, cyclohexyl-, and diethylketoxime tosylates. The constrained cyclopentyl and cyclohexyl systems cannot form a linear intermediate if this is the rate determining step. The relative rates observed, cyclopentyl:diethyl:cyclohexyl equals 1:2.8:21, show that the rate determining step is not migration to a linear structure but to a structure that is bent about the carbon-nitrogen double bond. Thus the relative positions of group attachment are not essentially altered in the rate determining step.

As seen, these polar and steric affects are not compatible for the direct formation of a nitrilium ion in the rate determining step. Further evidence is the appreciable rate of rearrangement of oxime tosylate in poorly ionizing solvents. From this evidence, Grob has proposed a rate determining intramolecular rearrangement to an iminotosylate, I, which rapidly goes to the corresponding nitrilium ion in ionizing solutions, from which the final products are formed. The transition state,



I

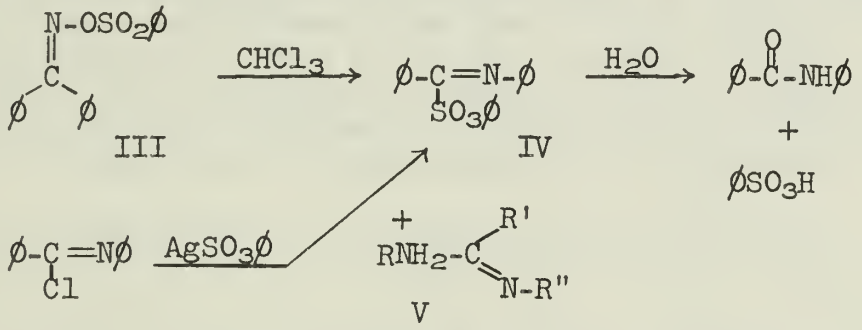


II

II, is formulated as an intimate ion pair which would explain the acceleration of reaction in polar solutions but avoids the appearance of a cationic center at the

oxime carbon. This description invokes simultaneous motion of R, R', X and the electron pair of nitrogen and explains the normal reaction rates of the cycloalkyloxime tosylates. The iminotosylate, I, ionizes rapidly in polar solutions with a rapid structural change to the more stable linear nitrilium ion from which fragmentation or addition of a nucleophile Y occurs to form the observed products. This mechanism, however, need not be in operation in the case of phenyl migration. The greater stability of a phenonium ion could stabilize a cationic transition state created by a one step simultaneous migration-ionization process which forms the nitrilium ion in the rate determining step. The two step migration-ionization mechanism should also change to a one step process forming the nitrilium ion when group X leaves through complex formation, i.e., when chloride leaves as a hexachloroantimonate anion. A simultaneous rearrangement-ionization to a nitrilium ion might also occur in the phosphorus pentachloride rearrangement in polar or nonpolar solvents. However, the two step rearrangement-ionization mechanism might still be operating.

That imidyl derivatives of type I are actual intermediates was first demonstrated by Kuhara in the rearrangement of the benenesulfonyl ester of benzophenoneoxime (III) in an inert solvent.[7] When compound III was rearranged in chloroform, an oil was obtained which readily reacted with water to give benzanilide and benenesulfonic acid. The oil was proposed to be phenylbenzimidobenzenesulfonate (IV) which was independently synthesized by the reaction of the corresponding chloride and silver benzenesulfonate. The two compounds were identical in their adsorption spectra and



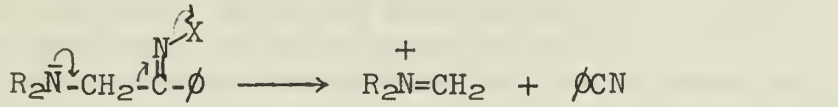
their reactivity toward water. Although the imidyl intermediates can seldom be isolated, Oxley and Short further demonstrated their existence by rearranging oxime sulfonates in the presence of amines to give amidine salts (V).[8] Rearrangement in the presence of alcohols, phenols, or amides also gives similar derivatives.

As indicated in the mechanistic scheme, the amide formation/fragmentation ratio depends upon the relative rates of the two rapid reactions of the nitrilium salt, k_3/k_4, as well as the rate of recombination of the nitrile and carbonium ion. Thus the degree of fragmentation depends upon the magnitude of the ratios k_3/k_4, k_4/k_{-4}, and the nucleophilicity of Y. In solutions where no good nucleophile is present, as in polyphosphoric acid or concentrated sulfuric acid solutions, fragmentation is determined by the rate ratio k_4/k_{-4}. The addition of water upon completion of the reaction converts the intermediates to an isolatable form.

