ORGANIC CHEMISTRY

A Series of Monographs — Volume 16 - I

Nonbenzenoid Aromatics

Volume I

ORGANIC CHEMISTRY

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Nonbenzenoid Aromatics

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Volume I

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Preface

For one hundred and fifty years chemical species possessing a cyclic array of parallel π orbitals occupied by six electrons have been catalogued as "aromatic" or "benzenoid." Remarkably, in one-tenth that time, the field of nonbenzenoid aromatics has undergone a minor revolution. Conjugated π-systems from two to thirty electrons have recently been generated as radicals, cations, carbanions, and a wide range of unusual neutral compounds. In addition, the ambiguities associated with the historical designation "aromatic" appear to be experiencing a clarification.

The last major attempt to survey this field was made in 1959 in the now classic compilation "Non-Benzenoid Aromatic Compounds."[1] No monocyclic nonbenzenoid aromatic species with other than 6π electrons was available for discussion in that volume. Although a number of excellent reviews have appeared in the interim,[2] this treatise is intended to provide an in-depth multiauthored evaluation of activity as it has developed in the last fifteen years. In view of the spectrum of interests represented by the individual contributions, the reader might anticipate a particular organization from volume to volume. Practical considerations on the contrary have resulted in a generous heterogeneity within each book. Nevertheless the theme that threads its way through the chapters is that of "aromaticity"; each author making an effort to evaluate this concept in light of his own work. It is with this in mind that this treatise is initiated with an historical account tracing the development of the idea up to the discovery of the electron. A later volume will bring the record to date.

During production of this volume, a report bearing directly on "The Cyclodecapentaene Problem" (Burkoth and van Tamelen, Chapter 3) ap-

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[1] David Ginsburg (ed.), "Non-Benzenoid Aromatic Compounds." Wiley (Interscience), New York, 1959.

[2] G. M. Badger, "Aromatic Character and Aromaticity." Cambridge Univ. Press, London and New York, 1969.
W. Baker, The widening outlook in aromatic chemistry, Part 1. *Chemistry in Britain,* p. 191, May, 1965.
W. Baker, The widening outlook in aromatic chemistry, Part 2. *Chemistry in Britain,* p. 250, June, 1965.
K. Hafner, Structure and aromatic character of non-benzenoid cyclically conjugated systems, *Angew. Chem. Internat. Ed.* **3** [No. 3] (1964).
M. E. Vol'pin, Non-benzenoid aromatic compounds and the concept of aromaticity, *Russian Chem. Rev.,* March, 1960.
A. J. Jones, Criteria for aromatic character, *Rev. Pure Appl. Chem.* **18**, 253 (1968).

peared in print. Masamune and Seidner[3] report generation of the elusive all-*cis*[10]annulene and a mono trans isomer by low temperature photolysis of *cis*-9,10-dihydronaphthalene. The labile substances were characterized by direct observation in the NMR at −60°, hydrogenation to cyclodecane (80%), and *in situ* rearrangement to known $C_{10}H_{10}$ hydrocarbons. The authors suggest that the NMR chemical shifts of the [10]annulenes provide evidence against a diamagnetic ring current, a surprising result in view of the work of Sondheimer *et al.*[4]

An expression of gratitude is owed the authors who made this volume possible and Marie Kouirinis whose patience and cooperation lightened the editorial task considerably. Thanks are likewise due Professor Alfred Blomquist (Cornell) for planting the seed and Professor David Harpp (McGill) for reading Chapter 1 and offering helpful suggestions. A final note of appreciation goes to C.G.D. for her gentle charm, enthusiasm, and lightheartedness, an indispensable influence in the consolidation of the work.

JAMES P. SNYDER

New York, New York
October, 1969

[3] S. Masamune and R. T. Seidner, *Chem. Commun.*, p. 542 (1969).

[4] F. Sondheimer, I. C. Calder, J. A. Elix, Y. Gaoni, P. J. Garratt, K. Frohmann, G. di Maio, J. Mayer, M. V. Sargent, and R. Wolovsky, *Spec. Publ.* No. 21, 75. The Chem. Soc., London, 1967.

