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ORGANIC SEMINAR ABSTRACTS

Summer, 1963

Department of Chemistry and Chemical Engineering
University of Illinois

SEMINAR TOPICS

Summer Session, 1963

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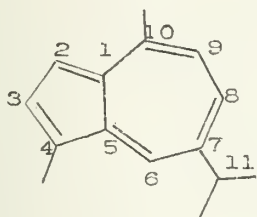
A NEW FAMILY OF SESQUITERPENE LACTONES

Reported by R. Feiertag

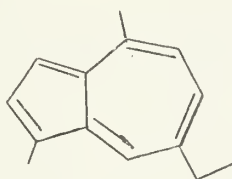
July 1, 1963

Introduction.--Recently several new sesquiterpene lactones have been isolated from plants of the genera Helenium, Parthenium, Ambrosia, and Balduina. It is the purpose of this seminar to review in detail the elucidation of the structures of the two most important members of this new family, tenulin and helenalin, to relate other members of the family to these two, and to review the known stereochemistry.

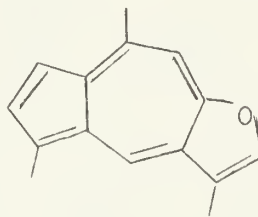
Before proceeding further, it will be helpful to mention briefly the methods used to determine the carbon skeletons of the compounds reviewed. In general, the compounds were reduced and then dehydrogenated over a suitable catalyst. Reduction was accomplished by hydrogenation over Raney nickel under moderately vigorous conditions (100° and 1500 p.s.i.) (1), and by the use of lithium aluminum hydride (2) or potassium borohydride (3). Dehydrogenation was carried out at elevated temperatures (300-360°) over selenium (1,4), palladium charcoal (1,3), or palladium (2). In one case (4) the compound was dehydrogenated directly without prior reduction. In all cases, the products were azulenes, whose structures are given. Several numbering systems are used for azulenic systems (5). The system shown will be used in this seminar.



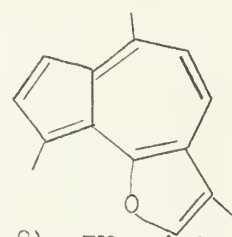
I. Guaiazulene



II. Chamazulene (6)

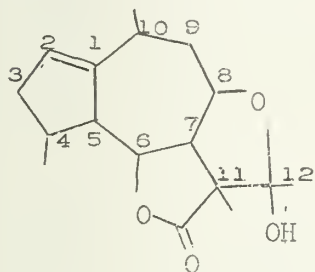


III Linderazulene (7,8)

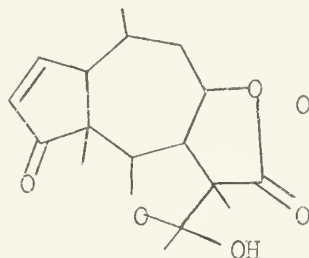


IV. Artemazulene

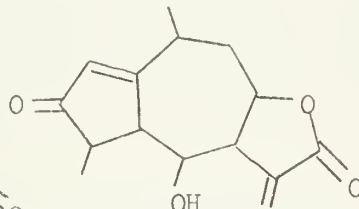
Tenulin and Helenalin.--Tenulin, $C_{17}H_{22}O_5$ (9), and helenalin, $C_{15}H_{18}O_4$ (10), are found in Helenium tenifolium L., (the bitterweed) and H. autumnale L., (the sneezeweed) respectively. On the basis of chemical and spectral evidence several formulas have been written for both tenulin and helenalin.



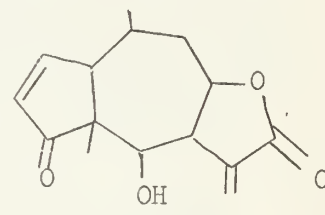
V



VI



VII



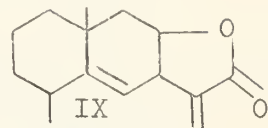
VIII

On dehydrogenation tenulin gives chamazulene (II) and linderazulene (III) (3), and helenalin, chamazulene and guaiazulene (I) (2,4). It is seen that for structures VI and VIII to be correct a methyl migration must have occurred during dehydrogenation. Analogous migrations are known (11). Moreover, aromatization would provide a strong driving force for migration.

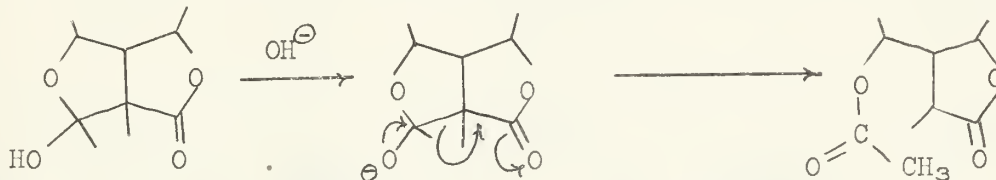
The infrared spectra of both tenulin and helenalin show absorptions near 1585 and 1700 cm^{-1} (12,3). Coupled with the ultraviolet spectra (tenulin: λ_{max} 226 $m\mu$, ϵ 7000; helenalin: λ_{max} 220 $m\mu$, ϵ 12200; λ_{max} 320 $m\mu$, ϵ 32), and chemical tests, these indicate the presence of an α,β -unsaturated ketone. Comparison with the infrared spectra of several conjugated 17-keto steroids (13) indicates the presence of cyclopentenone units.

The infrared spectra of both tenulin and helenalin show bands characteristic of the lactone functions drawn above (1772 cm^{-1} in tenulin (3); 1750 cm^{-1} in helenalin (12)). Helenalin reacts slowly with strong base to form a water-soluble compound and is reprecipitated on acidification (12). These observations indicate the presence of a lactone. Ozonolysis of helenalin yields formaldehyde, which shows the presence of a terminal methylene group (12). If hydrogenation of helenalin is

stopped after one mole of hydrogen has been taken up, the terminal double bond is preferentially saturated (1). Subtraction of the ultraviolet spectrum of dihydrohelenalin (λ_{\max} 229 m μ , ϵ 6500) from that of helenalin (λ_{\max} 220 m μ , ϵ 12200) yields a spectrum identical with that of alantolactone (IX) (λ_{\max} 210 m μ , ϵ 10000) (2,14). Therefore, it is probable that helenalin contains a chromophore like that of alantolactone.



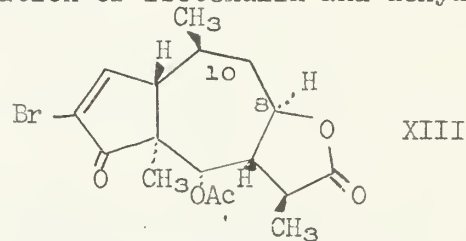
Tenulin rearranges to isotenulin under mildly basic conditions (9,15) unless the hydroxyl group is converted to an ether (16). Both dihydrotenulin and its oxime rearrange smoothly to the corresponding compounds of the isotenulin series. Therefore, the hemiketal is not linked vinylogously to the ketone group, and the ketone is not involved in the rearrangement, which probably occurs by the mechanism shown (3).



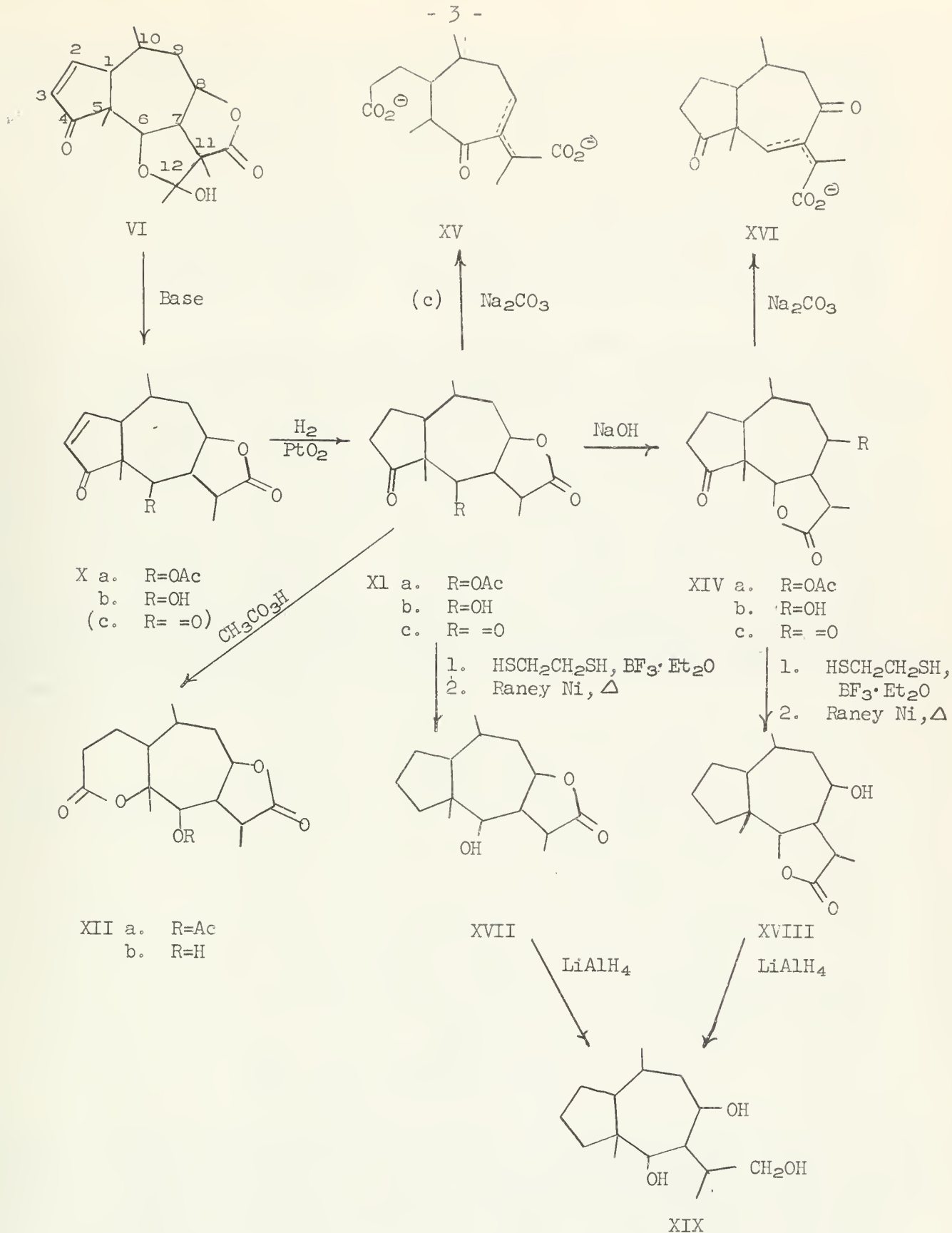
Although from the data presented thus far tenulin and helenalin might have either of the structures shown, n.m.r. spectroscopy (17) shows that structures VI and VIII respectively are the correct ones for these compounds. Because of the similarity of tenulin and helenalin, only the spectrum of tenulin will be treated in detail. Two vinyl protons are shown by the appearance of two pairs of doublets (intensity one proton each) at τ 2.45 and 3.90. This is clearly incompatible with structure V, but is easily explained in terms of structure VI, in which the vinyl protons split each other and are split by the C-1 proton. There are four methyl groups in the spectrum of tenulin--a singlet at τ 8.68 (intensity six protons), a doublet at τ 8.73, and a singlet at τ 8.69. One of the methyls at τ 8.68 is the masked acetyl, since it moves to τ 7.83 in the spectrum of isotenulin (Xa) in which there are also superimposed methyl doublets and a singlet at τ 8.80. The presence of a methyl singlet in the spectrum of isotenulin and three in that of tenulin is again incompatible with structure V but easily explained in terms of structure VI. Additional evidence for the correctness of this structure is provided by the peracetic acid oxidation of dihydroisotenulin (XIa) and desacetyldihydroisotenulin (XIb) to the corresponding lactones (XII), in whose spectra are found no new signals in the lactone range (τ 4.5-6.5). Therefore, the new lactone adjoins a quaternary carbon atom.

The orientation of the lactone ring may also be determined using n.m.r. A doublet at τ 4.40 (intensity one proton) in isotenulin moves to τ 5.8 on deacetylation and disappears from the spectrum of dehydrodesacetylisotenulin (Xc) in which the hydroxyl group has been oxidized to a carbonyl. Since the original peak is a doublet, the proton must be coupled to only one other, and the acetate is attached to C-6. A triplet ($J=9-11$ c.p.s.) at τ 4.67 in tenulin and τ 5.30 in isotenulin (intensity one proton), is further split ($J=2-4$ c.p.s.) by another proton. This signal is assigned to the C-8 proton. It changes only slightly during the transformations described above. Therefore, the lactone is attached to C-8.

Monobromoisotenulin (XIII) is prepared by bromination of isotenulin and dehydrobromination with potassium acetate (9). An X-ray study of this compound (18) confirms the assignments made with the use of n.m.r. In addition, the complete stereochemistry of the molecule is given. Both five-membered rings are trans-fused to the seven-membered ring. Non-bonded steric interactions between the angular methyl group and the hydrogens on C-8 and C-10 cause appreciable folding of the molecule.



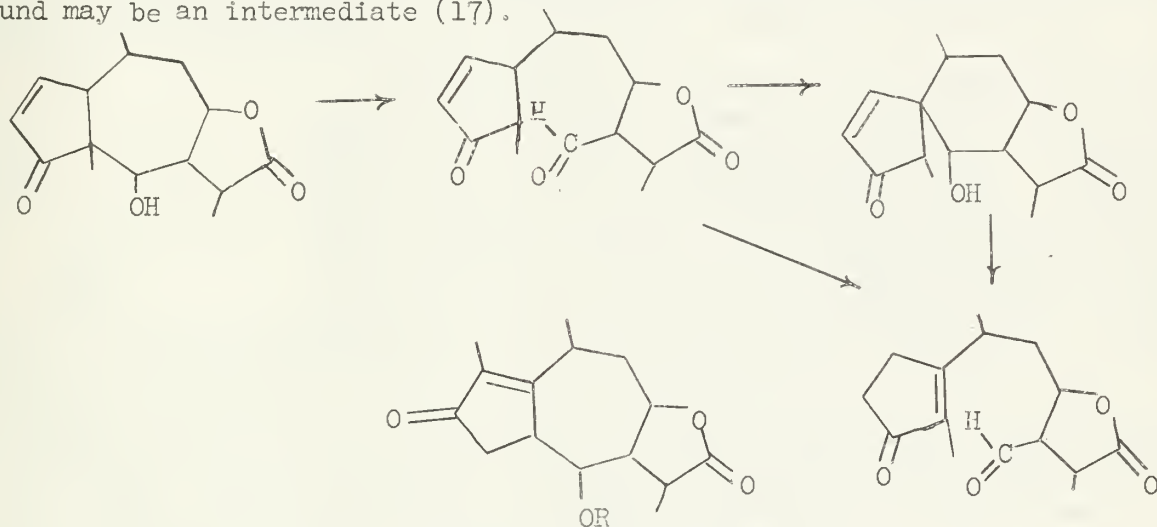
Basic hydrolysis of dihydroisotenulin leads to a mixture of desacetyldihydroisotenulin and a new compound, desacetyldehydroalloisotenulin (XIVb), an isomerization which involves reorientation of the lactone ring (19). The n.m.r. spectra (17) show this very clearly. A doublet at τ 5.34 in the spectrum of dihydroalloisotenulin (XIVa) is



assigned to the C-6 hydrogen, and a triplet at τ 4.88 which is further split by another proton, to the C-8 hydrogen. This second peak moves to τ 6.06 in desacetyl-dihydroalloisotenulin (XIVb) and disappears when the hydroxyl group is oxidized to a carbonyl in dehydrodesacetyldihydroalloisotenulin (XIVc). Further evidence for this rearrangement is the fact that dihydroisotenulin and desacetyldihydroisotenulin are easily isomerized to the corresponding allo- isomers in contrast to the pyrano-side ether of desacetyldihydroisotenulin (17). Both dehydrodesacetyldihydroisotenulin

(XIc) and its analog in the helenalin series are converted to dibasic α,β -unsaturated ketoacids (XV) when treated with sodium carbonate, while dehydrodesacetyldihydroalloyisotenulin (XIVc) is converted to a monobasic α,β -unsaturated ketoacid (XVI)(19). These transformations, difficult to explain in terms of structures V and VII, are seen to be caused by opening of the lactone and cleavage of a β -diketone in the case of the isotenulin and helenalin derivatives. In the case of the allo derivative, no β -diketone is present, and the second reaction cannot take place. A second difference between the two series may be observed. The carbonyl group in desacetyldihydroisotenulin (XIb)(17) and desacetyldihydroalloyisotenulin (XIVb)(19) may be reduced to give compounds XVII and XVIII. When these compounds are reduced with lithium aluminum hydride, two triols (XIX) which differ in optical rotation and melting point are obtained (17,19), indicating that epimerization has taken place at C-11.

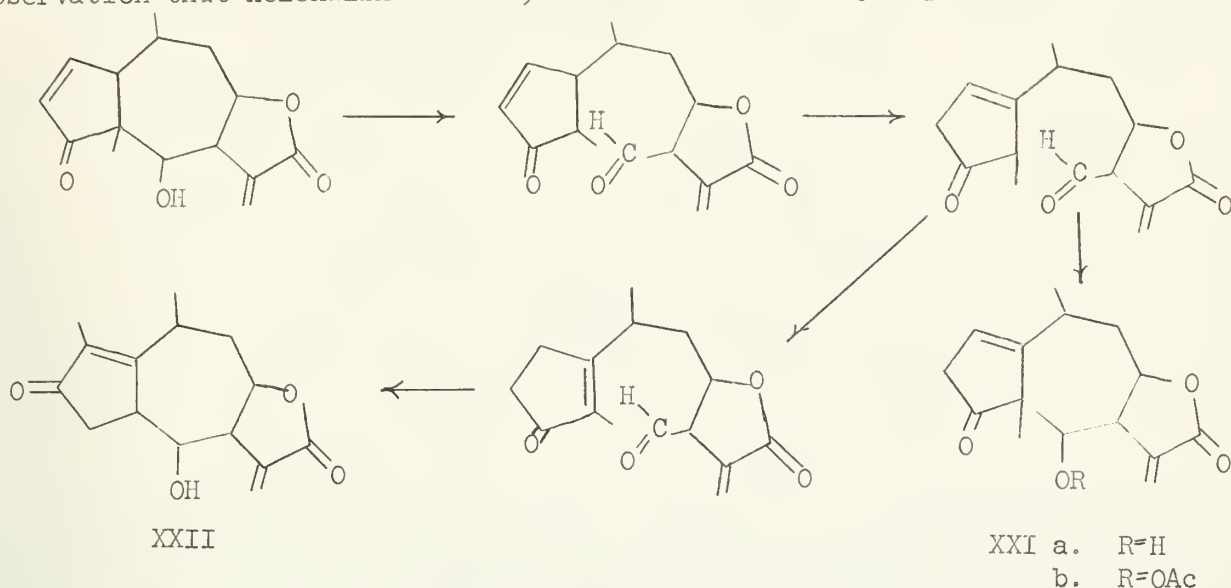
Treatment of tenulin with sodium bicarbonate gives a mixture of deacetyl-isotenulin and a new compound, desacetylneotenulin (3). Neohelenalin, which is found in *H. flexuosum* Raf. (20) and *H. mexicanum* H.B.K. (21), has also been obtained from the isomerization of helenalin during chromatography over basic alumina (22). The ultraviolet spectra (neotenulin: λ_{\max} 240 m μ , ϵ 16000; neohelenalin: λ_{\max} 235 m μ , ϵ 17800; λ_{\max} 208 m μ , ϵ 13800) show that no chromophores have been destroyed, but ozonolysis of these compounds yields acetic acid (ozonolysis of the parent compounds does not). The n.m.r. spectra of the two compounds (17,22) show no vinyl protons present in neotenulin and only two in neohelenalin instead of the four present in the spectrum of helenalin. In addition, no methyl singlet is observed. Instead, a new doublet (neotenulin: τ 8.25, $J=1.5$ c.p.s.; neohelenalin: τ 8.32, $J=2$ c.p.s.), intensity three protons, is found. This is most easily explained as a vinyl methyl group split by long range coupling. The conversion of tenulin to desacetylneotenulin involves isomerization to desacetylisotenulin which is then converted to desacetylneotenulin by the following reaction sequence in which the spirane compound may be an intermediate (17).



XX a. R=Ac (Neotenulin)
b. R=H

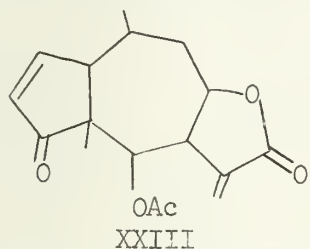
Hydrogen chloride-chloroform converts helenalin to a mixture of mexicanin A (21) and neohelenalin (22). Mexicanin A occurs naturally in *H. mexicanum* H.B.K. (21). The ultraviolet spectrum (λ_{\max} 212 m μ , ϵ 8400) indicates the possibility of an exocyclic double bond conjugated with a lactone as in alantolactone (IX)(14). The infrared spectrum shows a weak absorption at 1630 cm^{-1} which is assigned to an unconjugated double bond and a strong band at 1750 cm^{-1} which is assigned to a lactone and an unconjugated cyclopentanone. The n.m.r. spectrum of mexicanin A acetate shows only one vinyl proton, a triplet at τ 4.10. The only other difference between the spectra of mexicanin A acetate and helenalin acetate is the appearance of a triplet (intensity two protons) appearing at τ 7.14 in the spectrum of the former. Both dihydrohelenalin and dihydromexicanin A are isomerized to dihydroneohelenalin by methanolic potassium bicarbonate. These observations are best explained by saying

that mexicanin A differs from helenalin only in the position of the cyclopentenone double bond. Mexicanin A may be written as XXIIa and neohelenalin as XXII. The conversion of helenalin to neohelenalin and mexicanin A occurs by the following reaction sequence (23). Additional support for this sequence is gained from the observation that helenalin acetate, when treated with hydrogen chloride-chloroform,



does not isomerize, indicating the necessity for a free hydroxyl group.

Other Compounds of the Helenalin Series. --Balduilin, obtained from *Balduina uniflora* Nutt. (24), Linifolin A, obtained from *H. linifolium* Rydb. (25), and bigelovin, obtained from *H. bigelovii* Gray (26) all have the formula $C_{15}H_{20}O_5$. The infrared, ultraviolet, and n.m.r. spectra of these compounds are nearly identical to those of helenalin acetate, and they have been assigned structure XXIII. Chemical tests are in accord with this assignment.



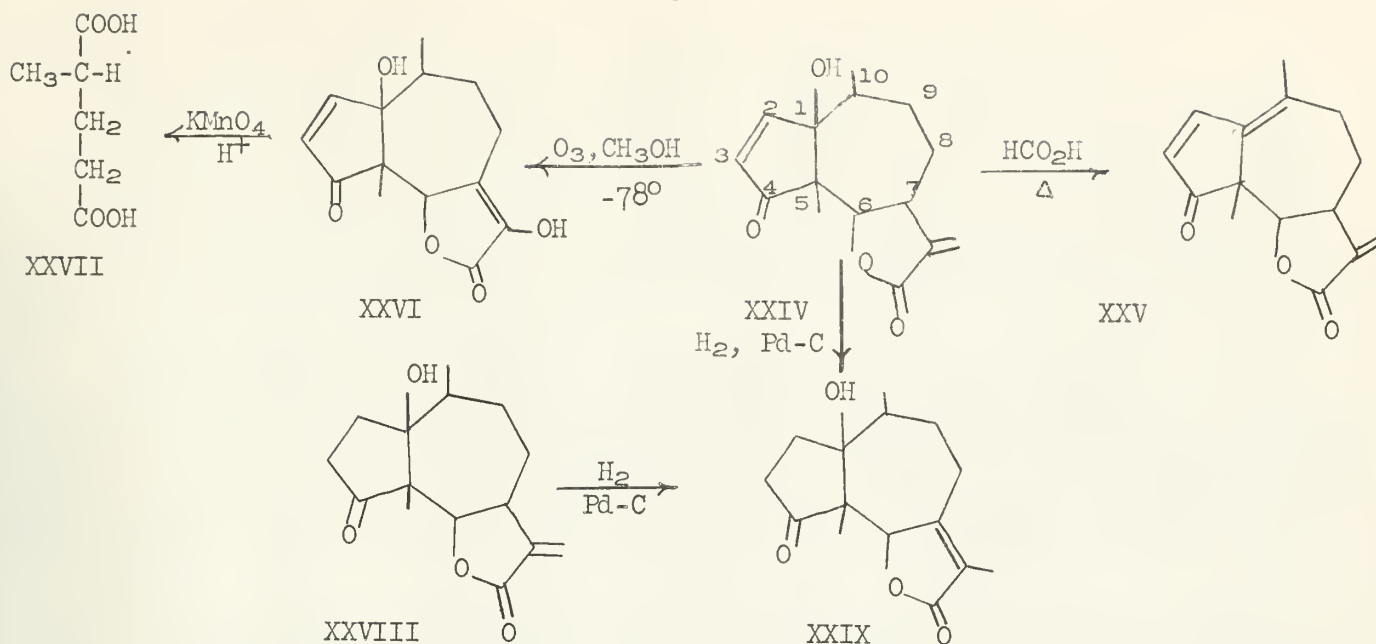
Hydrogenation of bigelovin to the dihydro compound reveals that, unlike helenalin, in which the exocyclic double bond is preferentially saturated (1), the cyclopentenone double bond is reduced first (26). In addition, both bigelovin and its derivatives decompose in both acidic and basic solutions. This instability may be explained by the ability of bigelovin to undergo retroaldol ring-cleavage, and subsequent further decomposition. However,

the reversal of dehydrogenation order as well as the relative stability of other isomers does not appear to have any simple explanation.

Linifolin B, $C_{15}H_{20}O_5$, is found in *H. linifolium* Rydb. (25). The infrared and ultraviolet spectra reveal that although it has the features of other members of the helenalin series, the conjugated cyclopentenone is no longer present. The n.m.r. spectrum is similar to that of the acetate of mexicanin A (XXIb), and on this basis it has been assigned the same gross structure.

Parthenin (XXIV) $C_{15}H_{18}O_4$, is found in *Parthenium hysterophorus* L. (27). Reduction and dehydrogenation yields artemazulene (IV), and the infrared and ultraviolet spectra show a lactone and a cyclopentenone, both conjugated with double bonds (28). In addition, a tertiary hydroxyl group is found. It is resistant to chromic acid oxidation and acetylation, and parthenin is easily dehydrated. The n.m.r. spectrum of parthenin shows a methyl singlet at τ 8.72 (C-5 methyl) and a methyl doublet at τ 8.89 (C-10 methyl) (27,29). When parthenin is dehydrated with anhydrous formic acid to anhydroparthenin (XXV), the methyl doublet disappears, and a singlet τ 7.97 appears. This is in the vinyl methyl region and indicates that the hydroxyl group is α to C-10, at C-1.

Formation of artemazulene suggests that the lactone ring is closed to C-6. This is confirmed by the n.m.r. spectrum which shows a doublet (intensity one proton) at τ 4.92. This is in the region of protons on carbon attached to a lactone or ester.



Further evidence for this structure is provided by the ozonolysis of parthenin in methanol at -78° (27). Permanganate oxidation of norparthenone (XXVI), the compound formed, yields S-(+)- α -methylglutaric acid (XXVII) (30). This is obtained from the fragment of norparthenone between C-7 and C-1, and demonstrates that the C-10 methyl group is β .

Coronopilin (XXVIII) is obtained from *Ambrosia artemisiifolia* L., the common ragweed (31). Both parthenin and coronopilin give dihydroisoparthenin (XXIX) on hydrogenation. On the basis of this reaction and spectral evidence it has been identified as 1,2-dihydroparthenin.

Ambrosin (XXX), $\text{C}_{15}\text{H}_{18}\text{O}_3$, and damsine, $\text{C}_{15}\text{H}_{20}\text{O}_3$, are found in *A. maritima* L. (32).

Reduction and dehydrogenation of ambrosin gives artemazulene (IV) (33). The infrared spectrum shows the presence of an α,β -unsaturated γ -lactone and an α,β -unsaturated cyclopentenone (32). However, there is no absorption in the hydroxyl region. Hydrogenation of anhydroparthenin (XXV) yields two hexahydro derivatives, one of which is identical with tetrahydroambrosin (27). The n.m.r. spectrum of ambrosin shows the same features as that of parthenin with the exception of the vinyl peaks. These are each split into pairs of doublets. It is apparent that the vinyl protons are splitting each other and are being further split by the C-1 proton.

Hydrogenation of ambrosin yields a dihydro and a tetrahydro derivative (32).