Grob has identified a nitrilium salt intermediate first isolated by Theilacker and Mohl.[9] Benzophenonechlorimine was rearranged by antimony pentachloride in chloroform, a poorly ionizing solvent. A compound was isolated in 90% yield and was identified as the N-phenylbenzonitrilium salt from its decomposition product and by infrared spectral comparison with an authentic sample. Grob similarly prepared the nitrilium salt, N-t-butylbenzonitrilium hexachloroantimonate, obtained from the rearrangement of pivalophenonechlorimine with antimony pentachloride in carbon tetrachloride. The isolated salt possessed an infrared absorption band (nujol) at 4.30 μ, identical with the authentic compound.

It is not unusual for Beckmann rearrangement products to be accompanied by nitriles and carbonium ion products. These unusual products occur from fragmentation upon rearrangement, and this process of formation has been termed the Beckmann fragmentation reaction. Beckmann fragmentation readily occurs when one of the groups attached to the oxime carbon is capable of forming a stabilized cation.

The fragmentation products are found for most aldoxime rearrangements and for rearrangements where the α-carbon is trisubstituted, a carboxyl, a carbonyl, or carries a hydroxy or amino group. Grob and coworkers[10] have shown that the fragmentation of an α-amino substituted ketoxime occurs by a synchronous elimination mechanism which proceeds much faster than the normal Beckmann rearrangement.

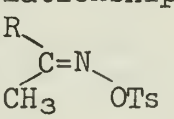


equation 1

X=ester or ether of a strong acid

Grob also suggests that this same mechanism should be operative for fragmentation when substituents on the α-carbon create a group with high electron donating character, as the groups named above possess. However the trisubstituted carbon is not capable of donating electrons so readily and a second mechanism may be operative in which fragmentation occurs from a normal rearrangement intermediate. With this in mind, Grob has interpreted his data to prove that this is indeed the case for α-trisubstituted ketoximes.

Grob examined the rates of reaction and the product composition of the oxime tosylates in 80% ethanol as listed in Table 2.[6] If the mechanism is direct fragmentation then the relative rates of oxime reaction would be of the same order as the corresponding alkyl chloride solvolysis under the same conditions. If the observed relative rates are different from that of alkyl chloride solvolysis, then the fragmentation is occurring from the normal Beckmann pathway. The amount of amide in the products was determined by isolation while the amount of nitrile was determined from isolation by distillation followed by hydrolysis and titration of the acid formed. As seen from the data, there is no relationship between the amount

Table 2. Relative Reaction Rates and Fragmentation of 

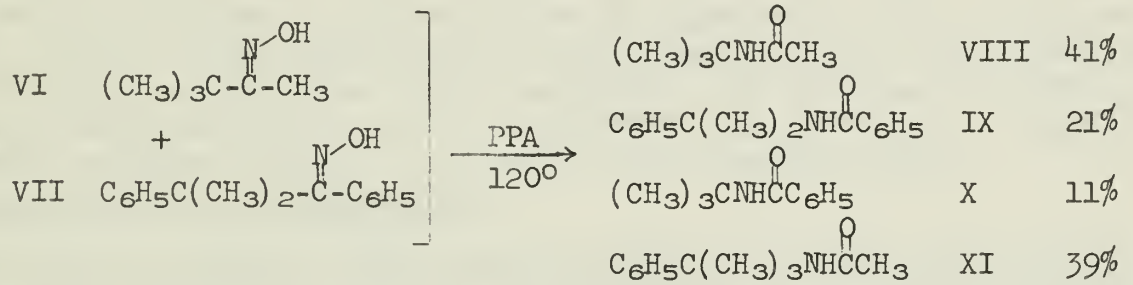
R	Fragmentation (%)	$k_{rel.}^{23°}$	$k_{rel.}^{25°}$ (RCl)
$CH(CH_3)_2$	--	1	<0.001
$C(CH_3)_3$	10	1.1	1
$CH(C_6H_5)_2$	54	0.05	186
$C(CH_3)(C_2H_5)C_6H_5$	80	1.01	572

of fragmentation and the rate of reaction. There also is no relationship between the rate of rearrangement and the rate of the corresponding chloride solvolysis. It is seen that the fragmentation yields follow the order of magnitude of the relative rates of ionization of the alkyl chlorides which shows that the degree of fragmentation corresponds to the stability of the carbonium ion formed. Thus by inspection of the relative rates one sees that fragmentation does not occur in the rate-determining step of a direct fragmentation mechanism such as in equation 1, but by secondary reaction of an intermediate formed after the rate determining step.