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Aromaticity: Preelectron Events

James P. Snyder

I. Introduction

The designation "aromatic" was first used by chemists to catagorize a specific class of substances in the first half of the nineteenth century. During the ensuing 150 years, a considerable number of research workers have been engaged in the task of detailing, defining, and defending the notions to which the term has been applied. Although our understanding of the molecular and electronic structure of matter is far more sophisticated than that of the early 1800's, a precise and generally acceptable definition of "aromaticity" remains elusive.

In spite of the uncertain condition of the concept, a plethora of subsidiary nomenclature has appeared in the last 25 years. Hybrid appelatives such as pseudo-, quasi-, homo-, anti-, non-, Hückel-, nonclassical-, and bicyclo-aromatic are now commonplace in the organic chemistry literature. More often than not, the application of such terminology is either without basis in experimental fact or is so ill-defined that it occasions additional and even less precise usage. Consequently, the diffusiveness associated with the mother-term is abetted. Modern textbooks continue to phrase inadequate or nondefinitions of "aromaticity," complemented generously with structural examples.

Within the mainstream of the development of this topic, two not necessarily conflicting extremes have emerged. The earlier and still widely acknowledged one focuses on reactivity or ground-transition-state characteristics of molecules as a reflection of aromatic properties. The alternative and increasingly popular view considers physical or ground-state-only properties as the key to this issue. The present conceptual reevaluation has been stimulated by a remarkable series of syntheses over a short span of 6 or 7 years.

In 1958, a single electronic type of "aromatic" series was known. All heteroatom and hydrocarbon combinations with varying claims to aromatic character (mono- and polycyclic, neutral and charged) were reducible to six π-electron systems. By 1968, monocyclic hydrocarbons with configurations of from 2 to 30 π-electrons had been identified. Although a thorough examination of this proliferation is far from complete, the preliminary studies offer a stimulating preview of the direction the field is taking. Without doubt, as the investigation runs its course, the meaning of aromaticity will be clarified if not ultimately defined in terms suitable for undergraduate digestion.

With the preceding in mind, it is the purpose of the present introductory chapter to trace the main historical events in the development of the idea of aromaticity up to 1916, the birthdate of the modern electronic theory of valence (see footnote 65). A subsequent chapter will continue the survey through the twentieth century, elaborate on our present understanding of aromaticity, and attempt to place current daughter terminology in perspective.

II. Developments Predating the Kekulé Benzene Theory

A. The Foundations of Organic Chemistry (1820–1860)

Although C. W. Scheele in Sweden as early as 1780 isolated and purified a number of carboxylic acid salts,[1a,b,c] the modern principles of organic chemistry find their origin in the first half of the nineteenth century. Chemists were devoted especially to isolating natural products, determining their elemental composition, and investigating their properties. Sugars, amino acids, alkaloids, fats, and dyes were all recognized as compound classes between 1800 and 1820. With pure substances in hand, quantitative elemental

[1a] A. J. Ihde, "The Development of Modern Chemistry." Harper, New York, 1964; This comprehensive treatise covers in a very readable fashion all aspects of chemical history. Unless otherwise documented, the early history of organic chemistry can be found in Ihde's work and in that of Findlay[1b] and Farber.[1c]

[1b] C. Findlay, "A Hundred Years of Chemistry." Duckworth, London, 1948.

[1c] E. Farber, "The Evolution of Chemistry." Ronald Press, New York, 1952.

analysis was necessitated. By 1830 Lavoisier's original combustion method received final refinement by Liebig, allowing accurate elemental mass ratios to be readily determined.