In the infrared spectra of these compounds

the carbonyl band moves to 1760 cm^{-1} , indicating that this group is no longer conjugated with a double bond. Damsine, although it contains an unconjugated cyclopentanone (infrared: 1754 cm^{-1}), is not identical with the dihydro compound. However, it yields a mixture of the dihydro and tetrahydro derivatives on hydrogenation (34). The dihydro compound is therefore dihydroisoambrosin (XXXI), and damsine has the structure XXXIII. This is confirmed by the n.m.r. spectrum (35) which has two vinyl doublets unsplit by any other proton.

Stereochemistry.--With the exception of bromoisotenulin (XIII) and isotenulin (Xa), the complete stereochemistry of the compounds in the helenalin series is not known. However, a number of optical rotatory dispersion studies have been made which allow partial determination of the absolute configurations.

The isomerization of tenulin (VI) to isotenulin (Xa) destroys only the asymmetric centers at C-11 and C-12. Therefore the stereochemistry at C-1, C-5, C-6, C-7, C-8, and C-10 is the same as that of bromoisotenulin (XIII).

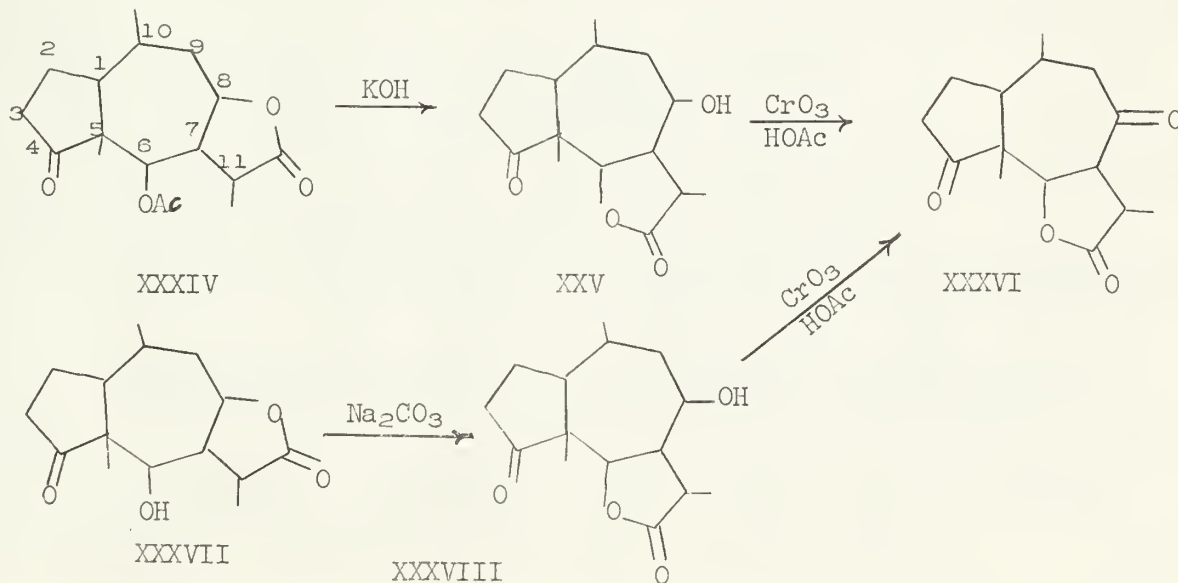
The optical rotatory dispersion curves of baldulin (XXIII)(23), helenalin (VIII), tenulin (VI), and isotenulin (Xa)(36) all show strong (-)-Cotton effects. Hydrogenation of the cyclopentenone double bond causes this effect to be reversed; the curve of dihydrohelenalin has a (-)-Cotton effect, but those of tetrahydrohelenalin, dihydrotenulin, and dihydroisotenulin all have (+)-Cotton effects (36). The curves of tetrahydroparthenin, tetrahydroambrosin (XXXII), and coronopilin (XXXIII) also have (+)-Cotton effects (27). Therefore, all these compounds have the same configuration at C-1 and C-5.

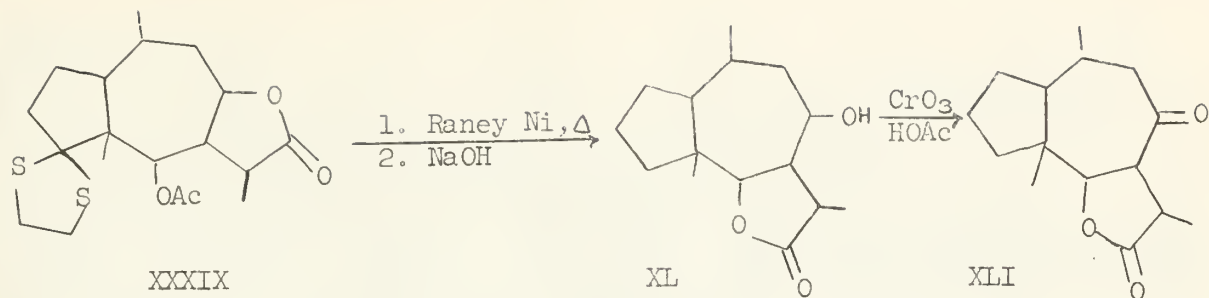
Tetrahydromexicanin A obviously differs from the others at either C-1 or C-5, for its curve shows a weak (-)-Cotton effect, which almost doubles on acetylation (23). It has been argued (23) that this is evidence for opening of the seven-membered ring in a reverse aldol reaction and reorientation of the C-5 methyl group rather than a simple migration of the double bond. However, it is possible that hydrogenation of the C-1, C-2 double bond has caused the configuration at C-1 to be reversed.

Isolation of S-(+)- α -methylglutaric acid (XXVII) from the oxidation of norparthenone (XXVI) demonstrates that the C-10 methyl group in parthenin (XXIV) is β (27). The equivalence of one of the hexahydro derivatives of anhydroparthenin (XXV) with tetrahydroambrosin (XXXII) shows that ambrosin (XXX) and parthenin (XXIV) have the same stereochemistry at C-5, C-6, C-7, and C-8, since only the asymmetric centers at C-1 and C-10 are destroyed during the conversion of parthenin to anhydroparthenin (27).

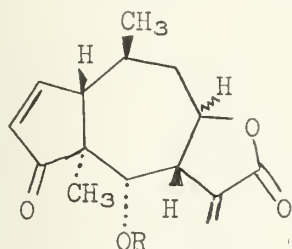
A series of chemical reactions has been used to establish that helenalin (VIII) and baldulin (XXIII)(24) are C-8 epimers. Saponification of tetrahydrobaldulin (XXXIV) is effected by refluxing with potassium hydroxide. Under these conditions two isomers, desacetyltetrahydrobaldulin A (XXXV) and desacetyltetrahydrobaldulin B are obtained. Reacetylation of these compounds yields acetates different from tetrahydrobaldulin (XXXIV), indicating that epimerization at C-11 and/or reorientation of the lactone ring has taken place. Chromic acid oxidation of tetrahydrobaldulin A (XXXV) yields a product identical with that obtained from allotetrahydrohelenalin (XXXVIII). Only the C-8 and C-11 asymmetric centers have been altered by these reactions. Therefore, baldulin (XXIII) has the same stereochemistry as helenalin (VIII) at C-1, C-5, C-6, C-7, and C-10. This leaves only the relative configuration at C-8 in doubt, since in the parent compounds there is no asymmetric center at C-11. Baldulin is different from helenalin acetate, and the two compounds must be C-8 epimers.

Treatment of the thioketal of tetrahydrobaldulin (XXXIX) with Raney nickel





followed by saponification with sodium hydroxide yields compound XL in which the lactone ring has been reoriented. Oxidation of this compound with chromic acid gives dehydrosesoxodesacetyldihydroalloisotenulin (XLI)(19). Therefore, balduilin and helenalin have the same configuration as isotenulin at C-1, C-5, C-6, C-7, and C-10. Helenalin may now be represented by XLIIa and balduilin by XLIIb.



XLII a. R=H
b. R=Ac

BIBLIOGRAPHY

1. R. Adams and W. Herz, J. Am. Chem. Soc., 71, 2554 (1949).
2. G. Büchi and D. Rosenthal, J. Am. Chem. Soc., 78, 3860 (1956).
3. D. H. R. Barton and P. deMayo, J. Chem. Soc., 142 (1956).
4. V. Herout, M. Romanuk and F. Sorm, Coll. Czech. Chem. Commun., 21, 1359 (1956).
5. M. Gordon, Chem. Revs., 50, 127 (1952).
6. A. Meisels and A. Weizmann, J. Am. Chem. Soc., 75, 3865 (1953).
7. K. Takeda and W. Nagata, Pharm. Bull. (Japan), 1, 164 (1953); C.A., 48, 7716g (1954).
8. K. Takeda, H. Minato and M. Ishikawa, Tetrahedron Letters, 3, 121 (1963).
9. E. P. Clark, J. Am. Chem. Soc., 61, 1836 (1939).
10. E. P. Clark, J. Am. Chem. Soc., 58, 1982 (1936).
11. (a) J. Simonsen and D. H. R. Barton, "The Terpenes", Vol. III, Cambridge Press, Cambridge, 1952, p. 34; (b) J. Simonsen and D. H. R. Barton, "The Terpenes", Vol. III, Cambridge Press, Cambridge, 1952, p. 84.
12. R. Adams and W. Herz, J. Am. Chem. Soc., 71, 2546 (1949).
13. R. N. Jones, V. Z. Williams, M. J. Whalen and K. Dobriner, J. Am. Chem. Soc., 70, 2024 (1948).
14. C. Asselineau and S. Bory, Compt. rend., 246, 1874 (1958).
15. E. P. Clark, J. Am. Chem. Soc., 62, 597 (1940).
16. E. P. Clark, J. Am. Chem. Soc., 62, 2154 (1940).
17. W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman and N. Viswanathan, J. Am. Chem. Soc., 84, 3857 (1962).
18. D. Rodgers and Mazhar-ul-Haque, Proc. Chem. Soc., 92, (1963).
19. B. H. Braun, W. Herz and K. Rabindran, J. Am. Chem. Soc., 78, 4423 (1956).
20. W. Herz, R. B. Mitra, K. Rabindran and W. A. Rohde, J. Am. Chem. Soc., 81, 1481 (1959).
21. A. Romo de Vivar and J. Romo, Chem. and Ind. (London), 882 (1959).
22. W. Herz, P. Jayaraman and H. Watanabe, J. Am. Chem. Soc., 82, 2276 (1960).
23. W. Herz, A. Romo de Vivar, J. Romo and N. Viswanathan, J. Am. Chem. Soc., 85, 19 (1963).
24. W. Herz, R. B. Mitra and P. Jayaraman, J. Am. Chem. Soc., 81, 6061 (1959).
25. W. Herz, J. Org. Chem., 27, 4043 (1962).
26. B. A. Parker and T. A. Geissman, J. Org. Chem., 27, 4127 (1962).

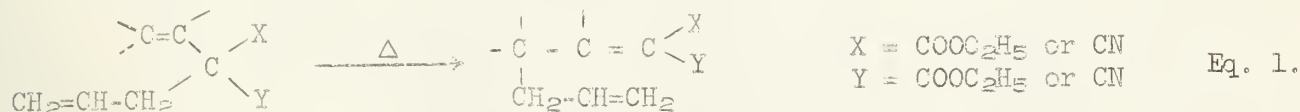
27. W. Herz, H. Watanabe, M. Miyazaki and Y. Kishida, J. Am. Chem. Soc., 84, 2601 (1962).
28. W. Herz, H. Watanabe and M. Miyazaki, J. Am. Chem. Soc., 81, 6088 (1959).
29. W. Herz, M. Miyazaki and Y. Kishida, Tetrahedron Letters, 2, 82 (1961).
30. A. Fredga, Arkiv. Kemi Mineral Geol., 24A, No. 32 (1947).
31. W. Herz and G. Högenaur, J. Org. Chem., 26, 5011 (1961).
32. H. Abu-Shady and T. D. Soine, J. Am. Pharm. Assoc., 42, 387 (1953).
33. F. Šorm, N. Suchý and V. Herout, Coll. Czech. Chem. Commun., 24, 1548 (1959).
34. H. Abu-Shady and T. D. Soine, J. Am. Pharm. Assoc., 43, 365 (1954).
35. R. B. Bates and V. Herout, private communication.
36. C. Djerassi, J. Osiecki and W. Herz, J. Org. Chem., 22, 1361 (1957).

The Cope Rearrangement

Reported by J.C. Gaal

July 22, 1963

Introduction: The thermal rearrangement of substituted 1,5-hexadienes was first reported by Cope and Hardy in 1940 (1) for a series of substituted malononitriles and malonic esters, as in equation 1. The reaction was proposed by Cope to be similar to the Claisen rearrangement of phenyl and vinyl allyl ethers but



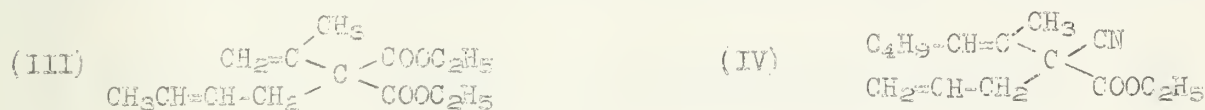
with the oxygen atom replaced by a carbon atom.

Scope of the Reaction: The rearrangement was further examined by Cope and coworkers and was shown to occur for a variety of 1,5-hexadienes with and without electronegative substitution (see Table 1), although these substituents enhance the rate (2). Vogel and coworkers (3,4) report that the reaction also occurs with cleavage of a cyclopropyl or cyclobutyl ring, so that cis-1,2-divinylcyclobutane (I) yields cis,cis-1,5-cyclooctadiene (II) at 120° C. Doering and Roth (6) have



pointed out that the cyclopropyl ring cleavage greatly increases the reaction rate, due mainly to the 19.1 kcal/mole released by opening this ring.

Intramolecularity and Allylic Requirements: Cope, Hofmann and Hardy showed that the rearrangement is intramolecular by following the reaction of mixtures of ethyl (1-methylvinyl)-2-butenylmalonate (III) and ethyl (1-methyl-1-hexenyl)-allylcianoacetate (IV) which have similar rates (7). These reactions resulted in



no cross products within their experimental error (the products were separated by fractional distillation). It should be noted that the structure of every reactant and product reported by Cope was demonstrated by the chemical methods available at the time.

Cope and coworkers have shown that the reaction requires the reversal of the allyl group with accompanying double bond shift and that it can be sterically inhibited by groups on the carbon to which the allyl is becoming bonded (7,8).

Kinetic Information. Cope (5) and Walling and Naimen (9) report first order kinetics for the reaction. A negative ΔS^\ddagger of about -11.5 e.u. was evaluated by Cope which he states is to be expected for a mechanism involving a cyclic transition state due to loss of degrees of freedom from restricted atomic motion. This value can be compared with those for the Claisen rearrangement (ca -12 e.u. from selected reactions run by White, et al. (10)) and the Diels-Adler reaction of cyclopentadiene (-29 e.u.) (11).

Another parameter which can be used to distinguish various reaction types is the volume of activation (ΔV^\ddagger), which is the change in volume when a compound goes to its transition state from its ground state. Hammann lists various reaction types and the expected sign of the ΔV^\ddagger (12). In a series of high pressure experiments, Walling and Naimen report that pressure enhances the reaction rate of the Cope rearrangement so that the ΔV^\ddagger is negative. Unfortunately, the usual method of treating pressure-rate data has been severely criticized recently by Benson and Berson (13), so that the exact value of ΔV^\ddagger from Walling's data depends on the

Table 1. Selected Cope Rearrangements

Compound	Temp.	Time	Yield	Ref.	Product
Ethyl (1-methylpropenyl)-allylcynoacetate	150°-160°C	4 hrs.	97%	(1)	ethyl(1,2-dimethyl-4-pentenylidene)-cyanoacetate
Ethyl (1-methyl-2-ethylvinyl)-allylcynoacetate	170°C	8 hrs.	81%	(5)	ethyl(1-methyl-2-ethyl-4-pentenylidene)-cyanoacetate
Ethyl (1-methyl-2-isopropylvinyl)-allylcynoacetate	170°C	9 hrs.	81%	(5)	ethyl(1-methyl-2-isopropyl-4-pentenylidene)-cyanoacetate
Ethyl (1-methyl-2-n-butylvinyl)-allylcynoacetate	200°C	9 hrs.	77%	(5)	ethyl(1-methyl-2-butyl-4-pentenylidene)-cyanoacetate
Ethyl (1-cyclohexenyl)-allylcynoacetate	170°C	8-10 hrs.	97%	(5)	ethyl(2-allylcyclohexylidene)-cyanoacetate
Ethyl (1-phenylvinyl)-allylcynoacetate	170°C	7 hrs.	78%	(5)	ethyl(1-phenyl-4-pentenylidene)-cyanoacetate
Ethyl (1-ethyl-2-methylvinyl)-allylcynoacetate	200°C	7 hrs.	70%	(5)	ethyl(1-ethyl-2-methyl-4-pentenylidene)-cyanoacetate
Ethyl (3-indenyl)-allylcynoacetate	125°C	3 hrs*	63%	(20)	Ethyl(2-allyl-1-indanylidene)-cyanoacetate
Ethyl (1-methylpropenyl)-crotylcynoacetate	180°C	5 hrs.	80%	(7)	Ethyl(1,2,3-trimethyl-4-pentenylidene)-cyanoacetate
1-ethylpropenyl-allylmalononitrile	150°C	4 hrs.	97%	(5)	1-ethyl-2-methyl-4-pentenylidene malononitrile
1-cyclohexenyl-allylmalononitrile	175°C	1-1/2 hrs.	97%	(5)	2-allylcyclohexylidene malononitrile
Ethyl (1-propenyl)-allylmalonate	200°C	8 hrs.	90%	(5)	Ethyl (2-methyl-4-pentenylidene)-malonate
Ethyl (1-butenyl)-allylmalonate	200°C	10 hrs.	68%	(5)	Ethyl (2-ethyl-4-pentenylidene)-malonate
Ethyl isopropenyl-crotylmalonate	185°C	2 hrs.	95%	(7)	Ethyl (1,3-dimethyl-4-pentenylidene)-malonate
3-phenyl-1,5-hexadiene	176-178°C	26 hrs.	72%	(2)	1-phenyl-1,5-hexadiene
3-phenyl-1,5-heptadiene	165-185°C	65 hrs.	72%	(2)	4-methyl-1-phenyl-1,5-hexadiene
3-methyl-4-phenyl-1,5-hexadiene	170-185°C	31 hrs.	90%	(2)	1-phenyl-1,5-heptadiene
3-methyl-1,5-hexadiene	300-305°C	24 hrs.	equil.		
rac-3,4-dimethyl-1,5-hexadiene	180°C	18 hrs.	mix(+)(2)		1,5-heptadiene
meso-3,4-dimethyl-1,5-hexadiene	280°C	24 hrs.	97%	(16)	trans,trans- and cis,cis-2,6-octadiene
cis-1,2-divinylcyclobutane	120°C	3 hrs.	95%	(3)	cis,trans-2,6-octadiene
cis-divinylcyclopropane	-45°C	less than 20 mins.	100%	(19)	cis,cis-1,5-cyclooctadiene
α-1-hydroxydicyclopentadiene	140°C	5 hrs.	equil.	(18)	syn-8-hydroxydicyclopentadiene
β-1-hydroxydicyclopentadiene	140°C	5 hrs.	equil.	(18)	anti-8-hydroxydicyclopentadiene

* 5 hrs. is much too long, the authors suggest 1-1/2 hrs.

+ rxn. run both ways with similar results

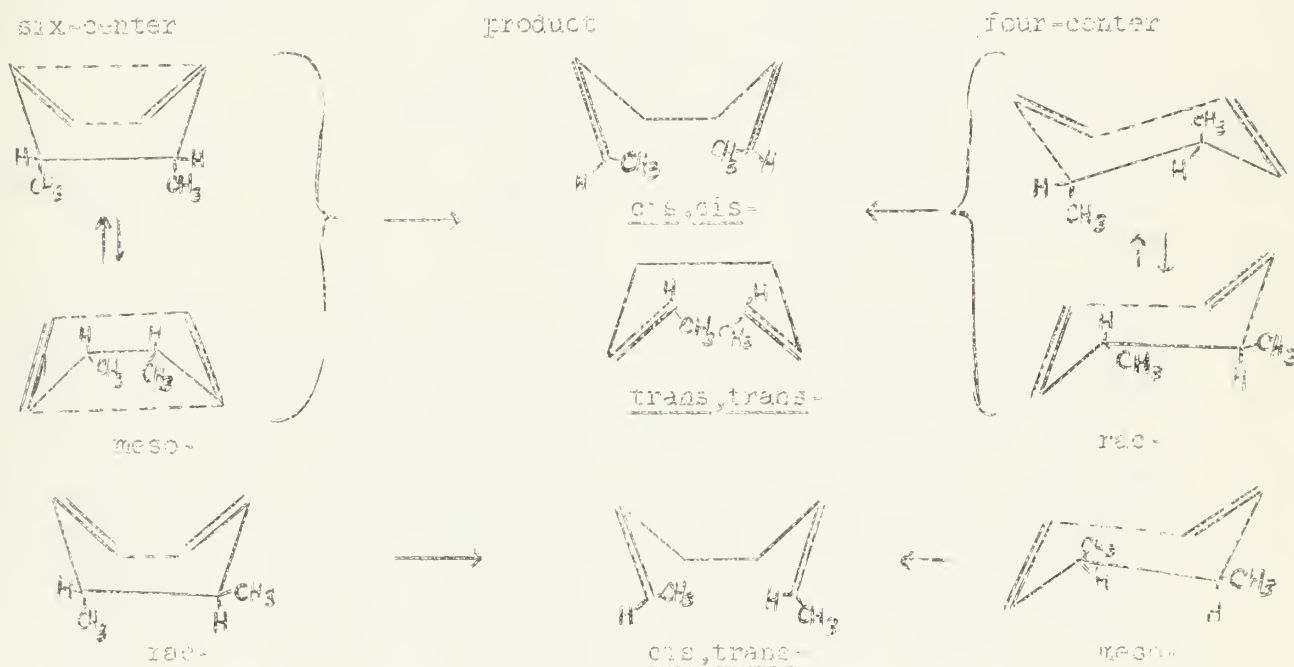
mathematical interpretation that is used. In spite of this interpretive problem, an important feature of the results is that the value is not solvent dependent. Benson and Berson also suggest that temperature effects due to adiabatic compression of the liquids could partially account for the small changes in rate which are observed by Walling.

Mechanism and Stereochemistry: Cope postulated a mechanism involving a cyclic transition state similar to the Claisen rearrangement for this reaction and showed the reversal of the point of attachment of the allyl group during the reaction (see above). Walling and Naimen interpreted their negative ΔV^\ddagger as suggesting an extensively bonded, cyclic transition state which is similar to the product.

Taking model compounds from Egloff (14), a difference of -16 to -18 cc/mole is calculated for linear and cyclic compounds which are somewhat similar to starting materials and cyclic transition states. Walling suggests that the values of ΔV^\ddagger should be somewhat less negative than these due to stretched bonds in the transition state (11,15). It seems that the field of pressure-rate studies as applied to organic mechanisms is on shakier ground than the mechanism of the Cope rearrangement, so that it can scarcely be used as a valid criterion for the nature of the transition state.

Stereochemical details for 3,4-dimethyl-1,5-hexadienes have recently been reported in a series of papers by Doering and Roth. They suggest that for hexadienes which have a choice of transition state geometry a four-center, chair-like arrangement is conformationally favored. The rearrangement of the 3,4-dimethylhexadienes to octadienes by the four- and six-center cyclic conformations proposed by Doering and Roth are shown in Figure 1(6).

Fig. 1



As is shown, if the meso-isomer follows a four-center mechanism the product should be cis,trans-2,6-octadiene and if the six-center path is followed, then cis,cis- and trans,trans-2,6-octadiene are the products. On the other hand racemic starting materials result in cis,trans-2,6-octadiene if the six-center path is followed and the four-center method leads to cis,cis- and trans,trans-2,6-octadiene.

Meso and racemic-3,4-dimethyl-1,5-hexadiene were separated by gas chromatography and structure proofs effected by ozonolysis and oxidation to the known 2,3-dimethylsuccinic acids (16). Structures of the rearrangement products, the octadienes, were

inferred from infrared spectra following their separation by gas chromatography. The octadienes do not interconvert when heated to 230°C. for 24 hours.

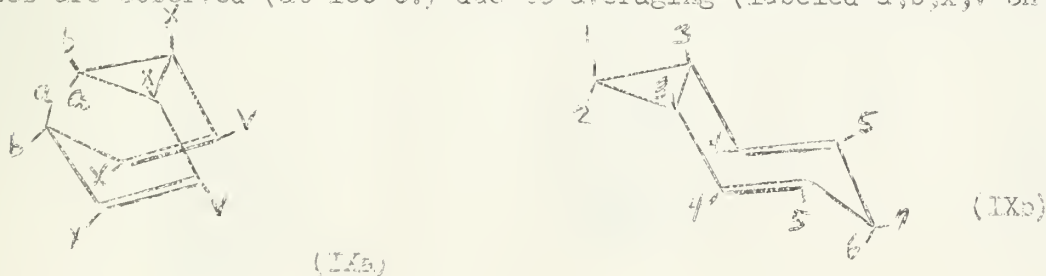
The product from the rearrangement of the meso-isomer after six hours at 225°C. was a mixture of 2,6-octadienes consisting of 99.7% cis,trans- and 0.3% trans,trans-isomers. The calculated difference in free energy of activation implied by these yields favors the four-center path by 5.7 kcal/mole. The racemic 3,4-dimethyl-1,5-hexadiene rearranges after 18 hours at 180°C. to 90% trans,trans-, 10% cis,cis- and less than 1% cis,trans-2,6-octadiene. Comparing the two four-center paths shows that the trans,trans-isomer is favored by approximately 2.0 kcal/mole, which is not unreasonable if the "axially" oriented methyl groups necessary for the cis,cis-isomer are considered (6,16).

Quantum mechanical considerations suggest that the interaction of allyl radicals in the six-center path is less favored than the four-center one because the second π orbital of the radical which contains the lone electron has a node at the central carbon atom (17). On the other hand, the electron density is equally distributed over all three carbons in the first π -orbital (filled). There is, therefore, always repulsion between the two central carbons of the radicals but there is a possibility of bonding forces between the terminal carbons which can overcome the repulsive forces.

Not all Cope rearrangements have a choice of transition state geometry, however. Rearrangement of cis-divinylcyclopropane to 1,4-cycloheptadiene (see above) and reactions of α - and β -1-hydroxydicyclopentadiene (V and VI) to syn- and anti-8-hydroxydicyclopentadiene reported by Woodward and Katz (18) must follow the six-center mechanism (16). Doering and Roth tried to isolate cis-divinylcyclopropane formed by the addition of methylene to cis,cis,cis-1,3,5-hexatriene, but report that even at -45°C. the rearrangement to cycloheptadiene is too rapid to allow isolation of the cyclopropyl compound (19).



"Fluctional" Isomerism: Upon investigation of bicyclo (5.1.0) 2,5-octadiene (IXa and IXb), Doering and Roth report that, by using n.m.r. spectra, they can detect a rearrangement at -50°C. which occurs approximately once per second per molecule and at 180°C. occurs approximately 250 times per second per molecule. Since the bicyclooctadiene is symmetrical, its rearrangement product is the same as starting material and it has therefore been called a "degenerate" rearrangement. Examination of the cis- (IXa) and trans-conformers (IXb) shows seven different types of hydrogens which might be differentiated by n.m.r. (labeled on IXb), but because the cis-conformer undergoes rapid Cope rearrangement, actually only four types are observed (at 180°C.) due to averaging (labeled a,b,x,v on IXa). A 2,6-



transannular interaction is proposed in the cis-conformation which makes the trans-conformer the major contributing structure at -50°C ., but as the temperature is increased this energy barrier is overcome to yield the cis-conformation which may undergo rearrangement so that at ca 20°C . the n.m.r. spectrum shows two smeared peaks.