Grob proposed that the oxime sulfonates all rearrange through the previously determined pathway to form an imino sulfonate which is the rate determining step as evidenced by the almost identical relative rate constants in Table 2. The imino sulfonate then rapidly changes to a linear nitrilium ion, from which the fragmentation occurs. That the nitrilium ion is the source of the fragmentation products is evidenced by the reaction of Pivalophenoneoxime sulfonate in 70% aqueous dioxane at thirty degrees to give 75% of the expected amide and 11% of the benzonitrile. N-t-butylbenzonitrilium tetrachloroferrate reacted under identical conditions but at zero

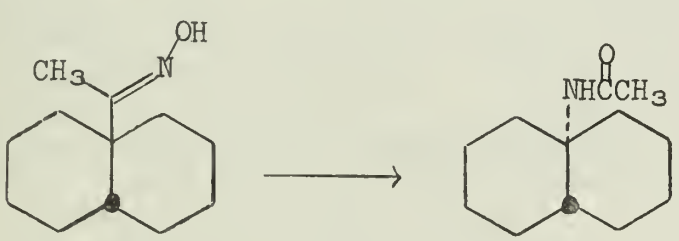
degrees gave 72% of the same amide and 27% of benzonitrile. Thus Beckmann fragmentation has adequately been demonstrated in this system to proceed from a nitrilium ion after the rate determining step of the normal Beckmann rearrangement.

Recently, Conley and Hill have presented evidence[11] that the fragmentation reaction proceeds by direct elimination from an oxime in polyphosphoric acid to give the fragmentation products, which can also recombine to yield the normal Beckmann rearrangement products. A crossover study was undertaken to demonstrate fragmentation. If a free carbonium ion and a nitrile are formed and recombine by a Ritter reaction, then two different oximes reacted together should give four amides as products. When equimolar quantities of pinacolone oxime (VI) and 2-methyl-2-phenylpropiophenone oxime (VII) were heated at 120° in polyphosphoric acid for ten minutes, four amides were obtained as shown plus 35% of benzamide, a known decomposition product of IX under these conditions. A check was made to show



that the normal amides VIII and IX were not involved in forming the crossed amides by heating a mixture of them under the reaction conditions. No crossed amides were found, and VIII was isolated in 94% yield, IX in 48% yield and benzamide in 40% yield.

A stereochemical study was carried out using cis-9-decalylmethylketoxime.[11] If fragmentation occurs followed by recombination, the amide formed should be a mixture of cis and trans isomers. The cis oxime was rearranged in polyphosphoric acid (PPA) and in sulfuric acid to give the trans amide in varying yields. However when rearrangement was effected by toluenesulfonyl chloride in pyridine, the cis amide was obtained in high yield. That cis amide does not rearrange to the trans form is evidenced by 90% recovery of the cis amide from PPA or sulfuric acid at room temperature.



PPA, 25°, 61% trans
PPA, 125°, 12% "
H_2SO_4 (85-90%), 40% "
H_2SO_4 (98%), 47% "

Hill and Conley interpret these data as evidence for the rearrangement of α-trisubstituted oximes to proceed through a two step fragmentation-recombination pathway in strong acid. However, both the crossover data and the stereoisomerization of the cis-decalin derivative may be explained by the normal Beckmann rearrangement to a nitrilium cation from which the observed fragmentation could take place. Until rate data comparable to that of Grob's are obtained or an optically active substrate is used there is no way of knowing by which path rearrangement or fragmentation products are being formed in polyphosphoric acid.

THE MECHANISM IN CONCENTRATED SULFURIC ACID

The mechanism of the sulfuric acid catalyzed Beckmann rearrangement has recently been somewhat clarified.[12] Vinnik and Zarakhani have studied the kinetics of the rearrangement of the oximes of cyclododecanone, cycloheptanone, cyclohexanone, and cyclopentanone in concentrated and fuming sulfuric acid. They concluded in all the cases studied that there are three oxime species present. Of the rate expressions derived for the possible active species, $RNOH_2^+$, RN^+, and the dehydrated ion pair

$RN^+ \cdot HSO_4^-$, the kinetic data satisfy the expression for the dehydrated ion pair XIII.

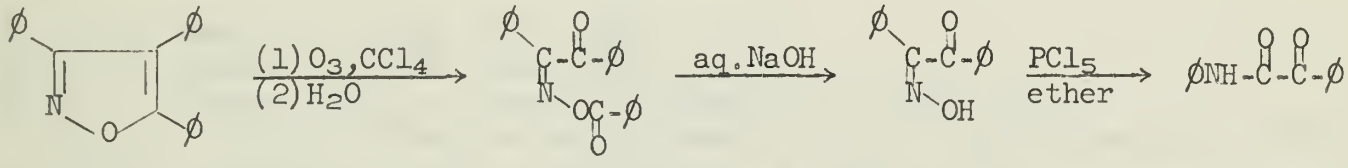
$$RNOH_2^+ + HSO_4^- \rightleftharpoons \underset{\text{(ion pair)}}{RNOH_2^+ \cdot HSO_4^-} \rightleftharpoons \underset{\text{(ion pair)}}{RN^+ \cdot HSO_4^-} + H_2O$$

XII XIII

The observed dependence of the rate constant on the acidity of the medium, the activity of water, and the activity of sulfuric acid is best explained by considering that the rate determining step occurs from the ion-pair species $RN^+ \cdot HSO_4^-$. Thus the rate determining step in high acid concentration is the migration from XIII, not its formation. This result explains earlier work in which at lower acid concentration, log k for the reaction varies linearly with the Hammett acidity function, Ho, while at very high acidities the rate levels off.[13] At lower concentrations the reaction rate depends upon the formation of the dehydrated ion pair XIII, while at high concentrations where there is much of the species XIII present, the rate is determined by the migration. No work has been done in light of the now defined migrating species to determine the mechanism of migration in concentrated sulfuric acid, i.e., to define the transition state.