Homologs and isomers were soon recognized and subsequently conceptualized and incorporated into the growing theory of organic chemistry. Preliminary consolidation was possible following the elucidation of the laws of definite proportions (Proust, 1799), multiple proportions, and the atomic theory (Dalton, 1803). Two extemely vital areas of interest, atomic weights and structure, proved to be most frustrating during this early period. The work of Gay-Lussac and Avogadro was equal to the task of providing an accurate atomic weight scale for elements contained in volatile materials by 1811. Nonetheless, the crucial correlations and public relations exercise come about largely as a result of the efforts of Cannizzaro as late as 1860.[2] During the intervening 50 years, the lack of accurate atomic weights as well as ignorance regarding the distinction between atoms, equivalents, and molecules further complicated the question of bonding and structure. The years from 1800 to 1858 witnessed no less than six different major attempts to define the structures of organic species. The earlier dualistic scheme (1812), that all compounds are composed of two discrete units held together by some sort of electrostatic force, gradually gave way to the unitary view that a substance may be an entity in itself (late 1840's). Throughout this period, of course, formula notation was primitive, inconsistent, frequently meaningless, and always confusing. The stage was set, however, for the brilliant, intuitive, structural revelations to follow. In 1852–1853, Frankland verbalized the concept of valence and exemplified it for nitrogen, sulfur, antimony, and arsenic. He was quickly followed by Kolbe (1855–1859) who developed a system of organic formulas, which, though inaccurate, nicely demonstrated the relationships between different compounds. It was at this point that the uncertainties of the previous 40 years began to dissipate and the initial contributions to structural organic chemistry as we know it today were made.

The first critical proposal came simultaneously from Couper[3a,b,c] and

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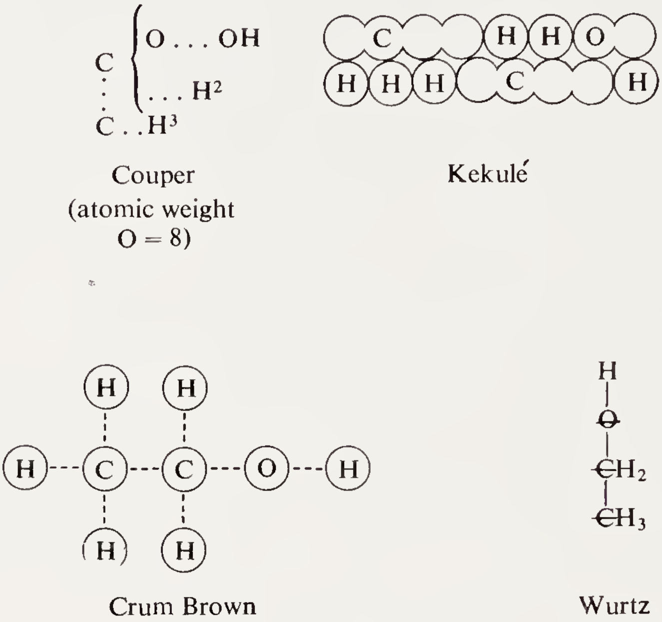
[2] Ihde[1a] relates briefly the intriguing political maneuvers necessary to secure recognition of Cannizzaro's views published 2 years earlier. The important role of public debate on controversial issues is highlighted.

[3a] A. S. Couper, *Compt. Rend. Acad. Sci.* **46**, 1157 (1858).

[3b] A. S. Couper, *Phil. Mag.* **16** (4) 104 (1858); *Ann. Chim. Paris* [3] **53**, 469 (1858). These latter two publications are the English and French translations, respectively, of the full paper following the initial note[3a] on Couper's "New Chemical Theory." They differ slightly in the way in which structural formulas are written, and the latter contains a cyclic formulation for cyanuric acid.

[3c] For a collection of Couper's six papers with interesting comments and interpretation see R. Anschütz, *Proc. Roy. Soc. Edinburgh*, **29**, 193 (1909); cf. Benfey,[5] pp. 132 and 136. Although Couper's insights into the structure of carbon compounds were as profound as Kekulé's, his work achieved little notice. Anschütz discusses the reasons for this.