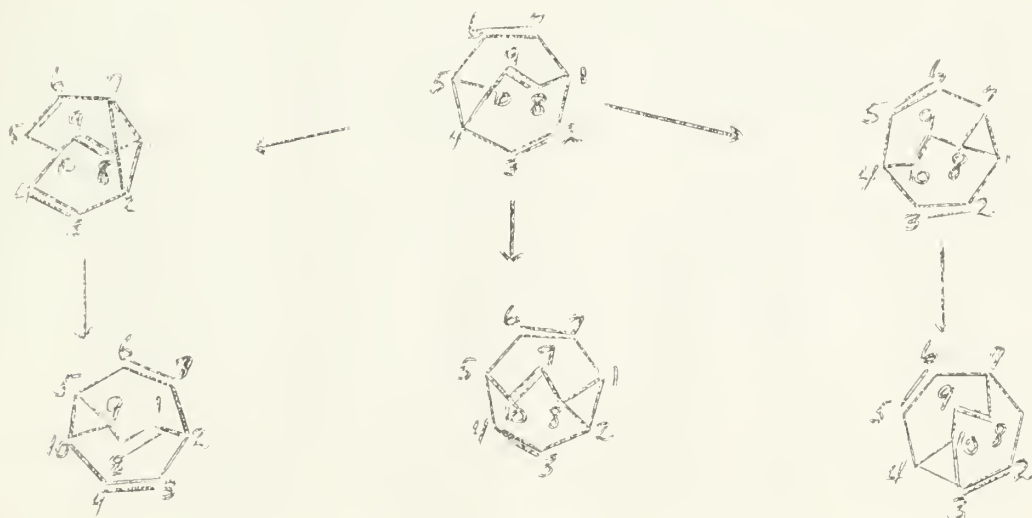
Because the compound undergoes such rapid rearrangement, Doering and Roth have called it a "fluxional" structure. They prevented the possibility of conformational interconversion due to transannular repulsion by preparing the ketone tricyclo(3.3.1.0)nona-2,7-dien-6-one (X) which is locked in the favorable cis-conformation. As a result of very rapid rearrangement, this compound shows only three types of hydrogens (instead of the expected five) in the n.m.r. spectrum even at -60°C .

The limit of a "fluxional" structure in this series as proposed by Doering and Roth is tricyclo(3.3.2.0)deca-2,7,9-triene (XI) for which the trivial name "bullvalene" has been suggested. If the Cope rearrangements of this molecule were very rapid (as they should be since it is held



in the favorable cis-conformation), then all ten carbons could exchange positions (see Fig. 2) so that the n.m.r. spectrum of "bullvalene" should show only one sharp peak which is an average of the properties of the protons in the following distribution among the various positions: 1/10 bridgehead character, 3/10 cyclopropyl character, 3/10 vinyl character (next to the bridgehead) and 3/10 vinyl character (next to the cyclopropyl ring) (19). Notice in Fig. 2 that any of the forms can be interconverted by an appropriate number of Cope rearrangements. Thus, for example, letting the bridgehead carbon be C-1, and numbering as in Fig. 2, the next bridgehead carbon must be either C-4, C-5, or C-10. It would take two rearrangements to get C-2, C-7, or C-8 at the bridgehead and three reactions for the remaining three carbons. This means that the more than 1.2 million isomers of "bullvalene" are easily interconvertible.

Fig. 2



Bibliography

1. A.C. Cope and E.M. Hardy, J. Am. Chem. Soc., 62, 441 (1940).
2. A.C. Cope and H. Levy, ibid., 66, 1684 (1944).
3. E. Vogel, O. Roos and K.H. Disch, Angew. Chem., 73, 342 (1961).
4. E. Vogel, K.H. Ott and K. Gajek, Ann., 644, 172 (1961).
5. A.C. Cope, K.E. Hoyle and D. Heyl, J. Am. Chem. Soc., 63, 1843 (1941).
6. W. von E. Doering and W.R. Roth, Angew. Chem., 75, 27 (1963).
7. A. C. Cope, C.M. Hofmann and E.M. Hardy, J. Am. Chem. Soc., 63, 1852 (1941).
8. E.G. Foster, A.C. Cope and F. Daniels, ibid., 69, 1893 (1947).
9. C. Walling and M. Naimen, ibid., 84, 2628 (1962).
10. W.N. White, D. Gwynn, R. Schlitt, C. Girard and W. Fife, ibid., 80, 3271 (1958).
11. C. Walling and H.J. Schugar, ibid., 85, 607 (1963).
12. S. Hammann, "Physico-Chemical Effects of Pressure", Acad. Press, Inc., New York, N.Y., 1957, Chap. 9.
13. S. W. Benson and J.A. Berson, J. Am. Chem. Soc., 84, 152 (1962).
14. G. Egloff, "Physical Constants of Hydrocarbons", Reinhold Publish. Corp., New York, N.Y., 1939, vols. I, II.
15. C. Walling and D. D. Tanner, J. Am. Chem. Soc., 85, 612 (1963).
16. W. von E. Doering and W.R. Roth, Tetrahedron, 18, 67 (1962).
17. R.S. Berry in Doering and Roth, ibid., 18, 67 (1962).
18. R.B. Woodward and T.J. Katz, ibid., 5, 70 (1959).
19. W. von E. Doering and W.R. Roth, ibid., 19, 715 (1963).
20. A.C. Cope and L. Field, J. Am. Chem. Soc., 71, 1589 (1949).

Reported by R. Lambert

July 24, 1963

I. Introduction.--The entire area of aryne chemistry has been reviewed rather extensively through the latter part of 1960 (1,2,3,4,5), therefore duplication will be avoided except for the summary in this section of the underlying principles. Since the initial studies by Wittig, Roberts and Huisgen*, aryne chemistry has progressed to a point where it is a useful synthetic tool as well as an area of continuing mechanistic interest. The following criteria may be considered qualitatively descriptive of aryne intermediates and reactions involving them; although any serious attempt to generalize the individual results is risky since the properties of a transient intermediate are apt to depend on the method and media in which it is generated.

(i) The intermediate is a short lived, extremely reactive electrophile, possessing the normal benzene ring structure with a special triple bond between two equivalent, hydrogenless sp^2 hybridized carbon atoms. This third bond results from the sideways overlap of these orbitals orthogonal to the π system of the ring and containing antiparallel electrons. The bond is necessarily a weak one since these orbitals are not mutually parallel, but its introduction into the benzene ring does not disturb the π clouds above and below it or its aromatic character.

(ii) The appearance of cine-substituted products whose isomer ratios are generally independent of the nature of the leaving group(s) and dependent upon the inductive and conjugative effect of ring substituents, and the steric requirements of the adduct and aryne.

(iii) A general failure of reactivity of benzyne toward nucleophiles to correlate with their pK_b values.

(iv) Formation of Diels-Alder adducts with dienes such as furan, anthracene, and tetracyclone. Bi- and triphenylene as well as biphenyl are characteristic products when the intermediate is generated in an environment free of nucleophiles. (Methods C, D, E, and F below)

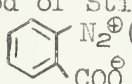
II. Methods of Generation and Characterization.--Only brief mention will be given to those methods which have been reviewed previously (1,2,3,4,5) (parts A-D below) or which have not received thorough investigation due to an inherently inefficient generation procedure (parts G-K below).

A) Reaction of KNH_2/NH_3 with haloarenes containing an ortho hydrogen atom.

B) Reaction of alkyl and aryl lithium compounds in ether, and R_2NLi/R_2NH with halo- and dihaloarenes.

C) Reaction of Li-Hg in ether with dihaloarenes.

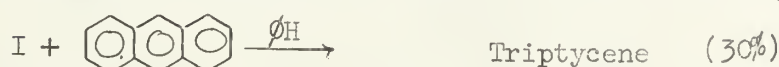
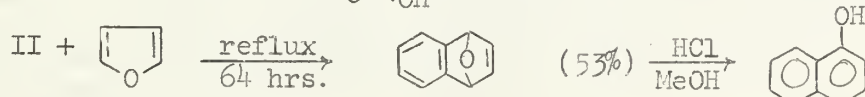
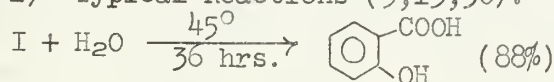
D) Reaction of Mg in ether with dihaloarenes.

E) Diazotization of anthranilic acid in a solution of concentrated ethanolic HCl with isomyl nitrite at $0^\circ C$. This method of Stiles (11,9,10,6) affords a 50-60% yield of benzenediazonium 2-carboxylate  (I). When I is warmed to $40-60^\circ$

in an inert solvent it slowly decomposes with loss of N_2 and CO_2 to yield benzyne. The yield of N_2 is usually quantitative (90-100%) while CO_2 appears to be the limiting factor (yields range from 32-80%). Friedman (12) has reduced the application of I to synthetic practice by diazotizing anthranilic acid with amyl nitrite in solvents such as CH_2Cl_2 , CH_3CN , THF, or acetone.

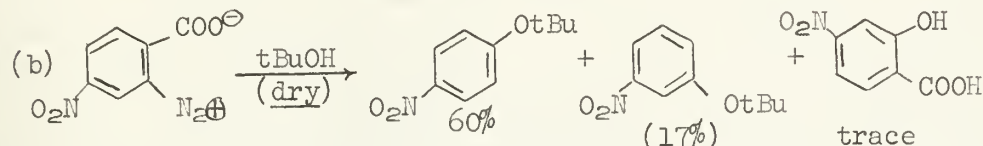
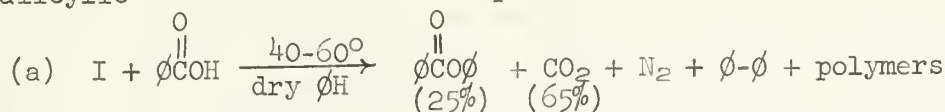
1) General Properties (9,10,30).--The inner salt I does not decompose at room temperature but detonates when shocked. It is soluble in water, insoluble in non-polar solvents and the appearance of a band at 2283 cm^{-1} in its IR spectrum suggests zwitterionic structure I over alternative cyclic species.

2) Typical Reactions (9,13,30).

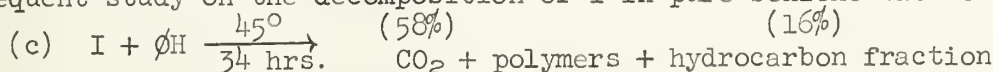


*See R. Heany's review (5) for leading references.

Equations (a) and (b) below illustrate how neutral generation can extend the realm of useful aryne chemistry. The addition of *t*-BuOH in 78% yield stands in sharp contrast with previous attempts at alkoxide additions which were mostly in the range of 0-9% yields. No explanation by the authors is offered for the trace of salicylic acid detected in the products of this reaction.

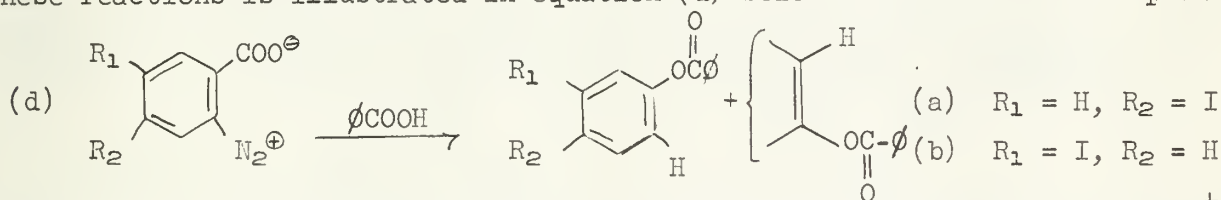


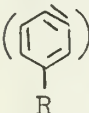
Since Stiles chose benzene as solvent in this work (equations (a) and (d)) a subsequent study on the decomposition of I in pure benzene was conducted.



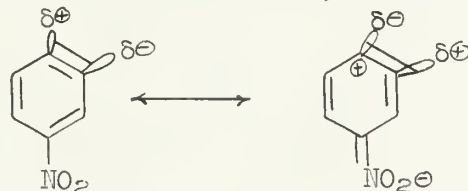
Most of the reaction mixture was unreacted benzene but neither the amount, isolation, nor characterization of the polymeric material is described. The appearance of ester bands in the IR spectrum of the polymeric fraction however, suggest that this might arise from an attack by benzyne on I. Further analysis of the reaction mixture showed the presence of 2, 8, and 6% yields of benzobicyclo (2.2.2)-octatriene, benzocyclooctatetraene, and biphenyl respectively. No bi- or triphenylene was reported, but Stiles postulates the formation of benzocyclooctatetraene from a ring expansion of dihydrobiphenylene.

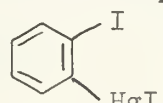
The best evidence for the existence of a symmetrical aryne intermediate in these reactions is illustrated in equation (d) below. The ratio of the para to meta



isomers from the two reactions was the same, within experimental error (1.6 ± 0.2). Deviations from a 50/50 p/m isomer ratio for the 5-nitro, and fluorocompounds (equation d, $\text{R}_2 = \text{F}$ or NO_2) could not be explained solely on the basis of substituent inductive effects (14,32,2) since the p/m ratio for the fluoro compound was 3.5 and that of the nitro compound was only 3.8. As Roberts points out (14), conjugative effects between the substituent and the entering group for 4-substituted benzyne () become important when a one step addition mechanism via a cyclic transition state is possible (as opposed to one that yields another charged intermediate). Assuming that this mechanism is operative here, Stiles argues that the conjugative effect of the nitro group acts in opposition to its field effect with regard to polarization of the triple bond in benzyne, whereas for the fluoro group these effects are complementary.

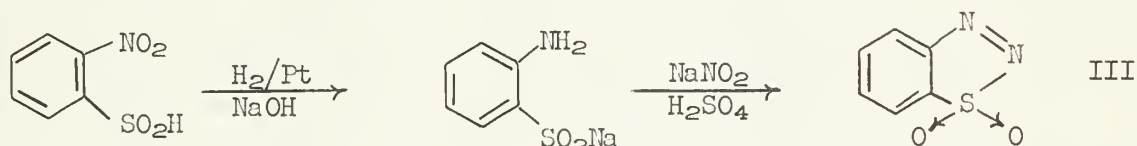
In a further attempt to characterize the intermediate produced from the starting material Berry, Spokes and Stiles (15,13) prepared a solid



film of I, flash photolyzed it and recorded the U.V. spectrum of a transient species leading to the product biphenylene. Since biphenylene's ground and excited state spectra were distinctly different from that of the transient species, the latter was assigned to benzyne. Another compound (16,17) benzyne under thermal decomposition, was used in a comparative run. It was estimated that under conditions leading to 80-90% reaction of I only  (II) 10-20% of II decomposed. Precise ϵ values are unavailable since length x conc. parameters are unknown. No

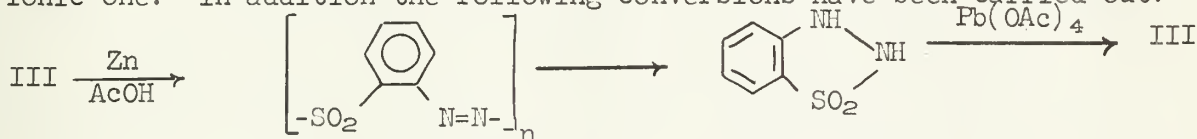
meaningful comparisons can be made therefore, of curves of absorbance vs. wavelength for the two compounds. After repeated photolysis of I, the ether soluble portion of the yellow precipitate which resulted was chromatographed on alumina. Bi- and triphenylene were isolated and their identity demonstrated by matching U.V. spectral data and melting points with literature values. The yields of biphenylene were higher than triphenylene. Biphenylene shows intense absorption bands in the 2400 Å region and weaker long wave bands, the strongest of which occur at 3543 Å. At 200-1000 micro-sec. after photolysis the absorption in the 3500 Å region is broader and shows a transient continuous band which blots out the characteristic 2400 Å biphenylene bands over the rest of the spectrum. One millisecond after photolysis the strongest long wavelength band comes at 3587 Å. The authors conclude from this that biphenylene is produced with excess vibrational energy. That the transient continuous absorption was not due to active biphenylene alone, was shown by irradiating biphenylene. The characteristic 2400 Å absorption was not blotted out. On the basis of similar short life time maxima from the photolysis of I and II Berry (15) et. al, chose to assign the transient spectrum to benzyne.

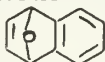
F) Wittig and Hoffmann (18,19,16,20) employing the diazonium salt of o-aminobenzenesulfinic acid as a benzyne source appear to have a more reactive, less stable system than Stiles, and have made a more detailed attempt to characterize the intermediate. When III is warmed in an inert solvent to 10° it decomposes with

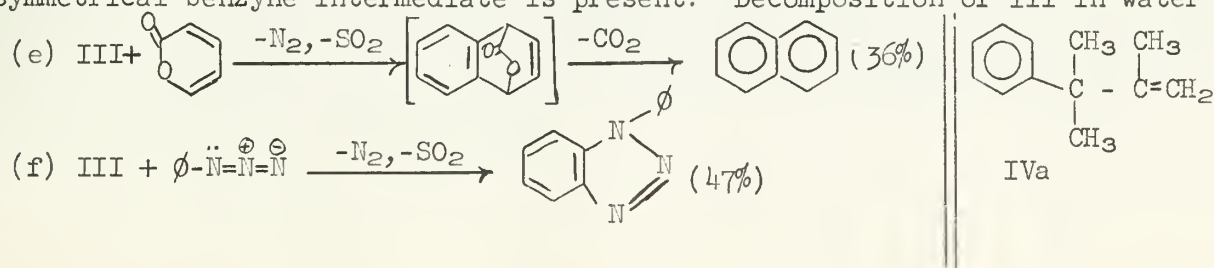


loss of N₂ and SO₂ to benzyne.

(i) General Properties.--III is insoluble in water, soluble in alcohol, ether and an ether-benzene mixture. Its solubility characteristics and the lack of a diazonium band at 2300 cm⁻¹ suggest the cyclic structure in preference to the zwitterionic one. In addition the following conversions have been carried out.

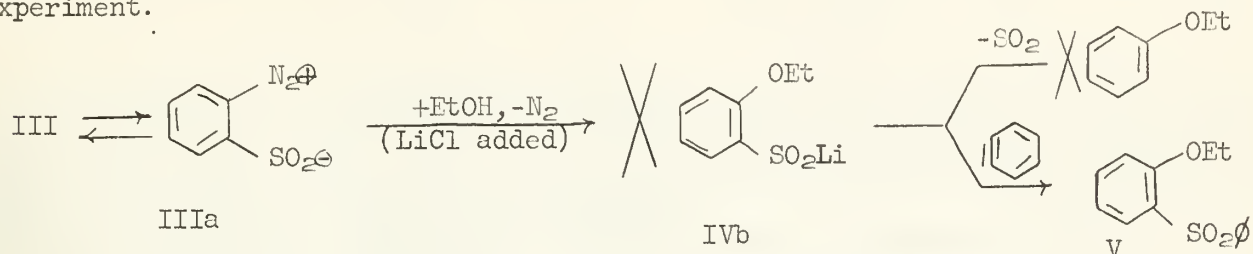


III + furan reacts to form 1-naphthol rather than the expected 1,4-dihydro-1,4-epoxy-naphthalene. That this was an air induced isomerization was shown by the isolation of  in 54% yield from the same reaction run in a N₂ atmosphere. The complementary experiment in which the epoxide is converted to naphthalene by air reflux was also reported. A solution of III in THF + anthracene gives 25-30% yields of triptycene. When III was treated with tetramethylethylene, a hydrocarbon C₁₂H₁₆ resulted which was then assigned structure IVa on the basis of its IR spectrum. In the light of Simmons (19) work, the sterically hindered 1,2-cycloaddition reaction would hardly be expected to occur instead of the observed allylic alkylation (29). The decomposition of III in the presence of alpha-pyrone gives a 36% yield of naphthalene in one step (equation e below). III reacts with phenylazide to give a 47% yield of 1-phenylbenzotriazole (equation f below). These adducts were unobtainable using base-generated benzyne. That no products corresponding to attack at the ester carbonyl of alpha pyrone were observed in the diene addition of equation (e) suggests strongly that an uncharged symmetrical benzyne intermediate is present. Decomposition of III in water gave a



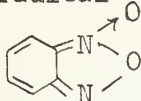
31% yield of phenol, and in ethanol it gave a 69% yield of phenetole. Since 70%

and 80% yields of N_2 and SO_2 were observed⁻¹⁹⁻ in the phenetole synthesis an almost quantitative addition of ethanol to benzyne was achieved. In order to show that these reactions proceed via a benzyne intermediate and not by the alternate substitution-elimination mechanism shown below, Wittig performed the following experiment.



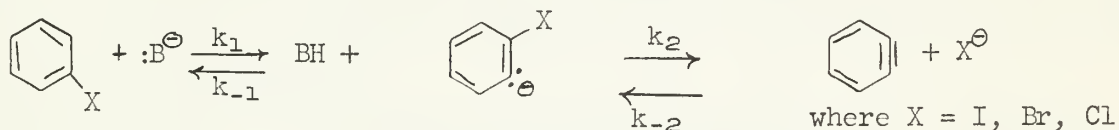
When an excess of independently prepared IVb was introduced into the ethanol III reaction mixture, IVb was recovered in over 80% yield while a small fraction went on to react with benzyne to yield V. The overall yield of phenetole was not specified.

When III was decomposed in weakly nucleophilic solvents such as ether, acetone, or chloroform, the benzyne formed attacked the undecomposed precursor (III). Chromatographic separation of the mixture gave sulfur and nitrogen containing oils with characteristic IR sulfone bands, as well as biphenylene in yields ranging from 2-9% (but no triphenylene). Biphenylene (38-52%) and triphenylene (2%) were obtained when III was detonated in a vacuum. For the chemical characterization of the intermediate from the gas phase decomposition of III, a Diels-Alder addition with furan vapor was attempted, and a 0.6% yield of the adduct 1-naphthol was isolated. In order to see if benzyne can appear as a diradical Wittig decomposed III in nitric oxide. The reaction products contained no (VI), but 2-nitrobiphenylene (2%)

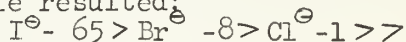


was isolated in addition to biphenylene (52%) and triphenylene (2%). Therefore, the existence of radical benzyne cannot be demonstrated by radical trapping.

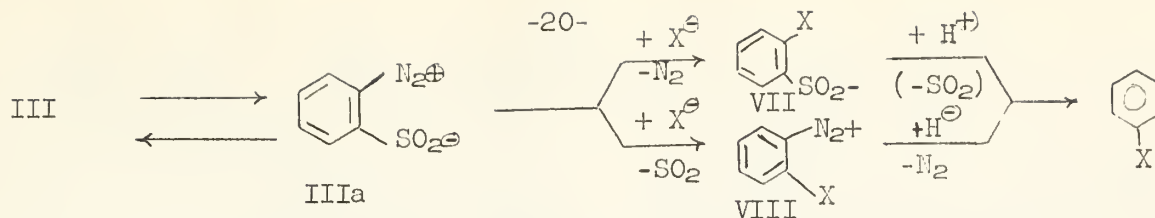
Since the decomposition of III avoids the use of strong bases Wittig (19) has been able to extend the benzyne nucleophilicity scale to include halide ions and alcohols. The mechanism for benzyne formation using Methods A and B above has been shown by earlier workers (1,2,3,4,5) to proceed according to the scheme below with the ratio of k_2 to k_{-1} depending on the nature of the leaving group, with k_1 the rate determining step. Wittig has demonstrated the reversibility of the second step through the isolation of aryl halides from the reaction of lithium halides with III in THF. The protons for reaction with the intermediate anion are believed to come from adventitious water.



From a series of competition reactions using lithium halides first in THF and then in ethanol, the following nucleophilicity scale resulted:



This scale indicates that benzyne is not the highly reactive, unselective intermediate previously proposed (1,2,3,4,5). In order to exclude the possibility that the reaction was proceeding through an intermediate other than benzyne the following experiment was performed. As shown in the scheme below, compounds VII and VIII have been shown to undergo the indicated substitution, however they both do so very much more slowly than III decomposes, and therefore cannot take part in the main reaction path. This, however, says nothing as to whether the hypothetical IIIa participates in the course of the main reaction.



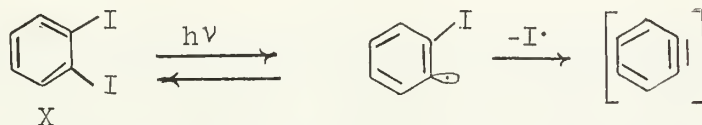
G) Wawzonek (21) reports the generation of benzyne by electrolytic reduction of halobenzenes. This method, if successful, would allow studies in both aprotic and protic media. Both dihalo and monohalobenzenes were used and attempts at trapping intermediate benzyne with furan showed isolated yields of alpha naphthol of 1%, but only for the o-Br substituted benzenes.

H) LeGoff (22) reports that diphenyliodonium 2-carboxylate (IX) may serve as an aprotic precursor of benzyne.



The intermediate has been trapped with tetracyclone to give a 68% yield of 1,2,3,4-tetraphenyl naphthalene and with anthracene to give a 23% yield of triptycene. At 325° IX gives biphenylene in low yield.

I) Kampmeier (23) reports the photolytic decomposition of o-diiodobenzene (X) to benzyne. The proposed scheme below shows that the initial liberation of I• is a highly reversible step which seriously hinders the reaction. Therefore, the total concentration of I2 was kept low by repeated extractions of the reaction mixture with NaHSO3.

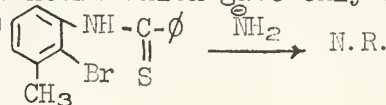


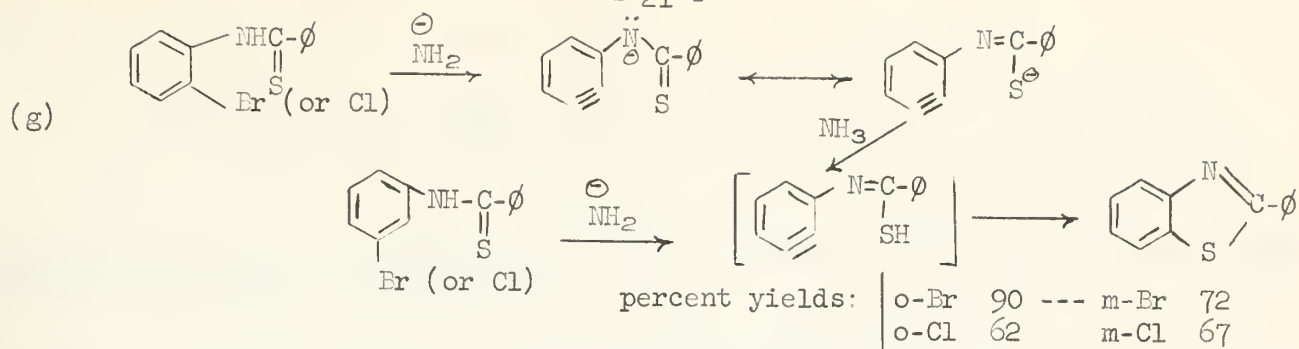
In cyclohexane X gave iodobenzene as the chief product and in benzene 2-iodo-biphenyl (42%) plus triphenylene (4%) and some biphenyl were isolated. That 2-iodobiphenyl may serve as the precursor of triphenylene was shown by irradiating some in benzene. A 7% yield of triphenylene resulted. Reactions involving the usual trapping agents were run - 2-iodobiphenyl was the chief product when tetracyclone was used, with 10% of the Diels-Alder adduct also being found. In none of these reactions was biphenylene ever isolated, or detected.

J) Wittig (16) has investigated the thermal decomposition of o-iodophenyl-mercuric iodide to benzyne but found it to be an inferior method of generation. Attack by I, Hg, and HgI complicate the studies considerably and seriously reduce the steady-state concentration of the intermediate. Phthaloyl peroxide has likewise been rejected by Wittig (17) as a suitable method.

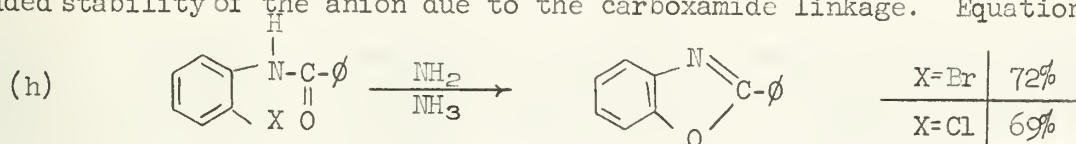
K) Simmons (24) has investigated the possibility of using silver o-halo-benzoates to generate benzyne. Of the many possibilities tried only the ortho chloro compound gave any results which could be interpreted to show that the reaction was proceeding via a benzyne mechanism. The yield of o-chlorophenylbenzoate from a 200° decomposition was 50%.