OXIME CONFIGURATION AND ISOMERIZATION

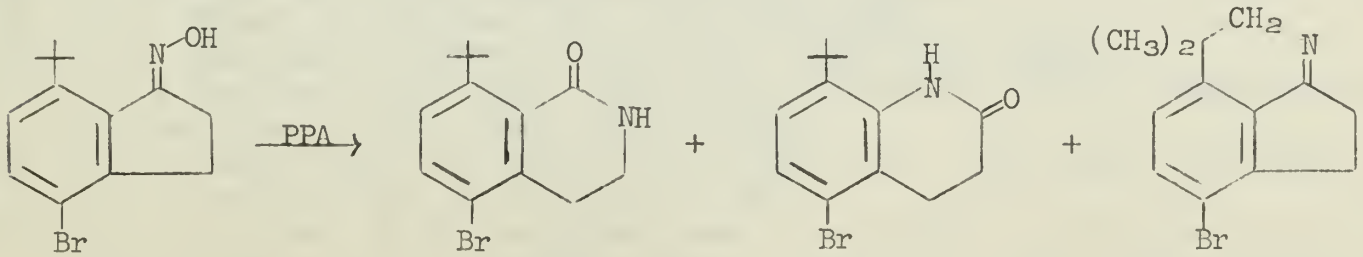
The concept of trans or anti migration relative to the oxime hydroxyl was first demonstrated by Meisenheimer[14] when he carefully degraded 3,4,5-triphenylisoxazole to observe the trans migration as shown below. Other examples of rearrangement of



specific compounds from known configurations[15-17] supported this concept and from these examples the concept of trans migration was extrapolated to cover all classes of oxime rearrangements under all conditions of rearrangement. There remains the possibility that there may be reaction media and appropriate oximes which can create a symmetrical species from which rearrangement occurs non-stereospecifically. This possibility should be in mind when determining oxime configuration via the Beckmann rearrangement since one often finds that the product is a mixture of amides formed from migration of both groups. This has been explained as occurring from configurational isomerization of the oximes to give a mixture of syn and anti isomers which then rearrange with trans migration. To prove that isomerization is indeed occurring from a pure isomer, both isomers should be observed in unreacted oxime isolated from the reaction solution.

Both acids[18] and bases[19] are known to catalyze isomerization to an equilibrium mixture of isomers. In general the rearrangement conditions which give a minimum of isomerization are phosphorus pentachloride in ether and arylsulfonyl chlorides in pyridine. Protonic solvents seem to favor the acid or base isomerization when the isomers are equally stable.[18b,20] Isomerizations often occur in hydrochloric, sulfuric, and polyphosphoric acid catalyzed rearrangements.

An unusual example of the Beckmann rearrangement in which the migration is non-stereospecific has been reported by Lansbury and Mancuso.[21] A substituted indanone oxime compound rearranged in polyphosphoric acid at 120° to give a lactam



mixture in which the alkyl/aryl ratio of migration was 4.3/1. This is ascribed to a combination of steric effects. A high degree of torsional strain in the transition state associated with this aryl migration[22] combined with steric inhibition by the t-butyl group severely hinders aryl migration as phosphate leaves the nitrogen. Thus a symmetrical iminium ion is formed to which unhindered alkyl migration can then occur. That this is the probable mechanism is evidenced by the presence of the imine, XIV, as the major product. Compound XIV is postulated as being formed from cationic insertion of the iminium ion in an adjacent carbon-hydrogen bond of the t-butyl group. That these steric effects are the cause of this unusual reaction is shown by the rearrangement of the identically substituted tetralone oxime to give 100% aryl migration.

CONCLUSION

The Beckmann rearrangement of oxime tosylates in aqueous ethanol has been seen to go through a nitrilium salt intermediate from which amide formation or fragmentation can occur. The transition state of the rate determining migration step is pictured as a simultaneous migration of the alkyl group and anion in the form of an intimate ion pair. Although there is yet no validity in extending this mechanism to include all rearrangements, it does appear to explain much of the data obtained from oxime rearrangement in other media. A systematic investigation of the rearrangement rates in other media is needed to determine if there are features of this mechanism which are general for the Beckmann reaction.

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