III. Synthetic Applications. --A) Aromatic Nucleophilic Cyclizations. The principle workers in this field have been Bunnett (25,26,27,28,4) and Huisgen (3). The intramolecular addition of a nucleophile situated on a side chain of an aryne is really just a special case of older intermolecular alkylations on arynes where nucleophiles, either in competition with the generating base or the base itself, were used as adducts. Successful ring closures using carbanions, nitranions, and sulfur anions have been reported (25,26,27) (equations g-l). Since approximately the same yields from ortho and meta isomers resulted, the elimination-addition mechanism is suggested. That direct displacement of bromine by RS⁻ does not occur was illustrated by: (i) refluxing XI or XII with NaOEt/EtOH for four hours which gave only 0.9% product; 97% starting material was recovered and (ii)

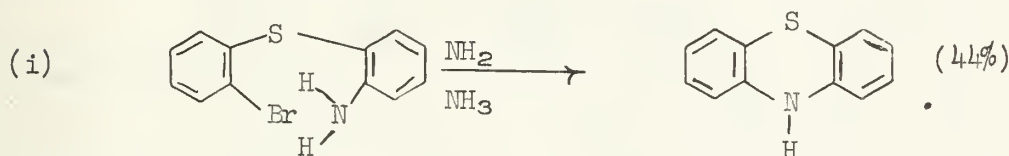




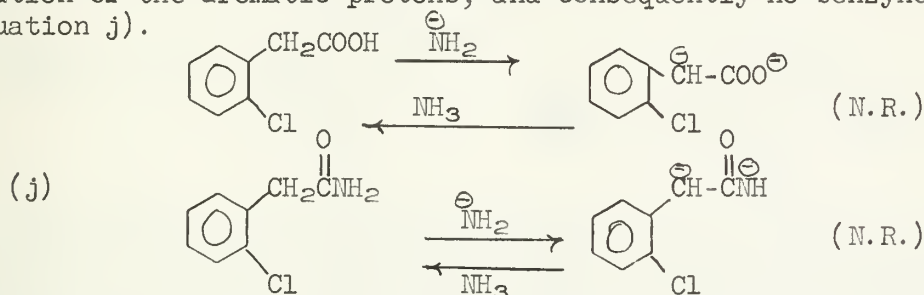
The difficulty in effecting alkoxide additions to benzyne has been noted by earlier workers (see section II) and Bunnett ascribes the singular success of this cyclization reaction (equation h) to the excellent stereochemical orientation and the added stability of the anion due to the carboxamide linkage. Equation (i) represents



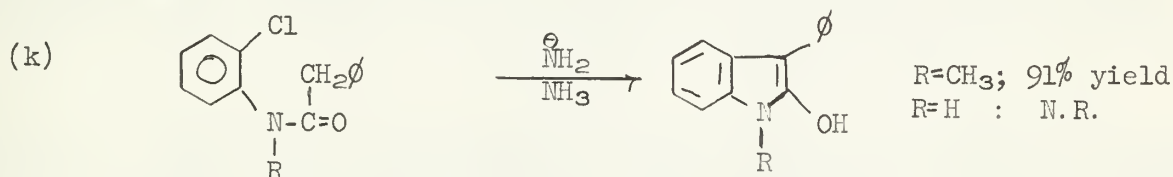
a typical nitranion addition to benzyne.



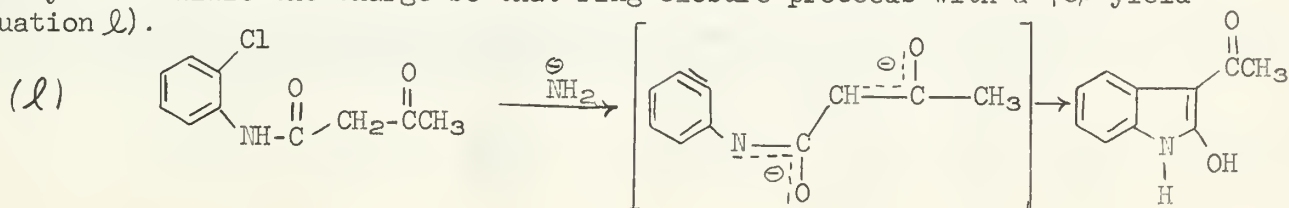
In studying the addition of carbanions to benzyne Bunnett (25,26) has uncovered a serious limitation to the scope of the ring closure reaction. If a side chain anion is produced with the negative charge on an atom adjacent to the aromatic ring, and if the greater portion of this charge is not concentrated in the side chain, then the negative charge will be smeared out on the ring (mesomerism) causing deacidification of the aromatic protons, and consequently no benzyne formation is achieved (equation j).



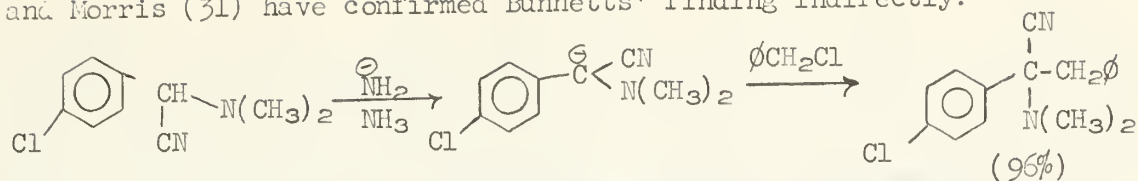
In equation (k) below if R=H, the base abstracts protons from both methylene and nitrogen atoms forming a dianion in which the negative charge is not sufficiently localized in the side chain, and therefore no reaction occurs.



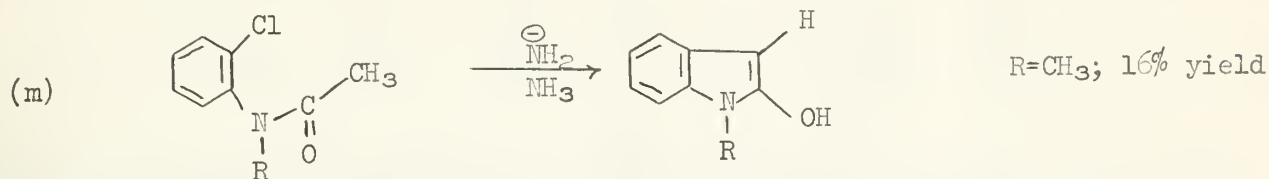
When an additional keto group is introduced in place of the phenyl group, then both carbonyls stabilize the charge so that ring closure proceeds with a 78% yield (equation l).



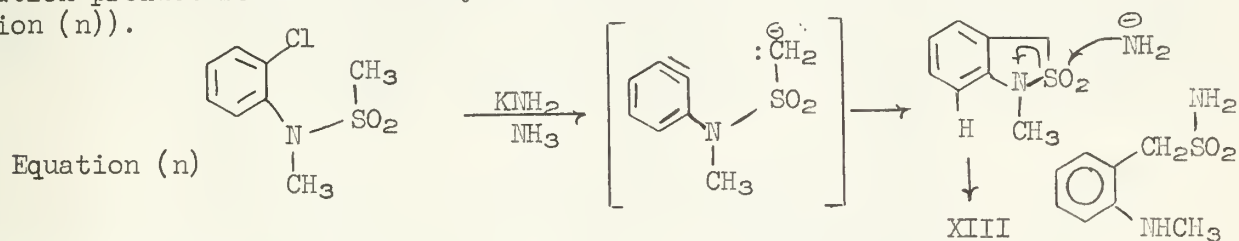
Hauser and Morris (31) have confirmed Bunnetts' finding indirectly.



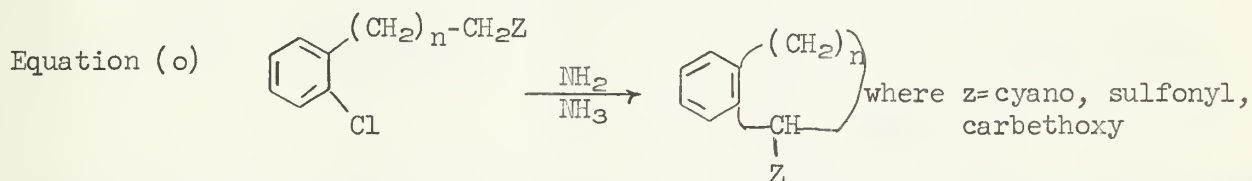
In reaction (m) below a 16% yield was taken as evidence for the activation of alpha hydrogen by an amide carbonyl group.



When $\text{R}=\text{H}$ cyclization takes place to form a benzoxazole ring (equation h) in 37% yield. If the amide carbonyl is replaced by a sulfonyl linkage the expected cyclization product formed initially reacts further with KNH_2 to reopen the ring (equation (n)).

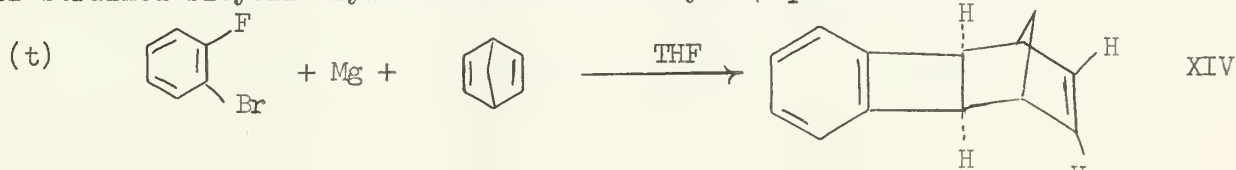


That attack by NH_2^- takes place at the sulfonyl group instead of on the ring hydrogen of the initial product is deduced from the reaction products in which no primary aromatic amine could be found, and from a comparison of XIII's n.m.r. spectra with a known sample of the initial product synthesized by an unequivocal route. Bunnett (26) has also found that aliphatic esters, nitriles, sulfones and ketones with ω -ortho chlorophenyl groups give homocyclic ring closure products (equation (o)).

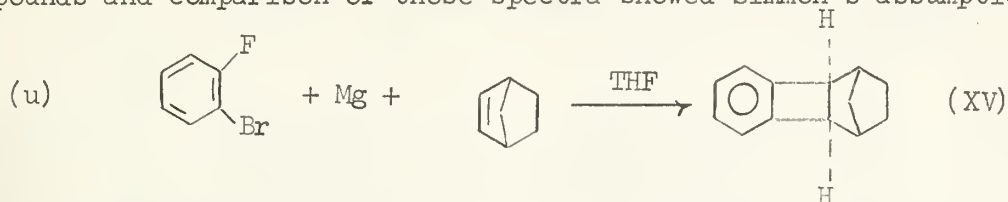


By varying both chain length and the nature of the activating group (Z), Bunnett hoped to gain mechanistic insight as well as to determine the optimum conditions for synthesis. The order: cyano, sulfonyl, carbethoxy, is roughly in accordance with the activation capacity for the group in terms of % yield. Ortho-chloro compounds were shown to give the same ring closure products as meta isomers but in higher yields. Reaction times were usually on the order of 15 minutes. Questions which remain unanswered from this work are: (i) Why is proton removal ortho to the side chain preferred, i.e., $\text{C}_6\text{H}_4\text{X-CH}_2\text{Z} \xrightarrow{+\text{B}^-} \text{C}_6\text{H}_4\text{X-CH}^-\text{Z} + \text{BH}$ rather than $\text{C}_6\text{H}_4\text{X-CH}_2\text{Z} \xrightarrow{+\text{B}^-} \text{C}_6\text{H}_4\text{X-CH}_2\text{Z}^- + \text{BH}$ seems to be the case since yields greater than 50% have been observed (see equations (g) and (h)). (ii) Is this additional reaction a two step or concerted process, i.e., is it the conjugate acid of the side chain anion which adds to benzyne in one step or does the side chain anion add to the benzyne bond to give an aryl anion which is subsequently protonated.

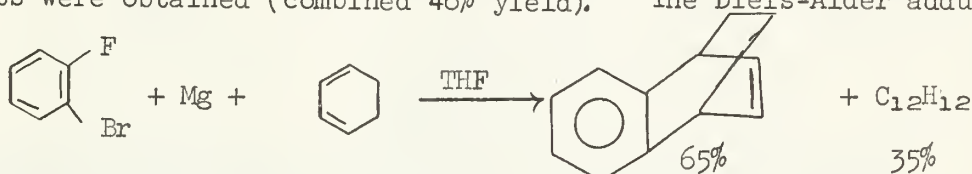
B) Diels-Alder and Analogous Additions.--Simmons (7) has investigated the reaction of strained bicyclic hydrocarbons with benzyne (equation t below).



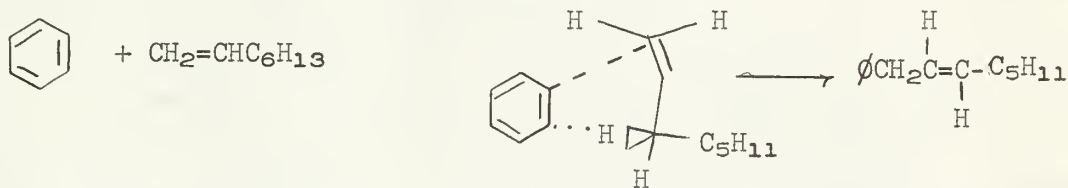
Only the exo isomer was uncovered in the products. XIV reacts with KMnO_4 and Br_2/CCl_4 , shows $\text{C}=\text{C}$ in IR at 6.39μ (1564 cm^{-1}) and n.m.r. showed it to be a 1:1 adduct $\text{C}_{13}\text{H}_{12}$. It was known that bicycloheptene double bonds give 1:1 adducts with dienophiles and that predominant formation of the exo isomer results. Simmons thought that the bulky benzyne molecule would give the exo adduct. Structure proof for the adduct was made through comparisons of its n.m.r. spectra with a known sample of the endo isomer. Subsequent chemical transformation, on both compounds and comparison of those spectra showed Simmons's assumption to be correct.



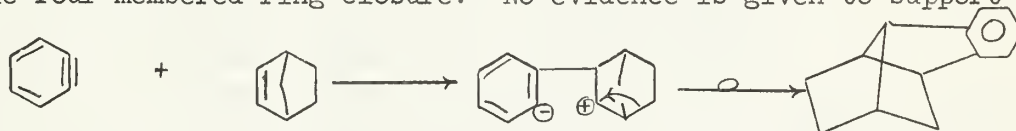
The hydrogenation product from XIV was shown to be identical with XV. The exclusive exo geometry has been attributed to the ease of steric approach to the less hindered side of the bicycloheptene double bond. Thus it would appear that benzyne reactions are more susceptible to steric controls than previously thought (1,2,3,4,5), and since reactions (t) and (u) both give exo adducts no unusual electronic factors need be invoked. In the reaction of benzyne with cyclohexadiene (7) two adducts were obtained (combined 46% yield). The Diels-Alder adduct was



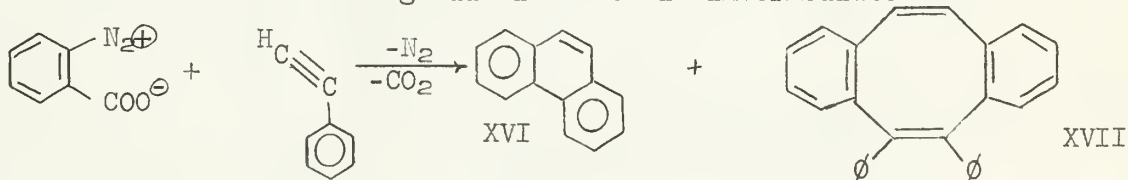
characterized by its IR and n.m.r. spectra and by analogy with Wittig's results (17). The $\text{C}_{12}\text{H}_{12}$ product could not be obtained pure by VPC but the n.m.r. spectra of the crude product showed it to be a 1:1 adduct with bands expected of a benzycyclobutene structure (a line of area two at $\tau = 6.51$). In the reaction of 1-octene a 17% yield of trans-1-phenyl-2-octene resulted. This hydrogen abstraction reaction is pictured as going through a cyclic quasi-six membered ring.



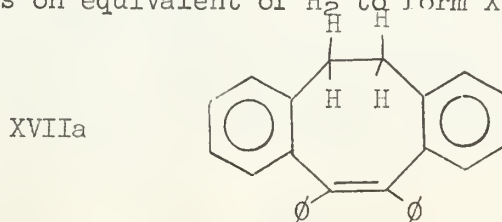
Although the molecular mechanism has not been established for these reactions Simmons feels that this is a likely guess since skeletal rearrangements in other cycloaddition reactions are absent. He argues that if the possibility of a zwitterion intermediate did exist then reaction (m) would undoubtedly have resulted in a rearranged product. Contingent to this argument however, is the assumption that such a rearrangement is faster than the four membered ring closure. No evidence is given to support this assumption.



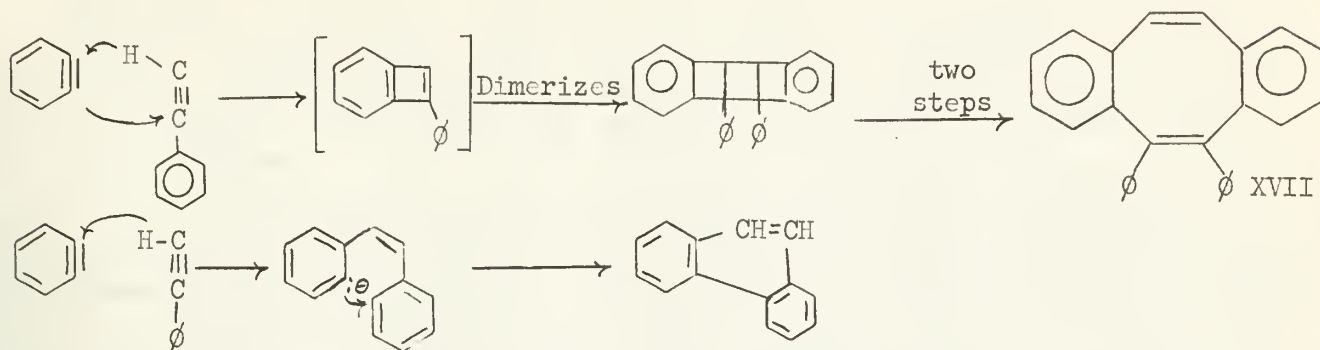
Stiles (10) has achieved the following additions to his intermediate.



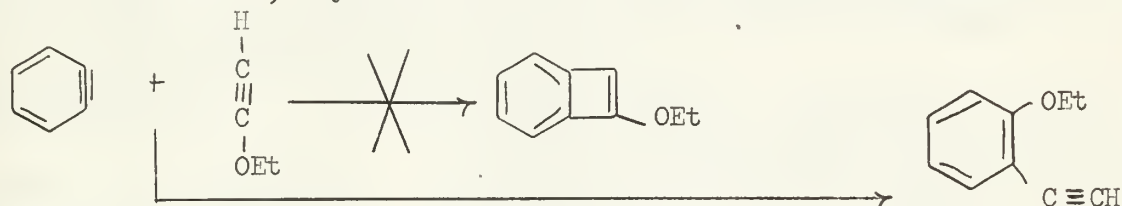
XVII on treatment with Pd/C absorbs on equivalent of H_2 to form XVIIa.



The proposed mechanism to explain the products is given below. XVII formation is shown as arising by a 1,2 cycloaddition reaction, and phenanthrene is pictured as arising by a 1,4 cycloaddition through an anion intermediate.



Attempts to extend the 1,2 cycloaddition reaction led to this result.



BIBLIOGRAPHY

1. G. Wittig, *Angew. Chem.*, **69**, 245 (1957).
2. J. D. Roberts, *Chem. Soc. (London) Spec. Publ. No. 12*, 115 (1958).
3. R. Huisgen, Chapt. 2 in "Organometallic Chemistry", H. H. Zeiss, ed., Reinhold Publishing Corp., New York, N.Y.
4. J. F. Bunnett, *J. Chem. Ed.*, **38**, 278 (1961).
5. H. Heaney, *Chem. Revs.*, **62**, 81 (1962).
6. M. Stiles, R. G. Miller and U. Burckhardt, *J. Am. Chem. Soc.*, **85**, 1792 (1963).
7. H. E. Simmons, *J. Am. Chem. Soc.*, **83**, 1657 (1961).
8. E. Wolthuis, *J. Org. Chem.*, **26**, 2215 (1961).
9. M. Stiles and R. Miller, *J. Am. Chem. Soc.*, **82**, 3802 (1960).
10. M. Stiles, U. Burckhardt and A. Haag, *J. Org. Chem.*, **27**, 4715 (1962).
11. R. G. Miller and M. Stiles, *J. Am. Chem. Soc.*, **85**, 1798 (1963).
12. L. Friedman and F. M. Logullo, *J. Am. Chem. Soc.*, **85**, 1549 (1963).
13. R. S. Berry, G. N. Spokes and M. Stiles, *J. Am. Chem. Soc.*, **82**, 5240 (1960).
14. J. D. Roberts, C. W. Vaughan, L. A. Carlsmith and D. A. Semenow, *J. Am. Chem. Soc.*, **78**, 611 (1956).
15. R. S. Berry, G. N. Spokes and M. Stiles, *J. Am. Chem. Soc.*, **84**, 3570 (1962).
16. G. Wittig and H. F. Ebel, *Ann.*, **650**, 20 (1961).
17. G. Wittig and R. W. Hoffmann, *Angew. Chem.*, **72**, 564 (1960).
18. G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2718 (1962).
19. G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2729 (1962).
20. G. Wittig and R. W. Hoffmann, *Angew. Chem.*, **73**, 435 (1961).
21. S. Wawzonek and J. H. Wagenknecht, *J. Electro. Chem. Soc.*, **110**, 420 (1963).
22. E. LeGoff, *J. Am. Chem. Soc.*, **84**, 3786 (1962).
23. J. A. Kampmeier and E. Hoffmeister, *J. Am. Chem. Soc.*, **84**, 3787 (1962).
24. H. E. Simmons, *J. Org. Chem.*, **25**, 691 (1960).
25. J. F. Bunnett, T. Kato, R. R. Flynn and J. A. Skorcz, *J. Org. Chem.*, **28**, 1 (1963).
26. J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).
27. J. F. Bunnett and A. J. Sisti, *J. Org. Chem.*, **26**, 3639 (1961).
28. J. F. Bunnett and B. F. Hrutfiord, *J. Am. Chem. Soc.*, **83**, 1691 (1961).
29. E. M. Arnett, *J. Org. Chem.*, **25**, 4740 (1961).
30. R. Huisgen and P. Knorr, *Naturwissenschaften*, **48**, 716 (1961).
31. C. R. Hauser and G. F. Morris, *J. Org. Chem.*, **26**, 4740 (1961).
32. G. E. Hall, E. M. Libby and E. L. James, *J. Org. Chem.*, **28**, 311 (1963).
33. F. N. Jones, M. F. Zinn and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).
34. G. Koebrich, *Angew. Chem.*, **74**, 428 (1962).
35. G. Wittig, *Angew. Chem. (Internat. Ed.)*, 415 (1962).

THE PROBLEM OF SOME THERMOCHROMIC ETHYLENES

Reported by R. Puckett

July 29, 1963

Introduction. - A number of organic compounds have been observed to change color upon heating both in the solid state and in solution. This phenomenon is known as thermochromism. Photochromism refers to the same type of behavior upon irradiation with light of a suitable wavelength. A number of these compounds have also been observed to undergo a color change when subjected to pressure. The latter has been called piezochromism.

A recent paper (1) on the crystal and molecular structures of the α and β polymorphic forms of 9,9'-bixanthenylidene (II) suggests that much of the evidence for the mechanism of thermochromism and related effects in the bixanthenylidenes and bianthronylidenes needs to be reevaluated. This seminar will deal with studies performed in this area on both these classes of compounds and will attempt to summarize the evidence available at the present time. A recent review (2) on the general topic of thermochromism treats these compounds briefly. Also, Kortum has summarized his own work, mainly on the bianthronylidenes, more thoroughly (3). This seminar will not deal with the thermochromism of the spiropyrans.

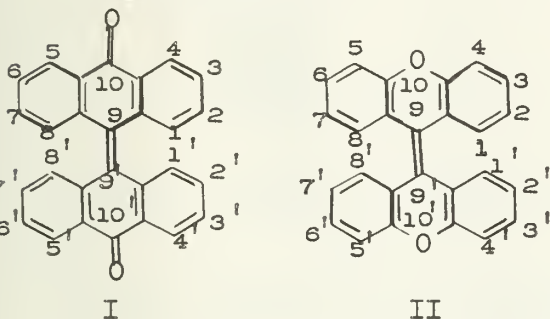
Experimental Facts. - Existence of Color Change. -- As early as 1909 (4) it was noted that warm solutions of 9,9'-bianthronylidene (I) were green while at room temperature they were lemon-yellow. In 1928 9,9'-bixanthenylidene was observed to behave similarly, changing from light yellow to blue-green (5). Crystals of bianthronylidene are pale yellow at room temperature (6). When heated to about 265°C., they are reported to become light green and then dark green. The color change is not reversible for the crystals once the dark green state has been attained; however, solutions of

bianthronylidene exhibit thermochromic behavior, the color change occurring at a much lower temperature (70°-180°C.) and being completely reversible (7).

The phenomenon of photochromism in these two classes of compounds seems to be closely related to that of thermochromism. Hirshberg first noted that at temperatures below -70°C. solutions of bianthronylidene changed color markedly when submitted to ultraviolet irradiation of frequency 27,400 cm.⁻¹ (8). The color was observed to fade upon warming to room temperature. Furthermore the phenomenon did not manifest itself if the irradiating light was less energetic than approximately 22,000 cm.⁻¹.

Ultraviolet and Visible Spectra. - In 1950, Theilacker et al. (7) studied the visible and ultraviolet absorption spectra of bianthronylidene at various temperatures (Fig. 1) and observed that there was a band in the visible region at 15,000 - 16,000 cm.⁻¹ which could be correlated with the color change and whose molar absorptivity coefficient showed a strong temperature dependence, decreasing with decreasing temperature and obeying the Beer-Lambert law. The remainder of the spectrum showed no strong temperature dependence. Thus this band was assigned as being characteristic of the thermochromic property of bianthronylidene. On the basis of the reversibility of the color change and the fact that a plot of log ϵ_{max} for the 15,000 cm.⁻¹ band versus 1/T gave a straight line, it was proposed that the thermochromism of this compound was caused by a thermal equilibrium between two different forms, A and B, of the molecule, form A being "normal" and form B being colored.

Grubb and Kistiakowsky obtained similar spectral results and were able to show a slight solvent dependence by employing both acetophenone and decalin (9). The spectral measurements were also duplicated by Hirshberg and Fischer, but they did not specify their solvent (10). The spectrum of the closely related compound 9,9'-bixanthenylidene (II) is substantially the same as that for 9,9'-bianthronylidene (I) except that molar absorptivity coefficients are somewhat smaller (7). Hirshberg showed that the temperature dependent band at 15,000-16,000 cm.⁻¹ of the colored thermochromic modification is practically identical with a corresponding band produced by the photochromic form (10).



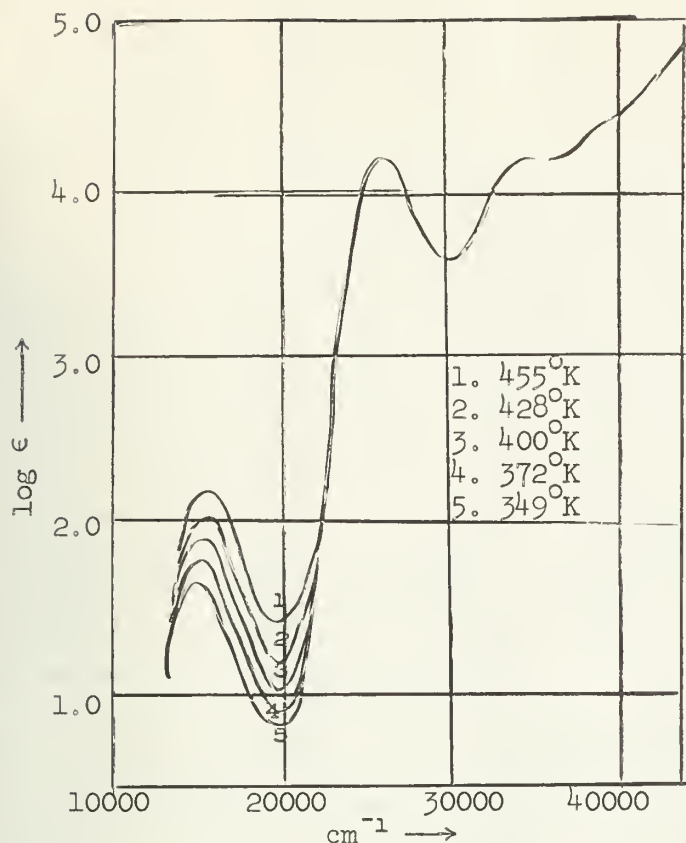
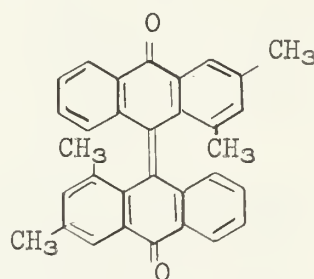


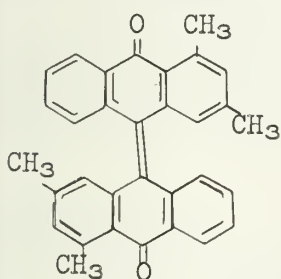
Fig. 1. Visible and ultraviolet spectrum of 9,9'-bianthronylidene (I).

Kortüm and Bayer in a recent communication have stated that 1,3,6',8'-tetramethyl-9,9'-dianthronylidene (III) exists in three forms in solution (11). Their evidence is mainly spectral. They report the photochromic form (form B) with the usual maximum at 15,000 cm^{-1} and another form (form C) with smaller maxima at 21,000 and 22,500 cm^{-1} . The uncolored form is denoted as form A. The remaining ultraviolet spectrum of form C is completely different from that of form A. Solvolysis of the sulfuric acid adduct of A in 10% aqueous alcohol at -90°C . is reported to give exclusively form B. Both B and C revert to A at higher temperatures.



III

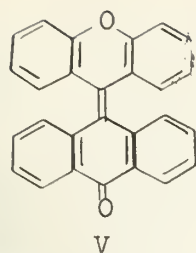
Thermodynamics and Kinetics of the Color Change. - Assuming that the colored and uncolored forms were in equilibrium, Theilacker has determined equilibrium constants from an evaluation of the molar absorptivity coefficients of the 15,000 - 16,000 cm^{-1} band at various temperatures (7). A plot of the equilibrium constant versus the reciprocal of the absolute temperature enabled him to obtain the heat of transformation between forms A and B. For 9,9'-bianthronylidene (I), a value of 3.4 ± 0.2 kcal./mole was obtained. The corresponding value for 9,9'-bixanthenylidene (II) was 4.9 ± 0.1 kcal./mole. Grubb and Kistiakowsky obtained similar results and were further able to show that the heat of transformation had a slight solvent dependence (9). In a later study, 2,4,5',7'-tetramethyl-9,9'-dianthronylidene (IV) was shown to have a ΔH value of 6.7 ± 0.3 kcal./mole (12).



IV

In 1953 Hirshberg and Fischer found that the frequency factors for the thermal reversion reaction were not smaller than those encountered in common first order reactions (10). This indicates that the reversion process is not due to a transition involving a change in electron spin multiplicity. Wasserman and Davis (13) report that the bleaching of the thermochromic, photochromic and piezochromic forms of 9,9'-bianthronylidene is a first order process in which the rate constants for all three forms are identical within "10% uncertainties". Their criterion of error is unspecified. They interpret this as evidence that all three forms are identical. However, as Mills and Nyburg have pointed out (14), this could merely mean that all three return to the colorless form by the same rate determining step. It has been noted that the lifetime of the photochromic state of 2,4,5',7'-tetramethyl-9,9'-dianthronylidene (IV) in solution is at least 10^4 larger than that of known triplet states of organic materials (usually several seconds) (15). This however does not discount the existence of the colored form of this compound in a triplet state.

Dipole Moment Studies. - In 1950, Bergmann and Fischer reported that 9,9'-bian-



thronylidene (I) in solution exhibited a dipole moment of 1 Debye (16). In contrast Kortüm and Buck have reported that both 9,9'-bianthronylidene and 9,9'-bixanthenylidene have no dipole moment in solution (17). Through a study of the molar polarizability of solutions, Hirshberg has demonstrated that the colored form of xanthylideneanthrone (V) produced by irradiation is more polar than the non-colored modification (10).

Magnetic Measurements.

- As we shall see, thermochromism and photochromism have been interpreted in terms of triplet-triplet transitions. Therefore, various magnetic measurements have been made with somewhat conflicting results. Nilson and Fraenkel found that solutions of bianthronylidene in decalin and dimethylphthalate at various concentrations showed paramagnetic absorption in the temperature range 140°-200°C. (18). In more concentrated samples the intensity of absorption was found to decrease with decreasing temperature to a point where it could no longer be detected. In more dilute solutions it was only possible to observe that no absorption could be detected below a certain temperature (generally 100°-150°C.). Kortüm and Theilacker observed that the photochromic form of bianthronylidene was paramagnetic by magnetic susceptibility measurements (15). These workers maintain that the thermochromic form is diamagnetic however, mainly on the failure to observe paramagnetism of the colored form produced at high temperature. It should be pointed out that they used a magnetic balance method which is considerably less sensitive than that of paramagnetic resonance absorption.

Wasserman has shown that pyridine solutions of bianthronylidene at 25°C. exhibit electron spin resonance which increases with temperature (19). The signal is reported to consist of five main components having relative intensities of 1:4:6:4:1, indicating the interaction of an unpaired electron with four equivalent protons. The absorption maximum at 15,950 cm.⁻¹ and shoulder at 17,390 cm.⁻¹ were described as being sensitive to both oxygen and excess bianthronylidene. Ether solutions of the green form of bianthronylidene (obtained by sublimation at reduced pressure) showed no absorption at -77°C., but did exhibit a resonance at -46°C. which then vanished as the color of the solution faded (19). Measurements on methyl 9,9'-bianthronylidene-3-carboxylate by magnetic balance measurements at 210°C. showed no evidence of a biradical (20). No ESR signal was observed in a series of substituted bianthronylidenes and bixanthenylidenes, but the authors admit that this may have been due to unusually broad resonance lines (21).

It has also been found that bianthronylidene shows a paramagnetic absorption at 265°C. in the solid state which is retained upon cooling (18). Matsunaga has reported that bianthronylidene shows a drastic decrease in diamagnetic susceptibility as the color change occurs in the solid state (22). The color change is also accompanied by complete vanishing of sharp x-ray powder diffraction patterns. Mills and Nyburg report no paramagnetic absorption in their solid α -modification of bixanthenylidene (14).

Stereochemical Studies. - In an effort to obtain some knowledge of the actual conformations of forms A and B, Kortüm and co-workers prepared a series of substituted bianthronylidenes and determined the presence or absence of thermochromic properties. The results are shown in Table 1.

Table 1

<u>Derivative of I</u>	<u>Thermochromic Properties</u>	<u>Reference</u>
2,4,5',7'-tetramethyl-	Thermochromic band at 155°C	12
1,3,6',8'-tetramethyl-	No Thermochromism	12
1,4,5',8'-tetramethyl-	No Thermochromism	12
2,3,6',7'-dibenzo-	Weakly Thermochromic	23
3,4,5',6'-dibenzo-	Thermochromic	23
1,2,7',8'-dibenzo-	No Thermochromism	23

These results indicate that substitution in the 1,1' or 8,8' positions prevents thermochromic behavior. Although 1,3,6',8'-tetramethyl-9,9'-bianthronylidene is non-thermochromic, Kortüm reports that in the preparation of this compound a deep green solution is formed which immediately reverts to the yellow color of the "normal" compound (12).

Some substituted bianthrnylidene which do not exhibit thermochromism have been shown to be photochromic. Photochromism is exhibited by 2,4,5',7'-tetramethyl-9,9'-bianthrnylidene (IV) (15) as well as 1,3,6',8'-tetramethyl-9,9'-bianthrnylidene (III) (11). In contrast, 9,9'-bixanthenylidene (II), which is thermochromic, does not exhibit photochromism (10).

An examination of models reveals that there is an exceptionally high amount of steric hindrance present at positions 1,1' and 8,8' even in unsubstituted bianthrnylidene. Indeed a completely coplanar system can be completely eliminated (Fig. 2).

Theilacker *et al.*, prepared the series of compounds VI-VIII in an effort to study their optical activity (24). These workers were able to resolve the quinine salts of VI; but upon acidification with HCl, racemization took place immediately. They were unsuccessful in attempts to resolve either VII or VIII. Recently it has been reported indirectly that the optically active isomers of 9,9'-bithioxanthenylidene-4-carboxylic acid (IX) racemize spontaneously in dioxane (25). The amount of crowding in the 1,1' and 8,8' positions in this compound is comparable to that in 9,9'-bianthrnylidene (I).

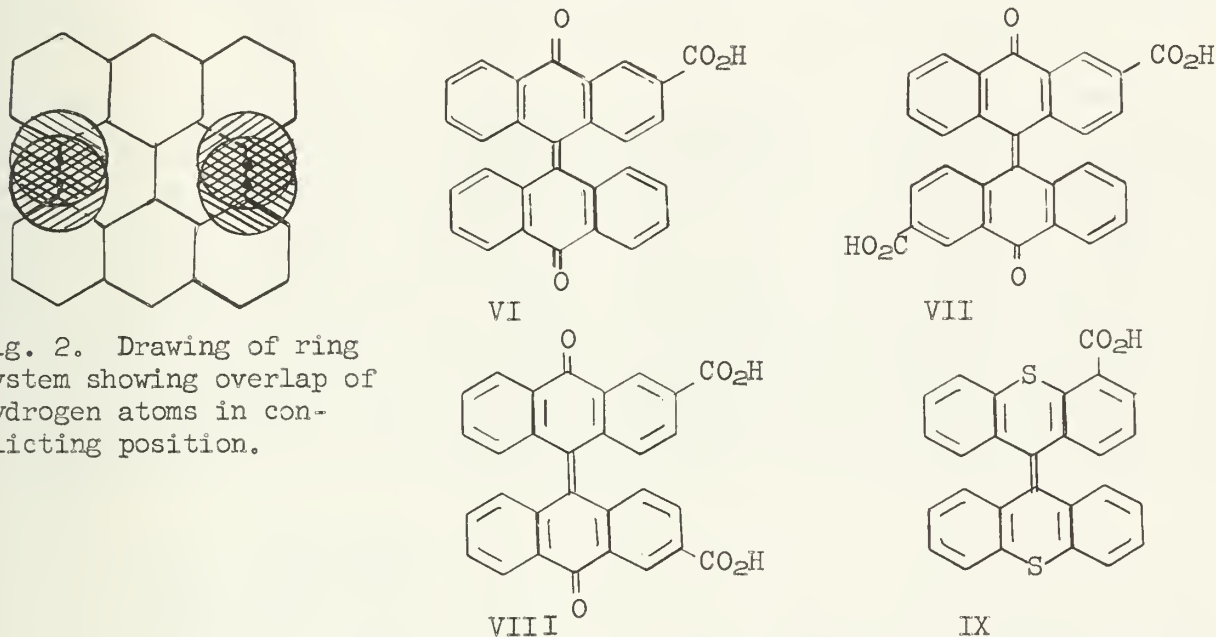


Fig. 2. Drawing of ring system showing overlap of hydrogen atoms in conflicting position.

However, this sulfur compound is not thermochromic; and at the time of this writing no thermochromic bianthrnylidene or bixanthenylidene has been resolved.

Structure of 9,9'-Bianthrnylidene. - In 1954, Harnik and Schmidt (26), as part of a study of the molecular and crystal structures of a series of "overcrowded" aromatic compounds, published the crystal structure of 9,9'-bianthrnylidene (I). By the application of two-dimensional molecular Fourier transform methods, they were able to elucidate the following structure. The "overcrowded" carbon atoms, 1,1' and 8,8', are found to be 2.90 Å apart, this being made possible by a 40° rotation of the benzene rings out of the plane of the central ethylenic system. The exocyclic bonds to the carbonyl carbon are deflected out of the planes of their respective benzene rings by 8°, thus giving a boat-like shape to the center rings. Furthermore the C=C=C bond angle is compressed from its normal value of 120° to 113°. All bond lengths are of approximately normal length. The conformation, because of the "wing-like" structure of each of the two molecular halves, has been called the "folded conformation" of bianthrnylidene.

Crystal and Molecular Structure of 9,9'-Bixanthenylidene. - Recently some very significant x-ray work (1) was done by Mills and Nyburg on 9,9'-bixanthenylidene (II). These workers were able to obtain good crystals of both the α (deep blue-green) form and the β (yellow) form. The α crystals were obtained by subliming the β form in a 250°-130°C. gradient at about 10⁻³ mm. Hg. Complete structural analyses were performed on both polymorphic forms, employing the Fourier molecular transform method. This study showed that both forms possessed the folded conformation previously assigned only to the yellow "normal" state. Bond lengths and distances are shown in Figures 3 and 4. Estimated errors are ± 0.02 Å in bond lengths and ± 1.5° in bond angles.

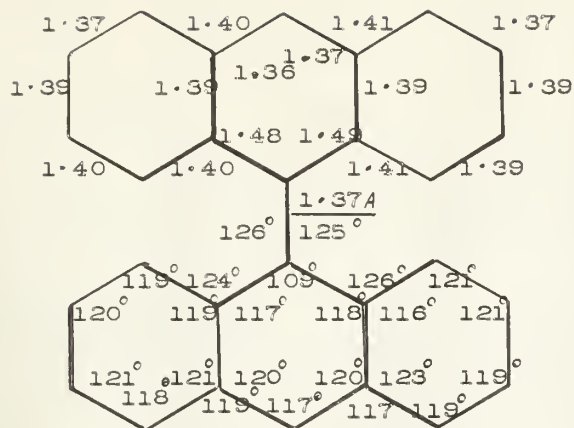


Fig. 3. α -form of 9,9'-bixanthenylidene.

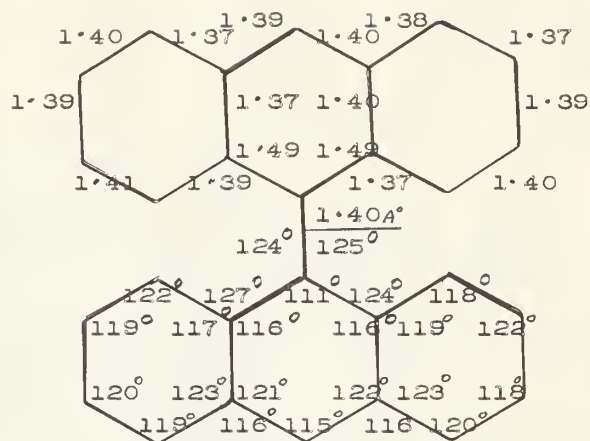


Fig. 4. β -form of 9,9'-bixanthenylidene.

As can be seen, there are no striking structural differences between the α and β polymorphs. In fact the only substantial differences between the two forms in the solid state are in the modes of molecular packing. These are shown in Figures 5 and 6. In both these figures the molecules drawn in full lines are those which have their midpoints lying in the center layer of the unit cell. The molecules in broken lines have their midpoints lying in layers half a cell above or below. In both cases the outer rings of the molecules stack on top of each other in a columnar array. The heterocyclic rings also stack in this manner in the α -form with oxygen atoms alternating from left to right; but in the β -form the heterocyclic rings do not stack in columns. Thus it has been shown that in 9,9'-bixanthenylidene both the "normal" and colored modifications have the same molecular conformation in the solid state, and thermochromism cannot be due to an equilibrium between two conformational forms of the molecule.

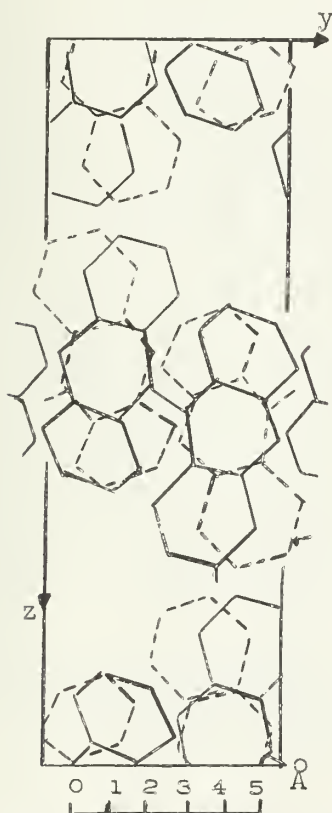


Fig. 5. α -bixanthenylidene in x-projection.

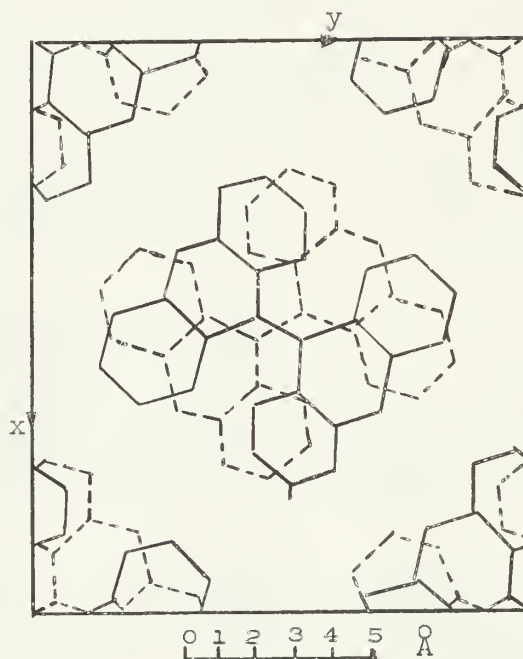
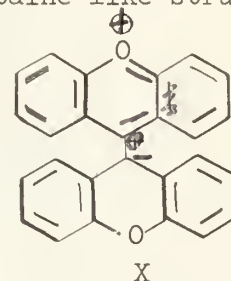


Fig. 6. β -bixanthenylidene in z-projection.

Theories - As the facts about these molecules have developed, a number of explanations of their thermochromic behavior have appeared. In retrospect some may now be dismissed out of hand. However, at present there is still no satisfactory accounting for the facts.

Betaine Theory . - Schönberg has proposed that form B has a betaine-like structure such as X (6). This theory has been discounted due to the independence of the thermochromic absorption spectrum on the acidity of the solvent and the fact that the rate of disappearance of the green modification at -50°C . is greater in ethanol than in isooctane by a factor of 2 (27).



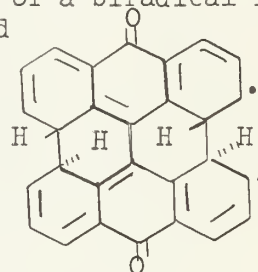
Biradical Theories. - Several workers (9), (28) have proposed that the colored modification produced by the photochromic technique is a biradical in which the two halves of the bianthronylidene molecule are twisted with respect to each other. Matlow has performed molecular orbital calculations on both bianthronylidene and bixanthenylidene to determine the relative magnitude of energy differences between the ground state and both coplanar and perpendicular triplet states (29). He has assumed the ground state is a coplanar singlet and has used 20 kcal./mole as an approximation to the potential barrier to twisting in the ground state. This figure was obtained by analogy with the racemization of optically active 2,2'-dibromo-4,4'-dicarboxydiphenyl. On the assumption that the steric hindrance of the singlet and triplet states is the same, the following results (Table 2) are obtained. Thus, these calculations indicate that the

Table 2

Compound	ΔE (kcal./mole)		
	Coplanar	Perpendicular	Obs. Thermal Exc.
bianthronylidene	15.996	3.3335	3.4-3.5
bixanthenylidene	26.1	10.8	4.9

perpendicular biradical is of considerably lower energy than the coplanar one. However it is also obvious that the calculations are valid only for order of magnitude comparisons.

Woodward and Wasserman have suggested XI as one resonance form of a biradical for the green form of bianthronylidene (23). A twisted biradical should be stabilized by substituents in the 1,1' and 8,8' positions. However Woodward noted that the opposite was true. This together with the observed ESR of this compound led to the proposal of the coplanar biradical. There has been some controversy as to whether the photochromic and thermochromic modifications are identical (30), (31), (32), (33). The majority of evidence seems to indicate that they are.



Obviously if any of the various biradical theories is to be given any sound basis, then quantitative magnetic measurements must be obtained which establish the presence of two unpaired electrons. As was seen in part I, some workers have reported that the colored forms of these compounds are paramagnetic, indicating the presence of a radical species; but experimental difficulties seem to have prevented quantitative measurements. At this point, the proposal of biradicals is unsupported by direct evidence.

Conformational Equilibrium Theory . - An examination of the stereochemical data suggests that the phenomenon of thermochromism of the bianthronylidenes is restricted by the amount of steric hindrance in the 1,1' and 8,8' positions. This would seem to indicate that planarity of the molecule is somehow connected with its thermochromic properties.

On this basis Kortüm has identified molecular form A with that conformation which was found to be present in the yellow crystalline form of 9,9'-bianthronylidene (I) by Harnik and Schmidt (26), the so-called "folded conformation" (Fig. 7). For form B he has proposed a model in which the two halves of the molecule are twisted with

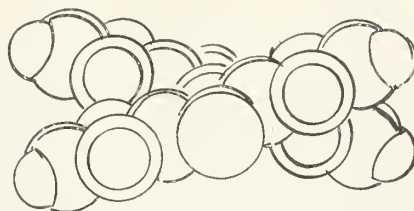
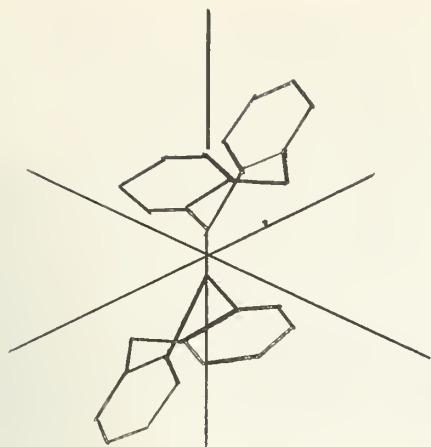


Fig. 8. Twisted conformation proposed for form B.

← Fig. 7. Folded conformation.

respect to each other, thus straining the ethylenic bond (Fig. 8). As is readily seen from an examination of the models, in order for a dianthrnylidene molecule to pass from form A to form B, it is necessary for either carbon atoms 1 and 1' or 8 and 8' to pass each other. This would be extremely unlikely, as the hydrogen nucleus of H-1 lies only 0.3 Å in projection from C-1' (14). [Studies on optical activity however seem to indicate indirectly that the conflicting carbon atoms can pass each other in solution (24), (25). With regard to this topic, Mills and Nyburg (14) have made the interesting if somewhat unprecedented suggestion that racemization may occur through the hydrogen atoms "changing their allegiance".]

In any event a thermal equilibrium between conformational forms cannot be valid for the thermochromism of bixanthenylidene in the solid state, and evidence seems to point against it in solution.

Spectroscopic Models.

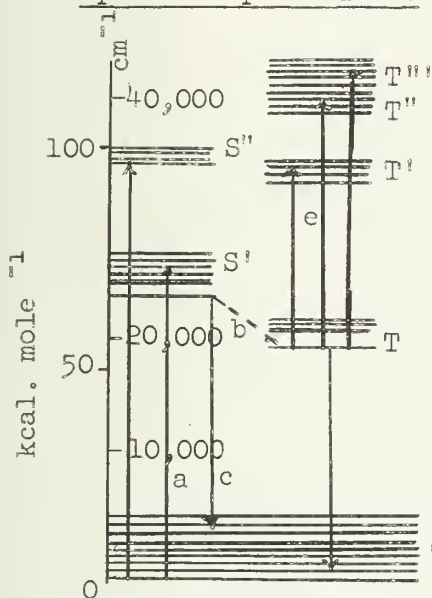


Fig. 9. Spectroscopic Model 1

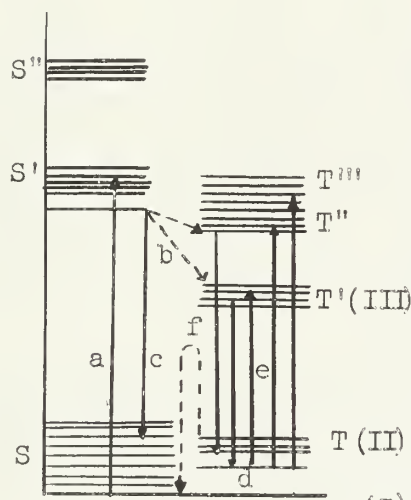


Fig. 10. Spectroscopic Model 2

Two models have been proposed to account for the thermochromism and photochromism of the bianthrnylidenes and bixanthenylidenes. The first (Fig. 9) was proposed by Kortüm (28) to explain the photochromic behavior of 2,4,5',7'-tetramethyl-9,9'-bianthrnylidene (IV). The second model (Fig. 10) was originally proposed by Grubb and Kistiakowsky (8) to account for both the thermochromism and photochromism of these types of compounds. In both models photochromic bands are attributed to transitions from low lying triplet states to upper excited triplet states. Kortüm has indicated that thermochromism could be attributed to the presence of a set of singlet states

of his proposed twisted conformation (34). In model 2, approximately 3-5 kcal. above the ground state I there is a thermally populated triplet state or set of triplet states II of the molecule. From state II there is a transition of 15,000-16,000 cm^{-1} to an upper triplet state or set of triplet states III. In this model both photochromic and thermochromic bands are represented by triplet-triplet transitions between states II and III. For a thermochromic compound such as bianthrnylidene, the lowest lying triplet state can be reached by thermal excitation. If the compound is non-thermochromic, then the lowest lying triplet state is too high to be attained thermally. The temperature dependence of the thermochromic bands is explained as follows. As the temperature increases, state II becomes increasingly populated, and thus the molar

absorptivity coefficient for the 15,000-16,000 cm^{-1} transition increases. As the temperature is decreased, state II becomes depopulated, accounting for the fading and final disappearance of color.

Mills and Nyburg support the hypothesis that the transition between states II and III is dependent on environment (14). There has not been a sufficient amount of work performed on the effect of solvents in solution thermochromism or intermolecular environment in solid state thermochromism for any valid conclusions to be drawn. Work in this area could possibly shed much light on the mechanism of thermochromism in these compounds.

It should be pointed out that neither the presence of a biradical nor a triplet state has been conclusively shown. The theory of thermochromism and related effects in the bianthrnylidenes and bixanthylenylidenes is at present very much open for concrete suggestions and valid working models.

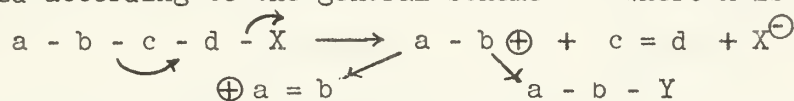
BIBLIOGRAPHY

1. J.F.D. Mills and S.C. Nyburg, J. Chem. Soc., 308 (1963).
2. J.H. Day, Chem. Rev., 63, 65 (1963).
3. G. Kortüm, Angew. Chem., 70, 14 (1958).
4. H. Meyer, Chem. Ber., 42, 143 (1909).
5. A. Schönberg and O. Scheutz, Chem. Ber., 61, 478 (1928).
6. A. Schönberg, A. Ismail and W. Asker, J. Chem. Soc., 442 (1946).
7. W. Theilacker, G. Kortüm and G. Friedheim, Chem. Ber., 83, 508 (1950).
8. Y. Hirshberg, Compt. rend., 231, 903 (1950).
9. W.T. Grubb and G.B. Kistiakowsky, J. Am. Chem. Soc., 72, 419 (1950).
10. Y. Hirshberg and E. Fischer, J. Chem. Soc., 629 (1953).
11. G. Kortüm and G. Bayer, Angew. Chem. (Int. Ed.), 2, 44 (1963).
12. G. Kortüm, W. Theilacker, H. Zeininger and H. Elliehausen, Chem. Ber., 86, 294 (1953).
13. E. Wasserman and R.E. Davis, J. Chem. Phys., 30, 1367 (1959).
14. J.F.D. Mills and S.C. Nyburg, J. Chem. Soc., 927 (1963).
15. G. Kortüm, W. Theilacker and G. Littmann, Z. Naturforsch., 12a, 401 (1957).
16. E.D. Bergmann and E. Fischer, Bull. Soc. Chim. France, 1084 (1950).
17. G. Kortüm and M. Buck, Z. Elektrochem., 60, 53 (1956).
18. W.G. Nilson and G.K. Fraenkel, J. Chem. Phys., 21, 1619 (1953).
19. E. Wasserman, J. Am. Chem. Soc., 81, 5006 (1959).
20. W. Theilacker, G. Kortüm and H. Elliehausen, Z. Naturforsch., 9b, 167 (1954).
21. Y. Hirshberg and S.I. Weissman, J. Chem. Phys., 28, 739 (1958).
22. Y. Matsunaga, Bull. Chem. Soc. Japan, 29, 582 (1956).
23. W. Theilacker, G. Kortüm, H. Elliehausen and H. Wilski, Chem. Ber., 89, 1578 (1956).
24. W. Theilacker, G. Kortüm and H. Elliehausen, Chem. Ber., 89, 2306 (1956).
25. J.F.D. Mills and S.C. Nyburg, Ref. 3, J. Chem. Soc., 308 (1963).
26. E. Harnik and G.M.J. Schmidt, J. Chem. Soc., 3295 (1954).
27. R.B. Woodward and E. Wasserman, J. Am. Chem. Soc., 81, 5007 (1959).
28. G. Kortüm, W. Theilacker and V. Braun, Z. Physik. Chem. (Frankfurt), 2, 179 (1954).
29. S. Matlow, J. Chem. Phys., 23, 152 (1955).
30. Y. Hirshberg and E. Fischer, J. Chem. Phys., 23, 1723 (1955).
31. G. Kortüm, W. Theilacker and V. Braun, J. Chem. Phys., 23, 1723 (1955).
32. Y. Hirshberg and E. Fischer, Angew. Chem., 70, 573 (1958).
33. G. Kortüm, Angew. Chem., 70, 573 (1958).
34. J.F.D. Mills and S.C. Nyburg, Ref. 9a., J. Chem. Soc., 927 (1963).

Reported by W. F. Pickens

August 5, 1963

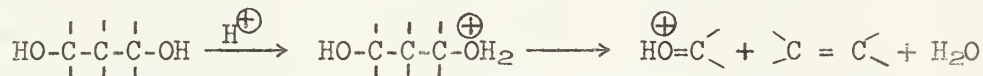
In the broadest sense fragmentation reactions comprise a large part of organic chemistry, including every example of the decomposition of a relatively large molecule into two or more smaller fragments. (Simple elimination reactions are not considered as fragmentation reactions.) Thus, retrograde condensations, thermal decompositions, degradations, and fragmentations observed in mass spectrometry studies are all formally part of this rather broad and diverse subject. It is the purpose of this seminar to consider only heterolytic fragmentation in solvolysis reactions, which may be formulated according to the general scheme ^{1,2} where X is a nucleophilic



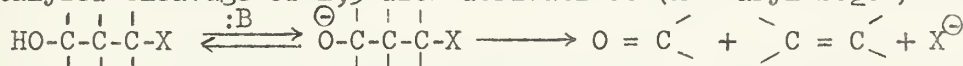
leaving group (e.g. X= halogen, -OTos, -NR₃, -OH₂, etc.), a is a group capable of donating electron density by either a conjugative or inductive effect (e.g. a= alkyl, aryl, -C⁻, HO-, RO-, R₂N-, etc.), and a,b,c, and d are atoms such as carbon, nitrogen, and oxygen which are capable of forming multiple bonds. The electron deficiency at d is relayed to b by heterolysis of the b-c bond, and is stabilized either transiently or permanently at b by electron release from a. In the third fragment, c=d, a multiple bond is formed, at least temporarily. The fate of the fragments a-b⁺ and c=d vary with their structure and environment.

Fragmentation reactions, although frequently observed, have received little attention from a mechanistic point of view, and have not been as thoroughly investigated as nucleophilic substitutions, eliminations, and rearrangements with which they often compete. Until recently no attempt had been made to incorporate fragmentation into a general system of chemical reactivity.

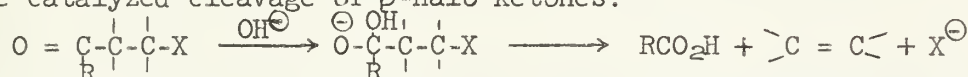
As is the case with many other kinds of reactions, certain fragmentations are subject to acid and base catalysis as shown in the acid catalyzed cleavage of 1,3-diols.³



the base catalyzed cleavage of 1,3-diol derivatives ($X = \text{aryl-SO}_2\text{O-}$)^{4,5}

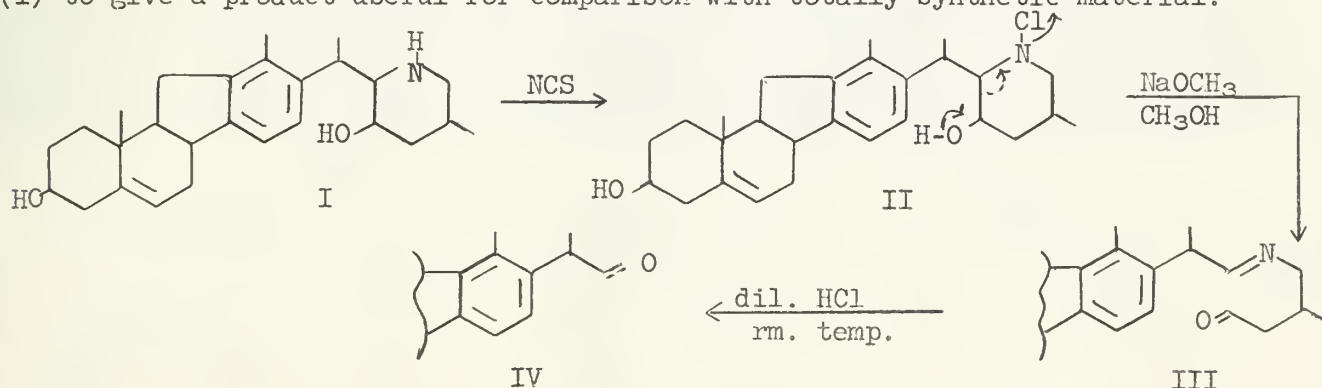


and the base catalyzed cleavage of β -halo ketones.⁶



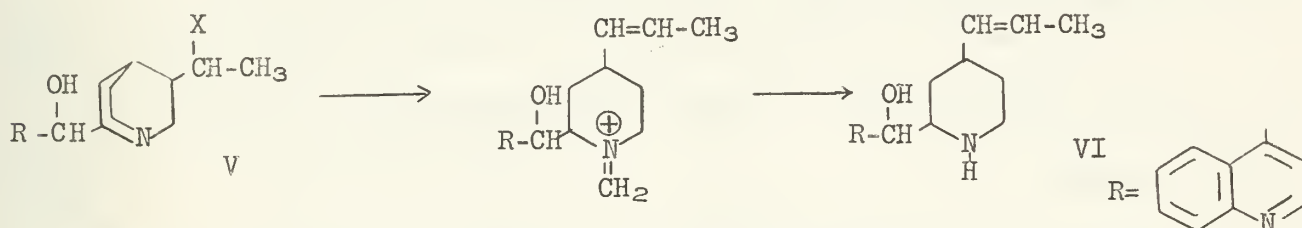
The general subject of fragmentation in solvolysis reactions has been discussed by C.A. Grob,^{7,8,9} mainly in terms of his own important contributions. This review shall emphasize the work published after 1961, up to August 1, 1963. Grob's most recent series of articles¹⁰⁻¹⁸ contains many older references not included here. The γ -amino halides will be treated in detail, and the principles elucidated from the study of this class of compounds will be applied to other systems.

Fragmentation in Degradation. - Fragmentation should be recognized as a useful degradation tool, as the following work by Franck and Johnson illustrates.¹⁷ These workers wanted to degrade the heterocyclic ring of the natural product veratramine (I) to give a product useful for comparison with totally synthetic material.

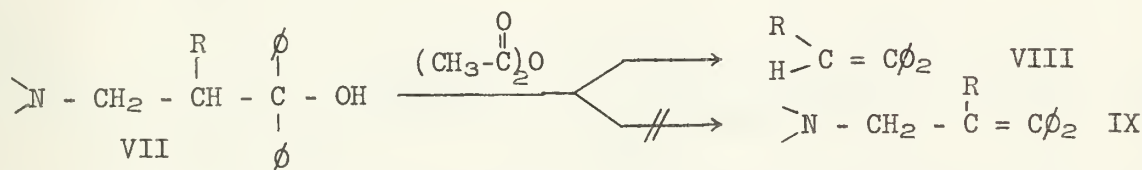


Treatment of I with N-chlorosuccinimide gave N-chloroveratramine (II) which presumably fragmented under solvolysis conditions to give the imino compound (III) which was not isolated but underwent hydrolysis to the aldehyde (IV) upon addition of hydrochloric acid. The overall yield (I \rightarrow IV) was 94%.

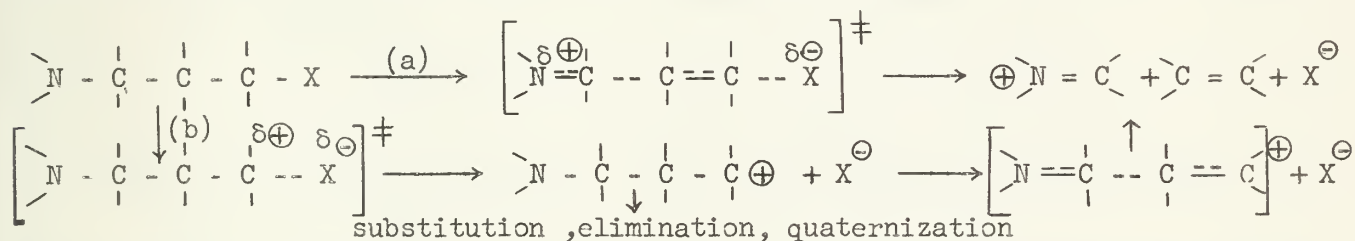
Fragmentation of γ -amino halides. - The γ -amino halides are particularly suitable models for a detailed study of mechanism and stereochemistry of fragmentation reactions.^{18,19} The stoichiometry and kinetics of their reactions are simple and representatives of different but fairly definite geometry are readily available. An early example of the fragmentation of γ -amino halides is the conversion of halogen-dihydroquinidine (V) to niquidine (VI).²⁰⁻²³



Also, Adamson reported that treating substituted γ -amino alcohols (VII) with boiling acetic anhydride gave diphenylethylene derivatives (VIII) instead of the expected amino olefins (IX).²⁴

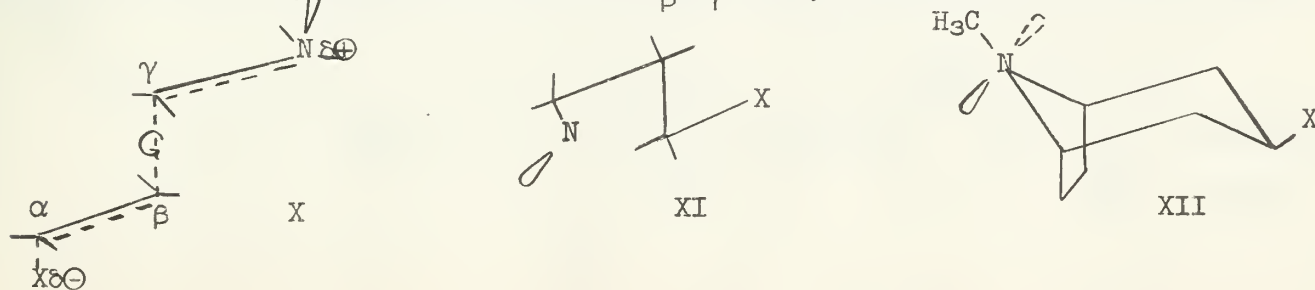


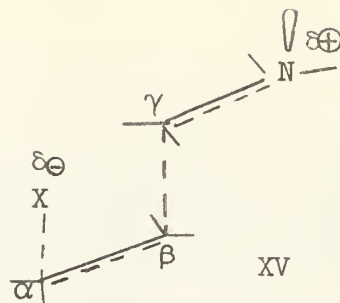
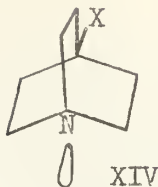
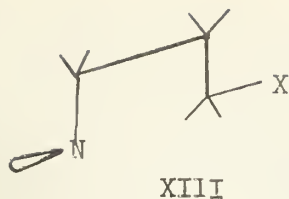
Grob has chosen the γ -amino halides as a major class of compounds for the elucidation of the factors involved in fragmentation. For γ -amino halides, two extreme mechanisms of fragmentation can be postulated: (a) a one-step, concerted process, and (b) a two-step process, both of which will obey first order kinetics.



In the one-step process (a) ionization is assisted by electron release from the amino group. The consequent acceleration of ionization, called the "frangomeric" effect, should make fragmentation the only observable reaction. In the two-step process (b) the amino group is not directly involved in the ionization step, and a carbonium ion is formed at a normal rate. Fragmentation then becomes one of several competing reactions in a fast, product-determining step.

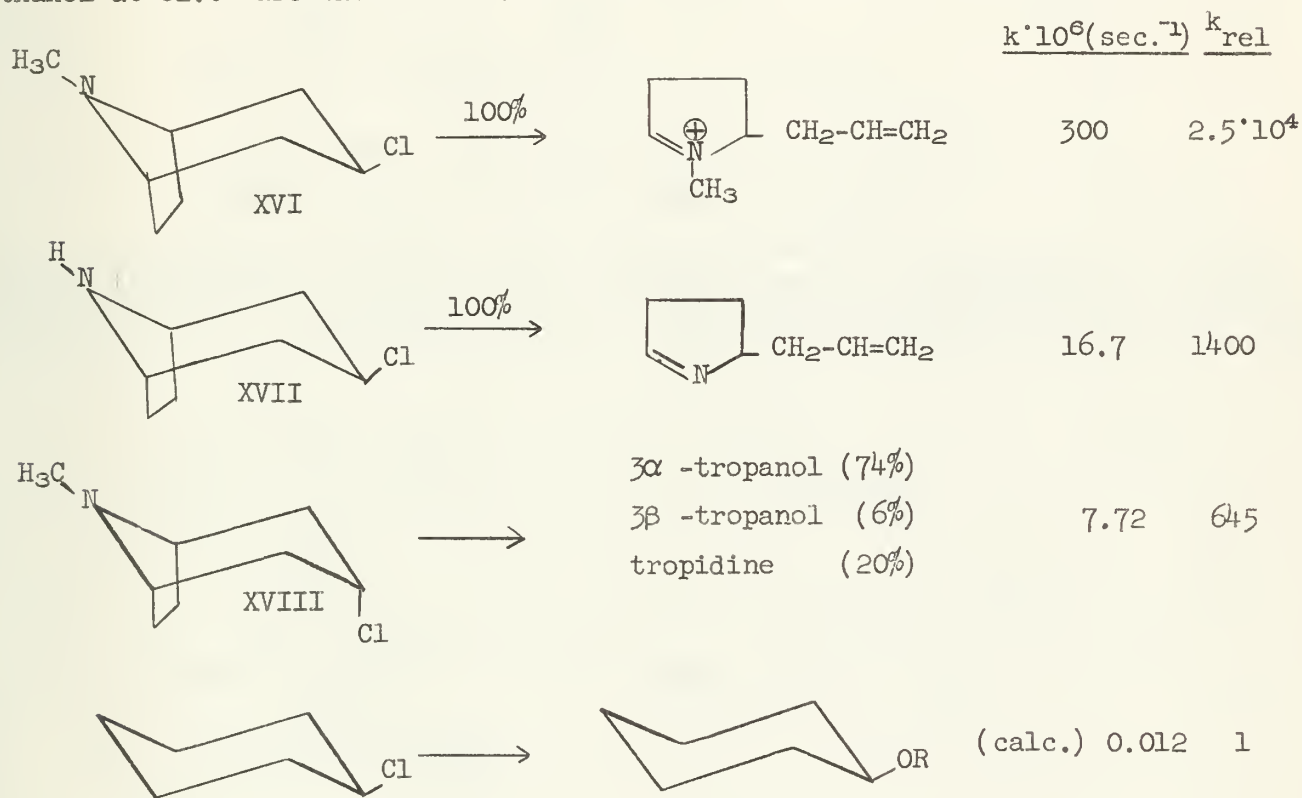
The one-step process (a) will occur most readily if all the electron pairs directly involved (e.g. the $\text{X}-\text{C}_\alpha$, $\text{C}_\alpha-\text{C}_\beta$, $\text{C}_\beta-\text{C}_\gamma$, and $\text{C}_\gamma-\text{N}$ bonds, and the lone pair on nitrogen) lie in one plane, or in two planes which intersect in the $\text{C}_\beta-\text{C}_\gamma$ bond.²⁵ Thus, stereoelectronically favorable conformations can be derived from the coplanar, staggered form (X) by rotation around the $\text{C}_\beta-\text{C}_\gamma$ bond, as indicated by the arrow. The





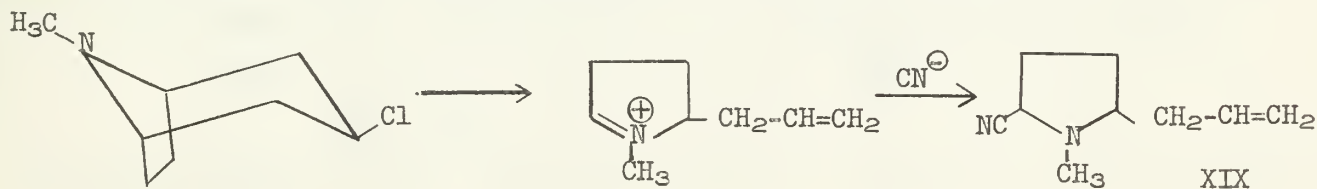
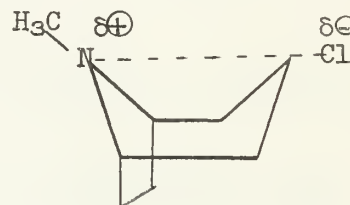
skew form (XI) is present in 3 β -substituted tropanes (XII), and the eclipsed form (XIII) is present in 4-substituted quinuclidines (XIV). Fragmentation of any of the rotational configurations of X corresponds to a trans elimination, whereas if the X-C $_{\alpha}$ and C $_{\beta}$ -C $_{\gamma}$ bonds are cis as in XV, the fragmentation corresponds to a less favorable cis elimination.

The results of a kinetic and product study of some 3-tropanyl chlorides in 80% ethanol at 62.0° are shown below.⁷



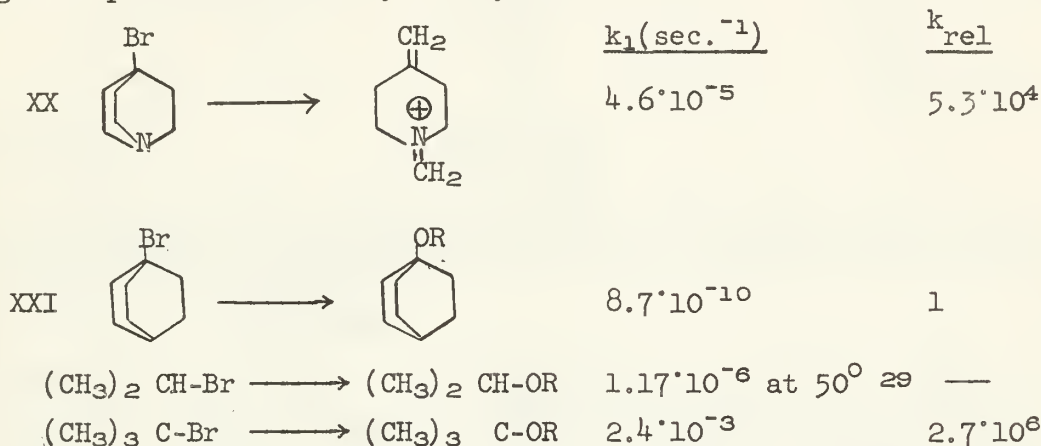
The more basic tertiary amine (XVI) reacts considerably faster than the secondary amine (XVII). In the α -isomer (XVIII) the Cl-C $_{\alpha}$ bond is not parallel with the C $_{\beta}$ -C $_{\gamma}$ bond, and no fragmentation is observed. The fact that the rate is increased relative to cyclohexyl chloride and that the major product (3 α -tropanol) has retention of configuration suggests that the basic nitrogen atom participates in the ionization as shown at the right.

Archer and coworkers have reported the cleavage of 3 β -tropanyl chloride with aqueous ethanol in the presence of potassium cyanide to give a mixture of 2-allyl-1-methylpyrrolidine-5-nitriles (XIX).²⁶⁻²⁸ The α -isomer (3 α -tropanyl chloride) gave

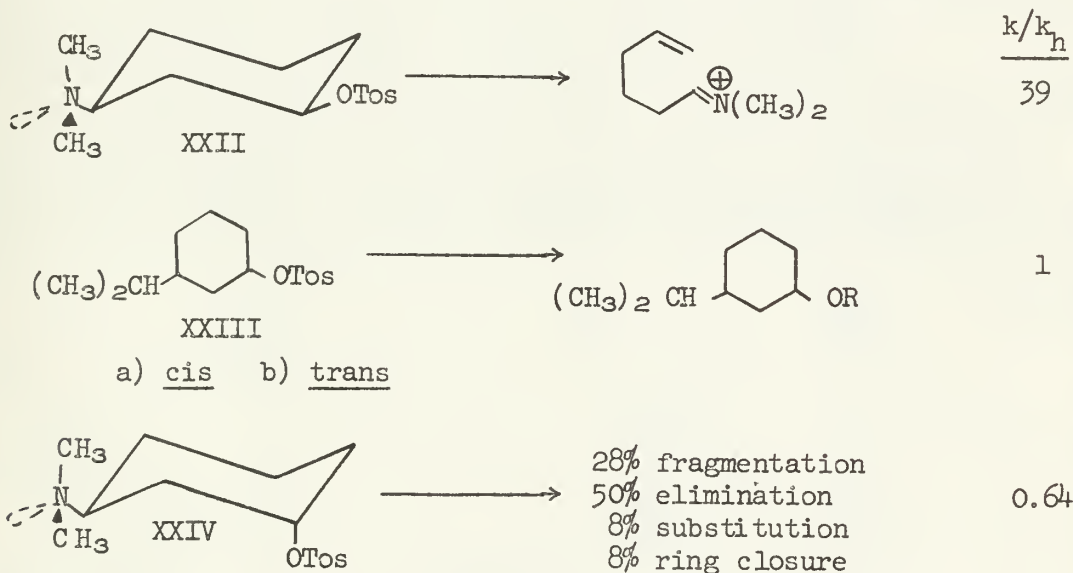


only substitution with nucleophilic reagents;²⁷ the products showed retention of configuration.

The coplanar γ -amino halide system 4-bromo quinuclidine (XX) also reacts by the synchronous fragmentation mechanism.⁷ Frangomeric assistance apparently is responsible for a very much faster rate of solvolysis of the bridgehead bromide (XX) compared to the carbon homomorph (XXI). Indeed, the rate of solvolysis of XX in 80% ethanol at 40°⁷ is faster than that of isopropyl bromide,²⁹ even though the leaving group is at the bridgehead position of a bicyclic system.

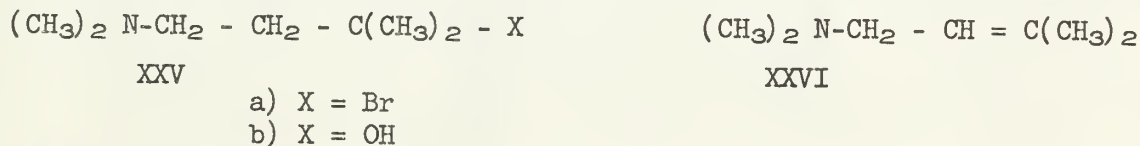


In an attempt to approach a rigid, coplanar staggered conformation of γ -amino alcohol derivatives, Grob has studied the cis-isomer of 3-dimethylamino cyclohexyl tosylate (XXII).⁹ A high rate relative to its carbon homomorph (XXIIIa) was observed, and fragmentation was the only reaction. The trans-isomer (XXIV) in which the break-



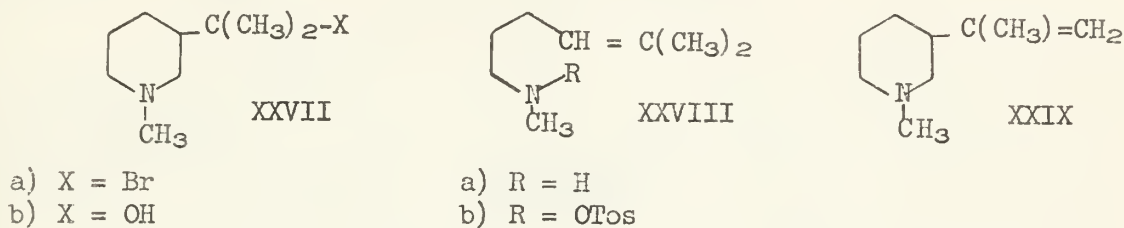
ing bonds are nonparallel reacts at a slightly lower overall rate than its homomorph (XXIIIb). This, along with the mixture of products formed, indicates an unaccelerated two-step process.⁹

The hydrolysis of 3-bromo-3,3-dimethyl-1-N,N-dimethyl butylamine (XXVa) at 60° in aqueous sodium hydroxide gave a 48% yield of dimethylamine by fragmentation, along with formaldehyde and isobutylene.¹⁰ Also a mixture (~1:1) of the amino alcohol (XXVb) and the amino olefin (XXVI) was found.

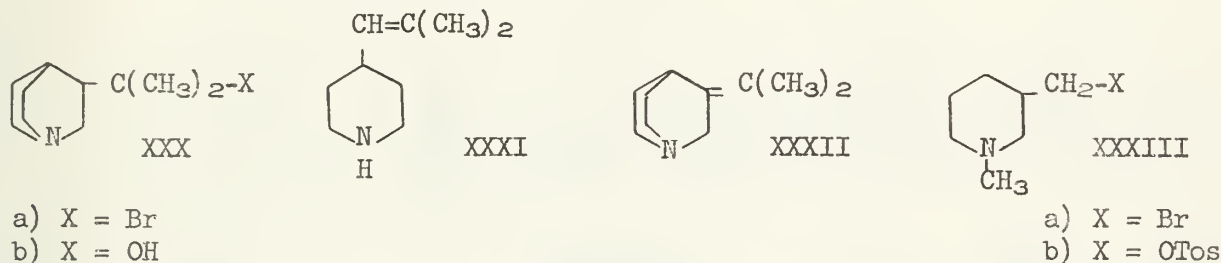


The bromide (XXV a) reacted with silver nitrate in acetonitrile in the presence of triethylamine to give 60% fragmentation.¹⁰

In the hydrolysis of 1-methyl-3 (1'-bromo-1'-methyl ethyl) piperidine (XXVII a) with aqueous sodium hydroxide, fragmentation occurred to the extent of 60% to give the secondary amine (XXVIII a) isolated as the tosylate (XXVIII b) and formaldehyde. Substitution gave 34% of the amino alcohol (XXVII b), and elimination gave 6% of a mixture of olefins in which the compound XXIX predominated.¹⁰

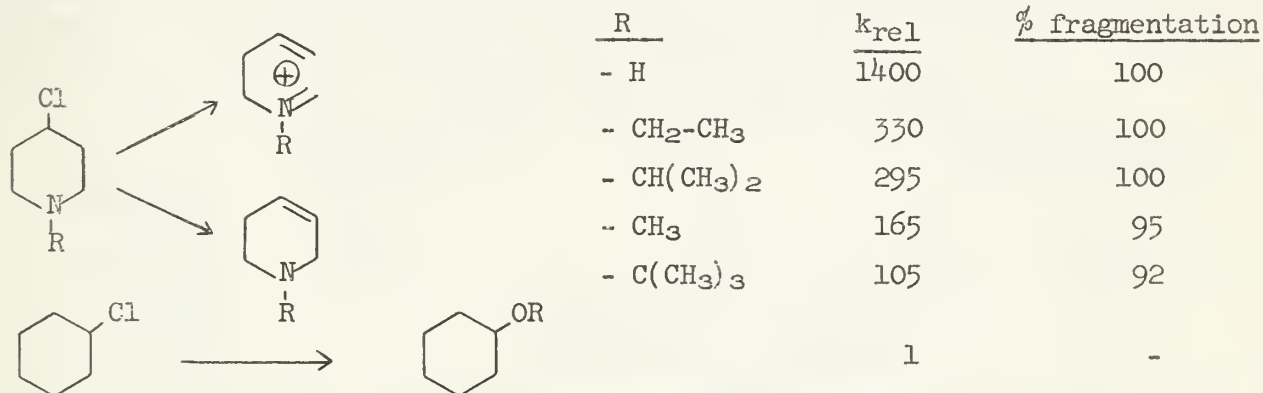


The 3-(1'-bromo-1'-methyl ethyl) quinuclidine (XXX a) gave 62% of XXXI by fragmentation, some of XXXII by elimination, and a little of XXX b by substitution when treated with aqueous sodium hydroxide.¹⁰



The primary bromide (XXXIII a) and the corresponding p-toluene sulfonate (XXXIII b) did not fragment due to the difficulty of ionization. Only substitution was observed with these compounds in aqueous sodium hydroxide.¹⁰

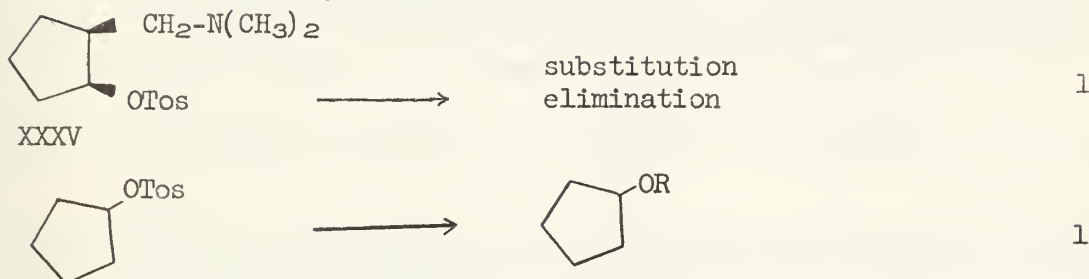
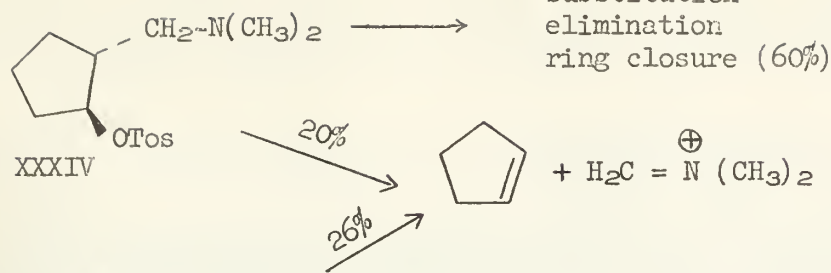
The fragmentation of secondary γ -amino halides of conformational ambiguity follows a more complex pattern. Several N-alkyl-4-chloro piperidine derivatives have been studied, but there is no simple relationship between the size of the substituent on nitrogen and the overall rate or the extent of fragmentation.⁹ These reactions appear to follow a two step accelerated mechanism involving nitrogen participation. The results of solvolysis in 80% ethanol at 62° are shown below.⁹



A further example of the failure of concerted fragmentation to occur when the bonds are not properly oriented is provided by a study of suitable cyclopentane derivatives.⁸ In the trans form of 2-(dimethylamino methyl)-cyclopentyl tosylate (XXXIV) the C α -OTos and C β -C γ bonds are not coplanar. In the cis compound (XXXV) the bonds are coplanar, but concerted fragmentation in this case would correspond to an unfavorable cis elimination. Both compounds (XXXIV and XXXV) solvolyze at about the same rate as cyclopentyl tosylate. Ring closure is favorable in the case of the trans isomer, as shown by the appearance of 60% of the azetidinium salt and a slight increase in rate due to a small participation effect of the amino group.⁸

k_{rel}

4



The effects of methyl groups in the α -, β -, and γ -positions of the γ -aminopropyl chain have been studied.⁹ In the case of primary or secondary chlorides, ring closure to an azetidinium salt is the only observable reaction in 80% ethanol at 56°. The rates of solvolysis of the γ -amino chlorides relative to the rates of solvolysis of their carbon homomorphs are shown below.

γ -amino chloride	homomorph	k/k_h	% ring closure
$(CH_3)_2 N-CH_2-CH_2-CH_2-Cl$	$(CH_3)_2 CH-CH_2-CH_2-CH_2-Cl$	$6 \cdot 10^3$	100
$(CH_3)_2 N-CH_2-C(CH_3)_2-CH_2-Cl$	$(CH_3)_2 CH-CH_2-C(CH_3)_2-CH_2-Cl$	$5 \cdot 10^6$	100
$(CH_3)_2 N-CH_2-CH_2-CH(CH_3)-Cl$	$(CH_3)_2 CH-CH_2-CH_2-CH(CH_3)-Cl$	225	100

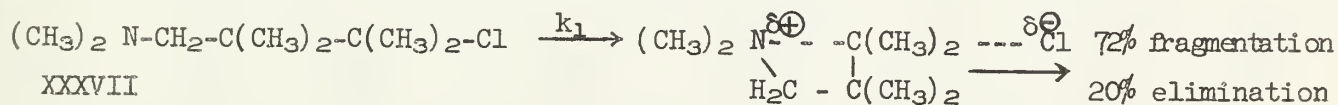
The chemistry of azetidines was reviewed in 1961.³⁰

In the case of tertiary chlorides, the rates of solvolysis of γ -amino chlorides are practically the same as the rates of solvolysis of their carbon homomorphs, indicating that the amino group is not participating in the rate determining step. In the stepwise process the nature of the γ -substituent should affect the product composition markedly, but only slightly the rate at which products are formed. In the examples below, solvolysis occurred at 56° in 80% ethanol.⁹

$R-CH_2-CH_2-C(CH_3)_2-Cl \xrightarrow{\text{slow}} R-CH_2-CH_2-\overset{\oplus}{C}(CH_3)_2 \xrightarrow{\text{fast}} \text{products}$			
R	$k \cdot 10^4 (\text{sec.}^{-1})$	k_{rel}	% fragmentation
$(CH_3)_2 CH-$	4.73	1.0	0
H_2N-	4.66	0.99	20
XXXVI $(CH_3)_2 N-$	3.55	0.75	50
$(CH_3)_2 \overset{\oplus}{N}H-$		(extrapolated) $1.5 \cdot 10^{-2}$	0
$(CH_3)_3 \overset{\oplus}{N}-$		(extrapolated) $9.6 \cdot 10^{-3}$	0

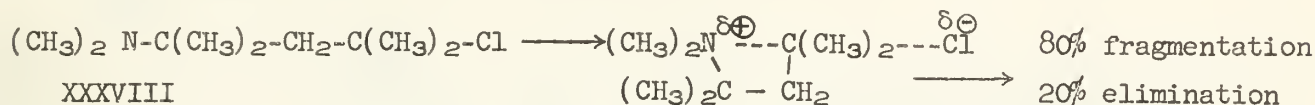
A more careful study of the N,N, α , α -tetramethyl- γ -aminopropyl chloride case (XXXVI) showed products corresponding to 44% fragmentation, 25% substitution, 25% elimination, and 3% ring closure.⁹

The mechanism changes again if two additional methyl groups are introduced into the β -position. The compound XXXVII solvolyzes 125 times as fast as its homomorph, indicating participation of the γ -amino group.⁹

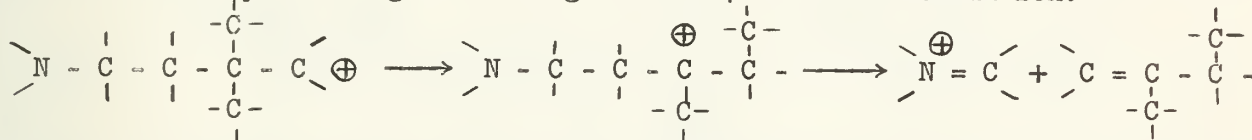


This effect can be explained by an internal solvolysis by the nitrogen assisting the ionization of the chloride ion without formation of a covalent bond, since the

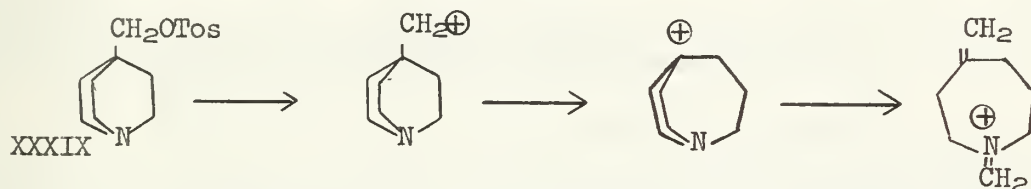
azetidinium salt (which is stable under the reaction conditions) is not formed. This mechanism also applies when the geminal methyl groups occupy the γ -position. The ratio of the rate of solvolysis for compound XXXVIII to the rate of solvolysis of its carbon homomorph is 27.⁹



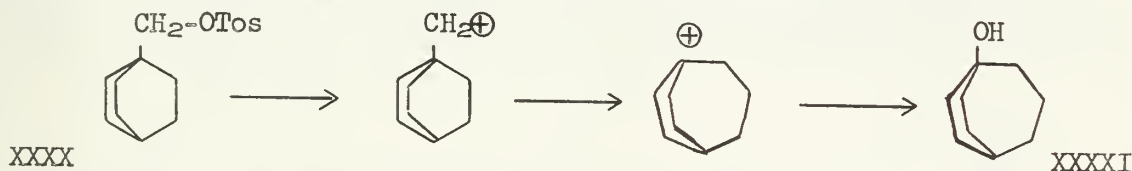
Fragmentation Induced by Rearrangement. - In unassisted fragmentations the carbonium ion center may be provided by preliminary rearrangement instead of initial ionization at that point. As shown in the reaction scheme below, a γ -amino carbonium ion may rearrange to a fragmentable γ -amino carbonium ion.¹²



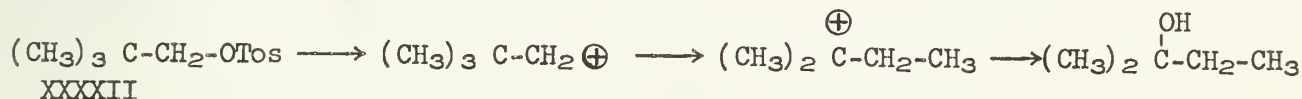
A suitable compound for this study was 4-tosyloxy-methyl quinuclidine (XXXIX) which was found to undergo the following reaction.¹²



Solvolysis of the homomorph, 1-tosyloxymethyl-bicyclo [2.2.2] octane (XXXX), had been investigated previously and was found to produce the alcohol (XXXXI).³¹



The kinetic measurement of the rate of solvolysis for neopentyl tosylate (XXXXII) was also carried out for comparison.¹²

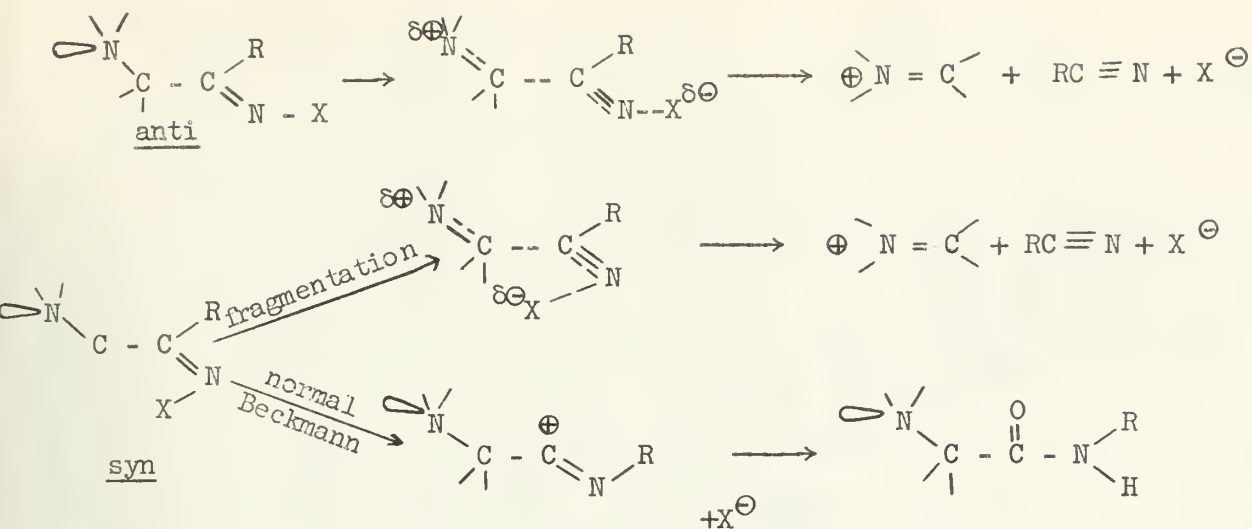


The results are summarized below for 0.01 M solutions in 80% ethanol with 0.0154 M trimethylamine at $116.00^\circ \pm 0.05^\circ$.¹²

compound	$k \cdot 10^5 (\text{sec.}^{-1})$	k_{rel}	Fragmentation of α -Amino Ketoximes (Second Order Beckmann Reactions). -
XXXIX	1.02 ± 0.05	1	Oximes of α -amino ketones represent
XXXX	4.42 ± 0.09	4.4	systems capable of fragmentation to
XXXXII	2.08 ± 0.02	2.1	nitriles and ternary iminium salts. ³²⁻³⁵
	2.09 ± 0.01 (0.0173M Et ₃ N)		The ability to fragment is greatly

enhanced by esterification or etheri-

fication of the hydroxyl group. Recent work by Grob^{14,15,16} describes the fragmentation of various tosylates, 2,4-dinitrophenyl ethers, and benzoates of α -amino ketoximes of known configuration.¹³ The field of abnormal Beckmann reactions has been well reviewed in these papers^{14,15} as well as in a recent general treatment of the Beckmann rearrangement.³⁶ Also, Grob's experimental work in this field cannot receive fair treatment here. Therefore, only a few general observations will be noted. The anti forms are much more reactive than the syn forms ($k_a/k_s \sim 2 \cdot 10^3$).¹⁴ Fragmentation of the anti compounds corresponds to a coplanar trans elimination, and proceeds quantitatively in 80% ethanol at 13° , whereas the syn compounds give both fragmentation (corresponding to a less favorable cis elimination) and the normal Beckmann rearrangement.¹⁴

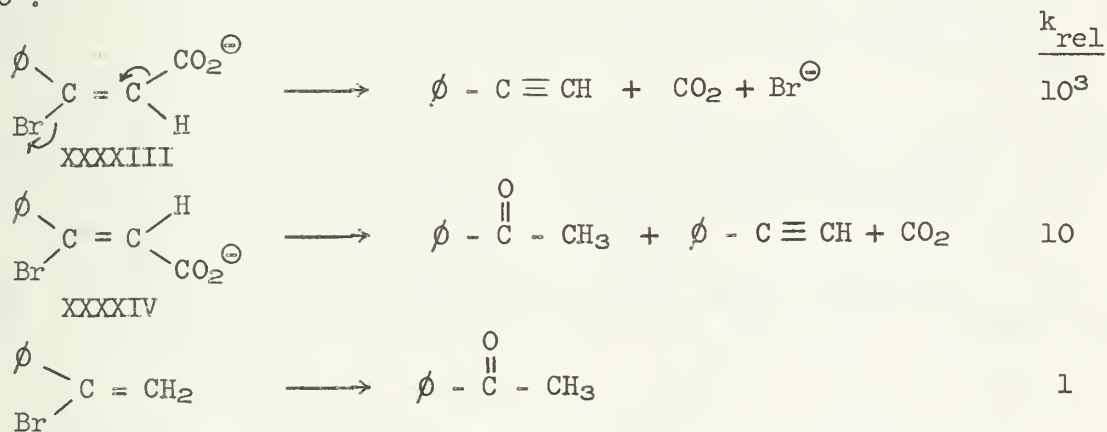


The fragmentation of β -keto ether-oximes³⁷ and of a γ -oximino ketone³⁸ has also been reported.

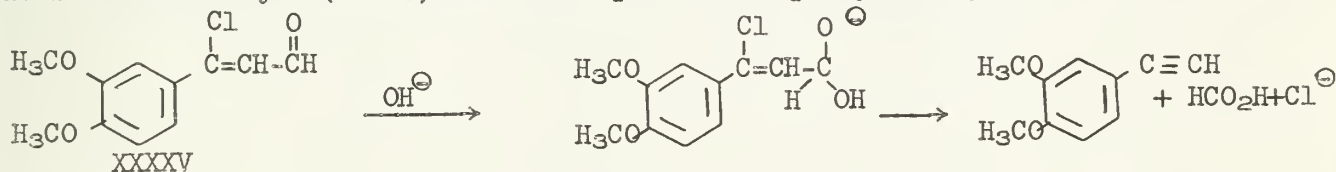
Fragmentation of β -Bromo Cinnamic Acids. - The conversion of cinnamic acid dibromide to β -bromostyrene has been well investigated.³⁹⁻⁴¹



The decarboxylations of β -bromo cinnamic acids provide further evidence for the stereospecificity of fragmentation.⁹ The sodium salt of the cis compound (XXXXIII), having the -Br and -CO₂[⊖] groups trans, reacts by an accelerated synchronous mechanism to give phenyl acetylene exclusively. The sodium salt of the trans compound (XXXXIV) reacts slower and gives both phenyl acetylene and acetophenone. The decarboxylation rates have been compared with the rate of solvolysis of α -bromostyrene in water at 100°.⁹



Another very similar fragmentation caused by the treatment of the α , β -unsaturated chloroaldehyde (XXXXV) with base produces a phenyl acetylene as shown below.⁴²



Bibliography

1. C.A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955).
2. C.A. Grob, *Experientia*, **13**, 126 (1957).
3. H.E. Zimmerman and J. English, Jr., *J. Am. Chem. Soc.*, **76**, 2294 (1954), and references therein.
4. R.B. Clayton, H.B. Henbest, and M. Smith, *J. Chem. Soc.*, **1957**, 1982.

5. H.B. Henbest and B.B. Millward, J. Chem. Soc., 1960, 3575.
6. F. Nerdel, H. Goetz, and M. Wolff, Ann. Chem., 632, 65 (1960).
7. C.A. Grob, in "Theoretical Organic Chemistry", (Report on the Kekulé Symposium, London, 1958), Butterworth, London, 1959, p. 114.
8. C.A. Grob, Bull. Soc. Chim. France, 1960, 1360.
9. C.A. Grob, Gazz. Chim. Ital., 92, 902 (1962).
10. C.A. Grob and F. Ostermayer, Helv. Chim. Acta, 45, 1119 (1962).
11. C.A. Grob, F. Ostermayer, and W. Raudenbusch, Helv. Chim. Acta, 45, 1672 (1962).
12. C.A. Grob, R.M. Hoegerle, and M. Ohta, Helv. Chim. Acta, 45, 1823 (1962).
13. H.P. Fischer and C.A. Grob, Helv. Chim. Acta, 45, 2528 (1962).
14. H.P. Fischer, C.A. Grob, and E. Renk, Helv. Chim. Acta, 45, 2539 (1962).
15. H.P. Fischer and C.A. Grob, Helv. Chim. Acta, 46, 936 (1963).
16. C.A. Grob, Helv. Chim. Acta, 46, 1190 (1963), in press.
17. R.W. Franck and W.S. Johnson, Tet. Letters, 1963, No. 9, 545.
18. C.A. Grob, Angew. Chem., 69, 680 (1957).
19. C.A. Grob and F.A. Jenny, Tet. Letters, 1960, No. 23, 25.
20. E.M. Gibbs and T.A. Henry, J. Chem. Soc., 1939, 240.
21. W. Solomon, J. Chem. Soc., 1941, 77.
22. H.S. Moscher, R. Forker, H.R. Williams, and T.S. Oakwood, J. Am. Chem. Soc., 74, 4627 (1952).
23. R.B. Turner and R.B. Woodward, in Manske and Holmes, "The Alkaloids", Academic Press, New York, N.Y., 1953, p. 21.
24. D.W. Adamson, Nature, 164, 500 (1949).
25. A.T. Bottini, C.A. Grob, and E. Schumacher, Chem. & Ind. (London), 1958, 757.
26. S. Archer, T.R. Lewis, and B. Zenitz, J. Am. Chem. Soc., 79, 3603 (1957).
27. S. Archer, M.R. Bell, T.R. Lewis, J.W. Schulenberg, and M.J. Unser, J. Am. Chem. Soc., 79, 6337 (1957).
28. S. Archer, T.R. Lewis, and B. Zenitz, J. Am. Chem. Soc., 80, 958 (1958).
29. C.G. Swain, R.B. Mosely, and D.E. Bown, J. Am. Chem. Soc., 77, 3731 (1955).
30. P. Tschampel, U. of Ill. Organic Seminar Abstracts, Semester II, 1960-61, p. 127.
31. C.A. Grob, M. Ohta, E. Renk, and A. Weiss, Helv. Chim. Acta, 41, 1191 (1958).
32. R.K. Hill and R.T. Conley, Chem. & Ind. (London), 1956, 1314.
33. R.K. Hill and R.T. Conley, J. Am. Chem. Soc., 82, 645 (1960), and references therein.
34. H.P. Fischer, C.A. Grob, and E. Renk, Helv. Chim. Acta, 42, 872 (1959).
35. H.P. Fischer and C.A. Grob, Tet. Letters, 1960, No. 26, 22.
36. L.G. Donaruma and W.Z. Heldt, in Adams, "Organic Reactions", Vol. 11, Wiley, New York, N.Y., 1961, p. 1.
37. R.K. Hill, J. Org. Chem., 27, 29 (1962), and references therein.
38. W. Eisele, C.A. Grob, and E. Renk, Tet. Letters, 1963, No. 2, 75.
39. E. Grovenstein, Jr., and D.E. Lee, J. Am. Chem. Soc., 75, 2639 (1953), and references therein.
40. S.J. Cristol and W.P. Norris, J. Am. Chem. Soc., 75, 2645 (1953), and references therein.
41. H. Sliwa and P. Maitte, Bull. Soc. Chim. France, 1962, 369.
42. K. Bodendorf and P. Kloss, Angew. Chem., 75, 139 (1963).

DIMETHYL SULFOXIDE AS SOLVENT AND REACTANT

Reported by P. Rivers

August 7, 1963

Dimethyl sulfoxide* is a colorless, nearly odorless liquid which boils at 180° (760 mm Hg) and melts at 18.5°. It has a specific gravity of 1.1014 at 20° and a refractive index of 1.4783 (at 20°). Although this compound has been known since 1867 (1) it is only within the last five years that it has become commercially available at reasonable prices. The two main sources of supply in this country are the Crown Zellerbach Corporation and Stepan Chemical Company. Commercially it is prepared by the oxidation of dimethyl sulfide using N₂O₃, NO₂, N₂O₄ or NO (with air). Other physical properties are given in Table I and a more comprehensive coverage can be found in a pamphlet distributed by Crown Zellerbach Corporation (2).

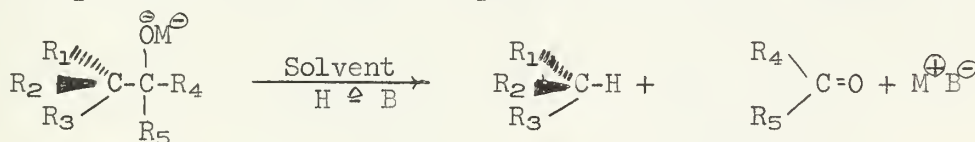
Table I

Heat of Vaporization	(189°)	132 cal/g
Heat of Solution	(20°)	60 cal/g
Heat of Fusion	(189°)	20 cal/g
Heat of Combustion	(25°)	6050 cal/g
Coefficient of Expansion		0.00088 per °C
Dielectric Constant		45
Molecular Weight		78.13

This discussion will be divided into two main sections; (I) DMSO as a reaction solvent and (II) those systems in which DMSO is both solvent and reactant.

I. DMSO as a Solvent.--This discussion will be restricted to reactions in which basic or neutral conditions are employed due to limitations of space, the recent interest in this particular area and its greater importance to synthetic and physical organic chemistry. In terms of its solvent properties, we are mainly concerned with two questions: how and why does DMSO differ from other solvents and what reactions can be carried out in DMSO most advantageously and why.

1. Base-Catalyzed Reactions. (a) Base catalyzed hydrogen-deuterium exchange. Recently Cram has conducted a study of the stereochemical factors which influence electrophilic substitution at saturated carbon atoms. His earlier work in this field has been covered in a previous University of Illinois Organic Seminar (3) and will not be discussed except in terms of its relevance to DMSO. Cram, *et al.* (4), have been able to show a wide variation in stereospecificity for electrophilic substitution at saturated carbon atoms, depending on the solvent employed. Suitable metal alkoxides were observed to undergo cleavage with retention of configuration in *t*-butyl alcohol. In sharp contrast, the same reaction occurred at much lower temperatures with almost complete racemization in DMSO. Significant



differences, in rates which were most pronounced in DMSO, were observed as the metal ion was changed; K > Na > Li.

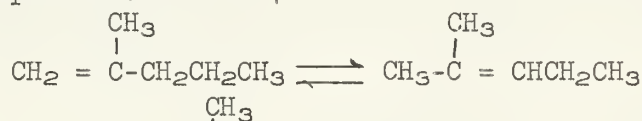
Recently, Cram described the base catalyzed hydrogen-deuterium exchange reaction of optically active 2-phenylbutane, 1-phenyl-1-methylethane and 2-methyl-3-phenylpropionitrile. Cram, Rickborn and Knox (5) found that these compounds could be racemized at 25° in DMSO at a rate that could be compared to that attained at 173° in *t*-butyl alcohol. Extrapolated rates of proton abstraction were calculated to be 10⁷ to 10⁸ times greater in DMSO than in *t*-butyl alcohol. Compared to results reported by Cram, Rickborn, Kingsbury and Haberfield (6) this would suggest a spread of eleven powers of ten in going from methoxide ion in methanol to *t*-butoxide ion in DMSO. It is important to note that the dielectric constants of the two solvents differ only slightly; 34 for methanol and 45 for DMSO.

*Throughout this discussion dimethylsulfoxide, (CH₃)₂SO, will be abbreviated as DMSO. In a few cases in the literature DMS is used but DMSO is the predominate form.

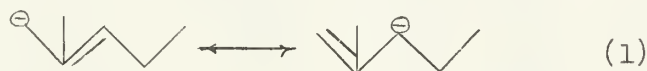
(b) Wolff-Kishner Reduction.--Evidence has been presented that the Wolff-Kishner reaction can be conducted at room temperature using sublimed potassium *t*-butoxide in DMSO (7) as compared to the normal reaction temperature of 100-200°. Yields ranging from 60-90% were obtained in all cases reported. Alkali metal *t*-butoxide, even when dried under the severest conditions, are known to exist as a complex of the salt and alcohol (9). The use of sublimed *t*-butoxide has been recommended by several authors (8,9,31) when an alcohol-free system is desired. The sublimed potassium salt is now commercially available (10).

(c) Acidity of Hydrocarbons.--Hofmann, Muller and Schriesheim (8) have studied the ionization rates of toluene and several polyalkyl benzenes using sublimed potassium *t*-butoxide in tritated DMSO. Since benzene and *t*-butylbenzene remained unchanged after extended reaction periods and elevated temperatures, it was concluded that only α -hydrogens can undergo exchange. It was predicted that this medium could be used to study hydrocarbons of $pK_a \sim 40$. ($NH_3 \approx 35$, $CH_4 \approx 58$) (47).

(d) Isomerization of Alkenes.--Schriesheim and Rowe (9), using 2-methyl-1-pentene found that anionic isomerization could be carried out in DMSO with sublimed *t*-butoxide salts at temperatures of 40-70°.

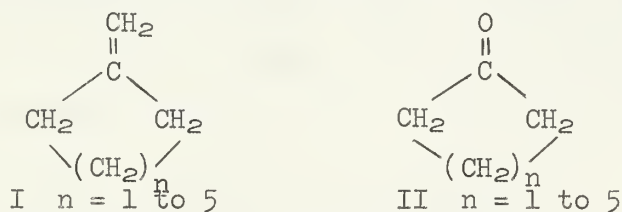


The formation of 4-methyl-1-pentene, $CH_3 - \overset{\overset{CH_3}{|}}{CH}CH_2CH = CH_2$, occurs only after extended reaction periods (230 hrs). These results are explained on the basis of the relative stabilities of the following carbanions. The resonance forms which would lead



to the formation to 4-methyl-1-pentene would be less favorable since they are similar to secondary and tertiary carbanions, while those resulting in 2-methyl-2-pentene involve primary and secondary carbanions.

Schriesheim, and co-workers (11,12,13), have investigated the effects of ring size on the rates of formation of anions from alkylidenecycloalkanes (I) and cycloalkanones (II). The base catalyzed exo- to endo-rearrangement using potassium *t*-



butoxide in DMSO and the base-catalyzed bromination of the ketones were studied and found to correlate closely. Since these results run counter to Brown's I-strain

<u>Exo-Endo</u> rearrangement		Bromination	
n	rel. rates ($C_6=1$)	n	rel. rates ($C_6=1$)
1	1070	1	15.5
2	454	2	9.9
3	1	3	1.0
4	5.8	4	1.7
5	17	5	3.4

theory (14), they were rationalized following the explanation of Corey (15) for the orientation of bromine in α -bromoketosteroids. According to this, the rate of proton removal will be greatest when there is maximum opportunity for overlap between

the $sp^3 \rightarrow p$ orbital made available by the leaving hydrogen and the π -orbitals of the exo-cyclic system. The authors state that Dreiding models show that this geometrical requirement follows the observed rate order.

(e) Nucleophilic Displacements.--When bromobenzene in DMSO was treated with a solution of sublimed potassium t-butoxide in DMSO at 25° for 15 hrs., the resulting product was t-butylphenylether in 86% yield (5). Similar results were obtained in t-butyl alcohol at 175° for nine hours in 37% yield. By competition experiments, fluorobenzene was found to react at 1/25 the rate of bromobenzene. o-Fluorotoluene could be converted to o-cresol, contaminated by less than 3% of the meta-isomer. o-Bromotoluene gave a mixture of 4 parts m-cresol and 1 part o-cresol. The parent compounds were suggested as being the corresponding t-butyl ethers which probably decomposed in the process of V.P.C. analysis. These results would definitely point to the possibility of an arylene intermediate.

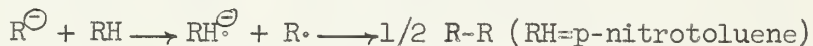
Kornblum, Berrigan and LeNoble (16,17) have observed definite solvent dependence in the course of the alkylation of ambident anions. Using sodium phenoxide (16) and sodium naphthoxide (18), it was concluded that the carbon to oxygen alkylation ratio reflected both the effects of dielectric constant and protonic nature of the solvent. Table II shows clearly that the nature of the substrate anion is also important in determining the c/o ratio.

Table II*

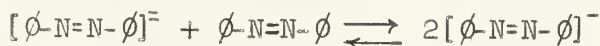
Solvent	Dielectric Constant	Phenoxide ion		Naphthoxide ion	
		C%	O%	C%	O%
Dimethylformamide	37	0	91	0	97
D.M.S.O.	45	--	--	0	95
Ethylene glycol dimethyl ether	7	0	99	22	70
Tetrahydrofuran	7	0	96	36	60
Methanol	34	0	96	34	57
Ethanol	24	0	99	28	52
2,2,2-trifluoroethanol	27	26	62	85	7
Water	80	24	65	84	10

*Taken from data on benzyl bromide

(f) Radical Anions.--Russell and Janzen (19) have reported the facile formation of radical anions from a variety of nitroaromatics in the presence of strong base, both in t-butyl alcohol and DMSO. Similar results were obtained from nitrobenzene (20) and from compounds capable of forming dianions in the

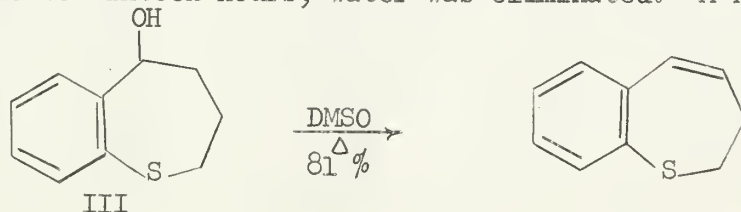


presence of their unsaturated analogues (21). The electron transfer was found

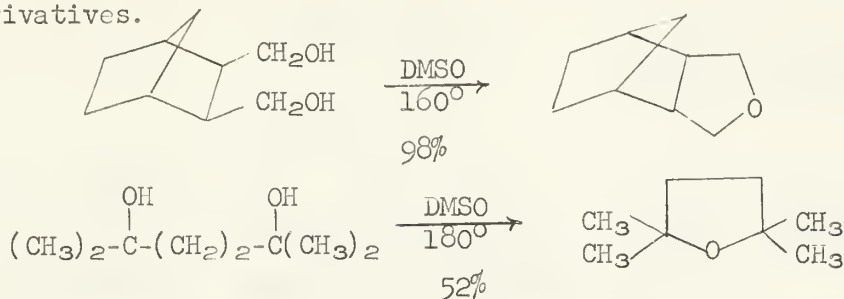


to take place most effectively in DMSO. Other results (22) seem to imply that electron transfer between organic donors and acceptors is a general reaction observable for numerous carbanions, nitranions, phenoxide and mecaptide anions even at dilute concentrations in DMSO and t-butyl alcohol.

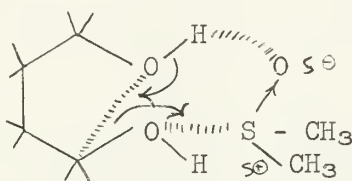
2. Reactions without Base-Catalysis.(a) Dehydration.--Traynelis, Hergenrother, Livingstone and Valicenti (23) observed that upon heating 2-hydroxy-2,3,4,5-tetrahydrobenzo [b] thiopin (III) in a large excess of DMSO at $160\text{--}180^\circ$ for nine to sixteen hours, water was eliminated. A number of alcohols



were shown to undergo this reaction in DMSO. The reaction does, however, appear to be limited to secondary alcohols. Subjection of 1-pentanol and β -phenethyl alcohol gave only unchanged starting materials. Gillis and Beck (24) had hoped that this would be a convenient route to the exomethylene norbornanes, but instead found that the reactions of 1,4 diols in DMSO led to high yields of tetrahydrofuran derivatives.

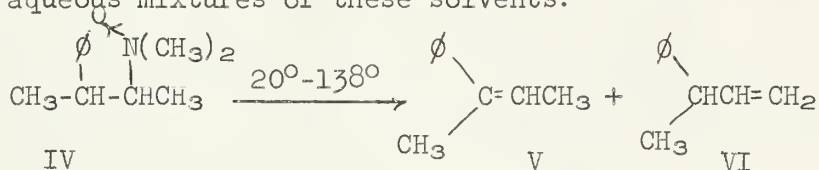


In the second reaction the expected dienes were also found and identified. The authors proposed a cyclic transition state. However, only polymeric and starting



materials were isolated when the reaction was attempted with cis-butene-1,4-diol.

(b) Elimination Reactions.--Recently, Cram has begun a study of solvent effects on the N-amine oxide elimination reaction (7). Threo and erythro-N,N-dimethyl-3-phenyl-2-butylamine oxide, which upon elimination yield cis and trans-2-phenyl-2-butene and 3-phenyl-1-butene, were studied in DMSO (25-50°), tetrahydrofuran (25-100°), and aqueous mixtures of these solvents.



The production of V was completely stereospecific in all media as measured by V.P.C. analysis. For the threo-isomer of IV the ratio of V to VI changed from 49 in DMSO to 19 in tetrahydrofuran to 7 in water (132°). The erythro isomer of IV for the same solvents gave ratios of 16, 19 and 11 respectively. All reactions were reported to be first order in substrate. Rate comparisons for the threo compounds at 25° are as follows:

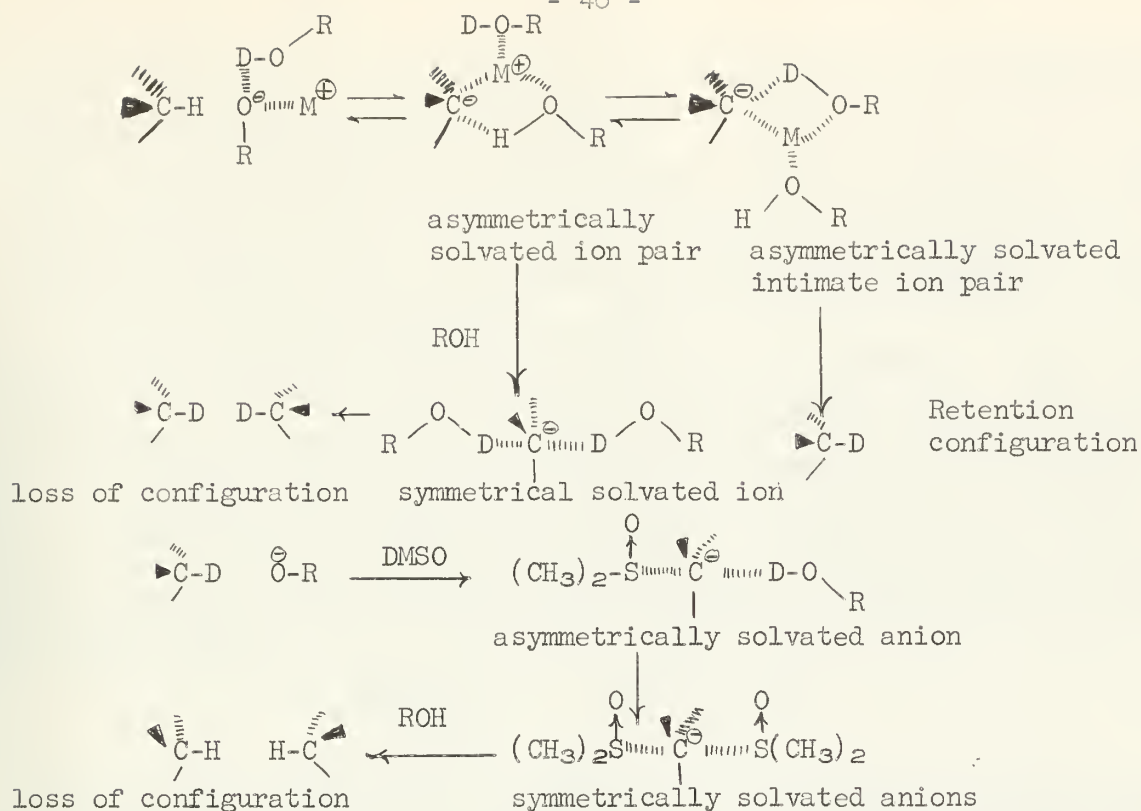
$$k_{\text{DMSO}}/k_{\text{H}_2\text{O}} \sim 10^5 \quad k_{\text{THF}}/k_{\text{H}_2\text{O}} \sim 10^6$$

and for the erythro:

$$k_{\text{DMSO}}/k_{\text{H}_2\text{O}} \sim 10^4 \quad k_{\text{THF}}/k_{\text{H}_2\text{O}} \sim 10^5$$

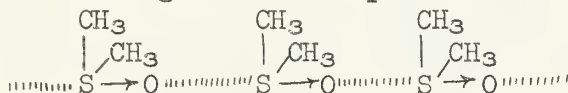
Rate depressions, relative to the pure solvent, of approximately 200 for 90% THF and 5 to 10 for 90% DMSO (10% H₂O) were noted. This effect reflects the deactivation of the N-amine oxide oxygen by hydrogen bonding. It is less in DMSO because the solvent is able to compete with the substrate for hydrogen bonds.

Any attempt to correlate the varied results obtained in any dipolar aprotic solvent is difficult and especially so in this case. It is felt, however, that most of the solvent properties of DMSO can be explained on the basis of its inability to solvate small anions through hydrogen bonding while possessing the ability to solvate cations and to function well as either a nucleophile or electrophile. Cram, Kingsbury and Rickborn (25) explain the difference between protonic "retention" solvents and aprotic "racemization" solvents, of which DMSO is an outstanding example, on the basis of asymmetric vs. symmetric solvation.



Hence the difference in the stereospecificity of base-catalyzed hydrogen-deuterium exchange in DMSO vs. *t*-butyl alcohol can possibly be explained on the basis of the inability of DMSO to contribute hydrogen bonding. The tremendous differences in reaction rates can also be related to this same feature. There is considerable evidence that anions are solvated in protonic solvents by hydrogen bonding. Cram has postulated that the alkoxide ion is present in DMSO as a "naked" anion, unstabilized by hydrogen bonding and hence is much more reactive than one well solvated. It has been shown in other cases that base strengths of anions are greatly enhanced in DMSO. It has even been claimed (26) that elimination of HBr from alkyl bromides can be catalyzed by fluoride ion in this solvent to yield the corresponding alkenes. This is probably a combination of base strength enhancement and the tendency of DMSO to solvate large, highly polarizable anions.

The dehydration reactions can possibly be related to the electrophilicity of the solvent, which is probably heightened at elevated temperatures. At room temperature, DMSO is believed to exist in chains with hydrogen bonding between the methyl hydrogens and oxygens (27) or more likely with sulfur-oxygen linkages (28). This order is reflected in its high heat of vaporization and low heat of fusion.



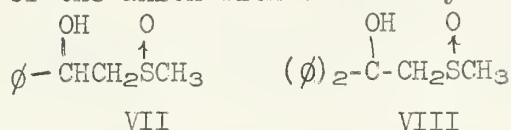
As with water at 37°, DMSO undergoes a structural change between 40 and 60°. Plots of physical properties against temperature show discontinuities at this point. The high polarizability of DMSO is certainly of assistance in the dehydrobromination reaction.

It is difficult, at this time, to correlate the effects of dielectric constants in most of the reactions discussed. The cases reported by Cram, where it appears to be unimportant, are in sharp contrast to its inferred prominence in the naphthoxide enolate work of Kornblum. Schriesheim (9) also found no obvious relationship between the isomerization rate of 2-methyl-1-pentene and the dielectric constant of the medium.

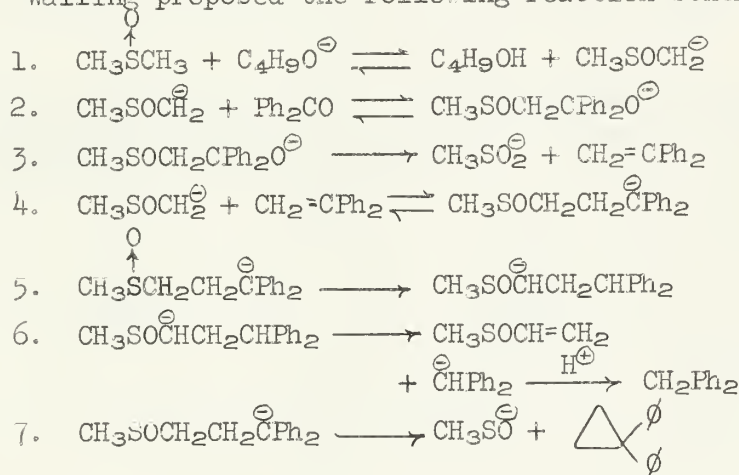
II. DMSO as Reactant and Solvent.--Up to this point we have considered DMSO as an inert solvent. A number of reactions of this solvent have been observed to take place, often under identical conditions to those in which we assume inertness.

New reactions of this solvent are constantly being reported. In considering the reactions previously discussed it should be remembered that in no case was the fate of the solvent thoroughly explored.

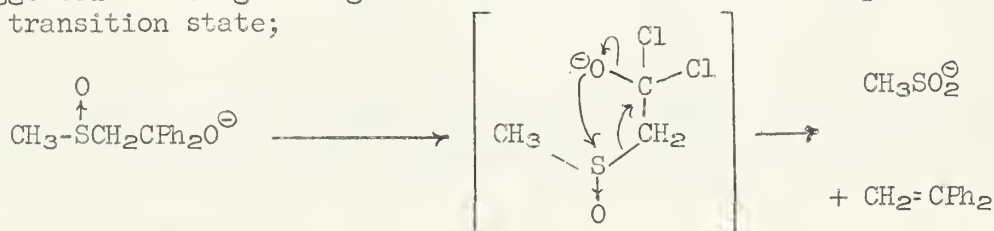
The stability of an anion α to the sulfoxide group has long been a highly debatable question, mainly because of the uncertainty in defining the nature of the sulfur-oxygen bond. Last year Corey and Chaykovsky (29) presented the first in a series of observations on the chemistry of the parent compound of a possible family of carbanions stabilized by the O group; methylsulfinylcarbanion. It is easily generated by dissolving (R-S-) sodium hydride or sublimed potassium *t*-butoxide in excess DMSO at 65-70° under nitrogen. Sodium amide has also been found to work equally well. The methylsulfinylcarbanion is strongly basic, as was shown by its reaction with triphenyl methane producing a deep red solution which was assumed to be the triphenylcarbanion. An equilibrium constant of 21 ± 4 (25°) was reported for the reaction, clearly showing that the methylsulfinylcarbanion is more basic than the triphenylcarbanion. Chlorobenzene was found to undergo substitution reactions with excess sulfinylcarbanion to yield methyl benzyl sulfoxide (6.7 mole excess) at room temperature. Reaction of the anion with benzaldehyde and benzophenone gave compounds VII and VIII



Observing that methylsulfinylcarbanion would react with phosphonium salts to form Wittig type ylides Corey and Chaykovsky (30) attempted the use of the carbanion itself as a Wittig reagent. Walling and Bollyky (31) found themselves in the same field when they attempted to study the base-catalyzed homogeneous hydrogenation of benzophenone in DMSO. In simultaneous publications both groups reported that the products of the reactions were 1,1-diphenyl ethylene, diphenylmethane and 1,1-diphenylcyclopropane. Both NaH and sublimed potassium *t*-butoxide were used as bases. Walling proposed the following reaction scheme:

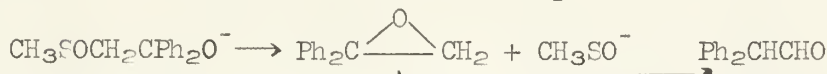


Step 3 is suggested as being analogous to the Wittig reaction and probably proceeds via a cyclic transition state;



Since 1,1-diphenylethylene was postulated as the intermediate in the formation of diphenylmethane and 1,1-diphenylcyclopropane, Walling and Bollyky subjected it to the reaction conditions and did obtain the expected diphenylmethane (17%) and 1,1-diphenyl cyclopropane (6%). However, the unexpected, and so far unexplained formation of 3,3-diphenylpropene was the major reaction (77%).

Similar results for the benzophenone reaction were also reported by Chaykovsky and Corey and interpreted in the same way. These workers, however, were able to identify two additional products; diphenylacetaldehyde and 1,1-diphenyl-2-methylthioethylene. The aldehyde formation was explained as follows:

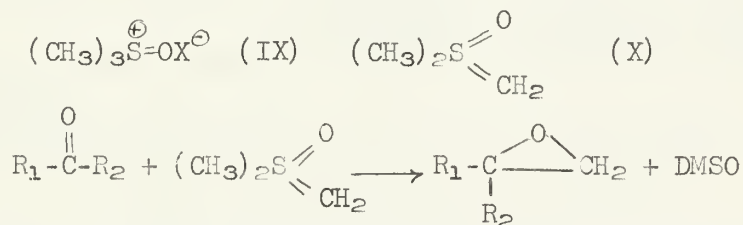


It should be pointed out that Cope (32) was unable to observe ring opening in the same epoxide in strong base, while Cristol, Douglass and Meek (48) were able to isolate diphenyl acetaldehyde upon treatment of the epoxide with phenyl lithium. No explanation was given for the production of 1,1-diphenyl-2-methylthioethylene; $\text{Ph}_2\text{C}=\text{CHSCH}_3$.

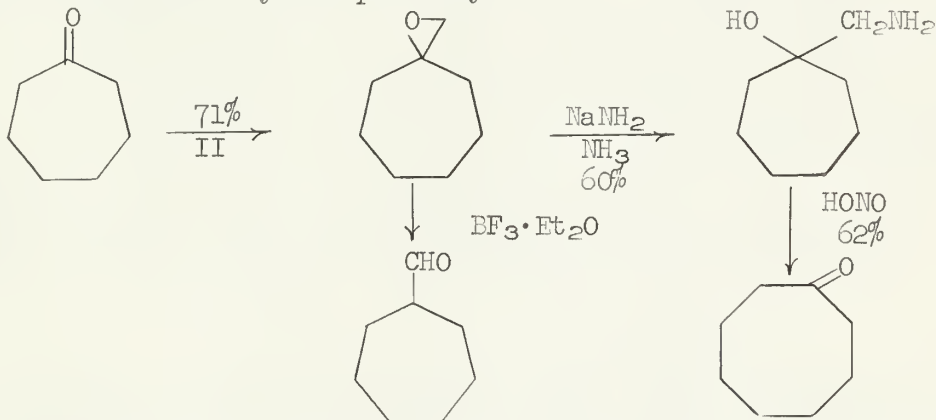
Greenwald, Chaykovsky and Corey (33) have shown that the addition of the anion to phosphonium salts greatly facilitates the Wittig reaction and even unreactive ketones like camphor gave a 74% yield under these reaction conditions.

Kuhn (34) and Kuhn and Trischman (35) observed that DMSO, in contrast to amine oxides, does not produce the expected alkylsulfonium halides in reaction with alkylhalides, but instead gives the trimethylsulfoxonium halides (Iodides being the only halide used). This was later confirmed by Major and Hess (36). Smith and Winstein (37) found that while o-alkylation was kinetically favored S-alkylation was thermodynamically preferable. It should be pointed out that other halides will not undergo the reaction under the conditions used with the iodides.

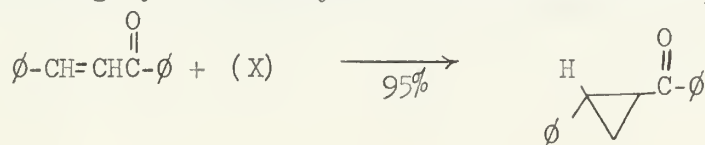
According to Corey and Chaykovsky (38), treatment of the trimethylsulfoxonium halides (IX) in DMSO with strong base, produces the dimethylsulfoxonium methylide (X). The methylide (X) was found to be highly reactive toward carbonyl



groups. All reactions were carried out at 25° for one hour and at 50° for an additional hour. The practicality of this reagent is demonstrated by the preparation of cyclooctanone and cycloheptaldehyde.

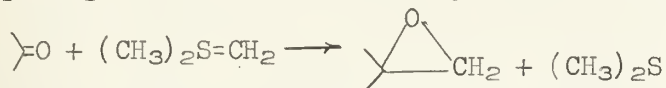


Compounds which are susceptible to Michael addition (e.g., benzalacetophenone) responded quite differently. The products in these cases were found to be cyclopropane derivatives in high yield. Only minor amounts of the epoxide could be isolated.



Because of the interesting and unusual results obtained with the sulfoxonium methylide, Corey and Chaykovsky (39) have begun a study of the dimethylsulfonium

methylide; $(\text{CH}_3)_2\text{S}=\text{CH}_2$ (XI). The sulfonium ylides had been reported earlier by Franzen, Schmidt and Mütz (40) to be unstable. Corey was able to prepare the dimethyl sulfonium methylide in DMSO-THF solution at -10° . It was found to have a half-life of a few minutes at 0° compared to the sulfoxonium ylide which can be stored for several days at 25° . The dimethylsulfonium methylide was found to react with a variety of aldehydes and ketones. Similar to the sulfoxonium ylide, the sulfonium compound gave rise to the corresponding epoxides. Yields ranged from 75 to 97%. In



contrast to the sulfoxonium ylides, which tend to form cyclopropanes with potential

Michael reactants, the sulfonium compound selectively affords the epoxides.

On the basis of relative stabilities of the sulfoxonium and sulfonium ylides, along with their relative rates of base-catalyzed hydrogen-deuterium exchange (46), Corey and Chaykovsky concluded that the sulfonium ylide is a much more effective methylene transfer agent than the sulfoxonium.

Replacement Reaction.--Rätz and Sweeting (40,41) have demonstrated another unusual reaction of DMSO. If 3,9-dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5] undecane-3,9-dioxide is dissolved in "anhydrous" DMSO the following general reaction occurs.



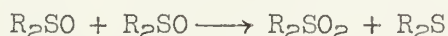
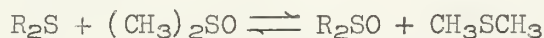
Oxygen Exchange.--Kornblum, et al. (12), in an earlier note reported transformation of phenacyl halides to keto-aldehydes by merely dissolving the halide in DMSO at room temperature for nine hours. Benzyl bromide was later (43) found to undergo



the reaction in the presence of sodium bicarbonate or if the halide is first converted to the tosylate and then treated with a mixture of sodium bicarbonate in DMSO. Nothing is said

about whether the medium was anhydrous so that water may have taken part in the reaction at some stage.

Searles and Hays (44) have oxidized sulfides to sulfoxides and these have been oxidized to sulfones (45).



Conclusion.--DMSO is an excellent solvent for systems in which very strongly basic conditions are desired. This partly explains the great interest being shown in this compound. Other strongly basic systems usually lack either ease of management, stability, reproducibility or all three. DMSO surmounts all of these problems. Aside from the numerous reactions already mentioned it should be interesting to observe the effects of DMSO on the formation of carbenes, pyrolysis of esters, the malonic ester synthesis, the Favorskii reaction, the Perkin ring closure, the Stevens rearrangement, the Smiles rearrangement, the Von Richter reaction, the study of carbanion geometry and nucleophilic displacements.

There are, however, other problems involved in the use of DMSO. It is known that the solvent disproportionates at elevated temperatures (160 - 180°).



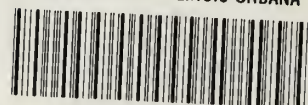
As pointed out earlier, no one has reported a thorough investigation of the solvent to ascertain what changes might have occurred. The normal workup by addition of water makes this somewhat difficult. Its hygroscopicity requires that care be taken if anhydrous conditions are desired. It is also known to react violently with some acyl halides and very strong acids.

It is certain that as our knowledge of DMSO increases so will its use and vice versa.

BIBLIOGRAPHY

1. A. Saytzeff, *Ann.*, 144, 148 (1867).
2. "Technical Information on Dimethylsulfoxide", Crown Zellerbach Corporation, Camus, Washington.
3. D. F. O'Brien, University of Illinois Organic Seminar, 2nd Semester, 1959-1960.
4. D. J. Cram, J. L. Mateos, F. Hanck, A. Langemann, K. R. Kopecky, W. D. Nielsen, and J. Allinger, *J. Am. Chem. Soc.*, 81, 5774 (1959) and preceeding papers in the series.
5. D. J. Cram, B. Rickborn and G. R. Knox, *J. Am. Chem. Soc.*, 82, 6412 (1960).
6. D. J. Cram, B. Rickborn, C. A. Kingsbury and P. Haberfield, *J. Am. Chem. Soc.*, 83, 3678 (1961).
7. D. J. Cram, M. R. V. Sahyun and G. R. Knox, *J. Am. Chem. Soc.*, 84, 1734 (1962).
8. J. E. Hofmann, R. J. Muller and A. Schriesheim, in press.
9. A. Schriesheim and C. A. Rowe, *J. Am. Chem. Soc.*, 84, 3160 (1962).
10. Mine Safety Applcance Company.
11. A. Schriesheim, R. J. Muller, C. A. Rowe, Jr., *J. Am. Chem. Soc.*, 84, 3164 (1962).
12. A. Schriesheim, C. A. Rowe, Jr. and L. Maslund, *J. Am. Chem. Soc.*, 85, 2111 (1963).
13. S. Bank, C. A. Rowe, Jr. and A. Schriesheim, *J. Am. Chem. Soc.*, 85, 2115 (1963).
14. H. C. Brown, J. H. Brewster and H. Shechter, *J. Am. Chem. Soc.*, 76, 467 (1954).
15. E. J. Corey, *J. Am. Chem. Soc.*, 76, 175 (1954).
16. N. Kornblum, P. H. Berrigan and W. J. LeNoble, *J. Am. Chem. Soc.*, 85, 1141 (1963).
17. N. Kornblum, P. H. Berrigan and W. J. LeNoble, *J. Am. Chem. Soc.*, 82, 1257 (1960).
18. N. Kornblum, R. Seltzer and P. Haberfield, *J. Am. Chem. Soc.*, 85, 1148 (1963).
19. G. A. Russell and E. Janzen, *J. Am. Chem. Soc.*, 84, 4153 (1962).
20. G. A. Russell, A. J. Moye and K. Nagpal, *J. Am. Chem. Soc.*, 84, 4154 (1962).
21. G. A. Russell, E. G. Janzen and E. T. Strom, *J. Am. Chem. Soc.*, 84, 4155 (1962).
22. Private communication
23. V. J. Traynelis, W. J. Hergenrother, J. R. Livingstone and J. H. Valicenti, *J. Org. Chem.*, 27, 2377 (1962).
24. B. T. Gillis and P. E. Beck, *J. Org. Chem.*, 28, 1308 (1963).
25. D. J. Cram, C. A. Kingsbury and B. Rickborn, *J. Am. Chem. Soc.*, 83, 3688 (1961).
26. A. J. Parker and Banthorpe, unpublished work from Reference 28.
27. H. L. Schäfer and W. Schaffernicht, *Angew. Chem.*, 72, 618 (1960).
28. A. J. Parker, *Quart. Rev.*, 16, 163 (1962).
29. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 84, 866 (1962).
30. M. Chaykovsky and E. J. Corey, *J. Org. Chem.*, 28, 254 (1963).
31. C. Walling and L. Bollyky, *J. Org. Chem.*, 28, 256 (1963).
32. A. Cope, P. A. Trumbull and E. R. Trumbull, *J. Am. Chem. Soc.*, 80, 2844 (1958).
33. R. Greenwald, M. Chaykovsky and E. J. Corey, *J. Org. Chem.*, 28, 1128 (1963).
34. R. Kuhn, *Angew. Chem.*, 69, 570 (1957).
35. R. Kuhn and H. Trischmann, *Ann.*, 611, 117 (1958).
36. R. T. Major and H. J. Hess, *J. Org. Chem.*, 23, 1563 (1958).
37. S. G. Smith and S. Winstein, *Tet.*, 3, 317 (1958).
38. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 84, 867 (1962).
39. E. J. Corey and M. Chaykovsky, *Tet. Letters*, 169 (1963).
40. R. Rätz and O. J. Sweeting, *Tet. Letters*, 529 (1963).
41. R. Rätz and O. J. Sweeting, *J. Org. Chem.*, 28, 1612 (1963).
42. N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Leonard and W. M. Weaver, *J. Am. Chem. Soc.*, 79, 6562 (1957).
43. N. Kornblum, W. J. Jones and G. J. Anderson, *J. Am. Chem. Soc.*, 81, 4113 (1959).
44. S. Searles and H. R. Hays, *J. Org. Chem.*, 23, 2028 (1958).
45. F. Ostermeyer and D. S. Tarbell, *J. Am. Chem. Soc.*, 82, 3572 (1960).
46. W. von E. Doering and A. H. Hoffmann, *J. Am. Chem. Soc.*, 77, 521 (1955).
47. R. P. Bell, *Proton in Chemistry*, Cornell University Press, Ithaca, New York (1959), p. 87.
48. S. J. Cristol, J. R. Douglass and J. S. Meek, *J. Am. Chem. Soc.*, 73, 816 (1951).

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