Kekulé[4,5] in 1858, who recognized the tretravalent nature of carbon and its ability to catenate. The basis for structural representation of organic substances was established (Fig. 1). Couper wrote formulas which represented the chemical bond with a line, although dotted, as is done today. Kekulé's graphics, on the other hand, indicated bonding by means of his famous sausage formulas. Following the lead of Butlerov, Erlenmeyer, Crum Brown, Wurtz, Hofmann[6] and others, Kekulé abandoned his difficult-to-reproduce formulas in favor of the more conventional line and letter symbolism.



Couper
(atomic weight
O = 8)

Kekulé

Crum Brown

Wurtz

FIG. 1. Formulas for ethyl alcohol.

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[4] A. Kekulé, *Ann.* **106**, 129 (1858); cf. Benfey,[5] p. 109.

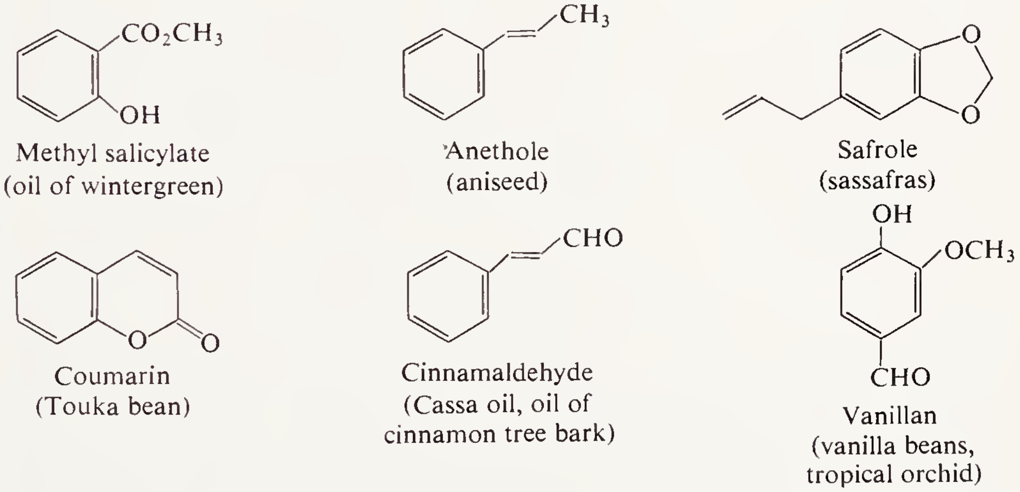
[5] English translations of the first key papers on chemical bonding have been collected by O. T. Benfey, ed., "Classics in the Theory of Chemical Combination." Dover, New York, 1963.

[6] A. W. Hofmann, *Proc. Roy. Inst.* **4**, 416 (1865); Hofmann was one of the first to make use of molecular ball-and-stick models to demonstrate structure. His carbons and four ligands assumed a square planar rather than a tetrahedral arrangement in accord with the general practice of using written structures and models to represent bonding rather than spatial relationships. Anticipating the development of stereochemistry, Kekulé constructed a three dimensional tetrahedral carbon for use in his lectures and research.[7,10] Butlerov, the earliest to apply the tetrahedron concept to carbon (1862), albeit by attributing variable character to the four valences,[8] most likely inspired Kekulé in this regard.[9a,b]

The second breakthrough permitting the early finishing touches to be put on the chemist's structural formulations was Cannizzaro's clarification of the atomic weight scale in 1860, as mentioned above. Immediately, vast numbers of organic substances could be assigned reasonable and consistent structures. The aliphatic series,[11] one of the two major classes of organic compounds a large number of which were known to be natural fatty acids or their derivatives, was amenable to structural classification. The aromatic series, however, was viewed as an exception to the Couper-Kekulé scheme.

B. THE ORIGINS OF AROMATICITY

Initially, compounds belonging to the aromatic class were so named and distinguished from the aliphatics because of their pleasant olfactory properties. Natural products such as oil of wintergreen, aniseed, sassafras, touka beans, oil of cinnamon, and vanilla beans contained as principal components the benzenoid compounds indicated in Fig. 2.



Methyl salicylate (oil of wintergreen)

Anethole (aniseed)

Safrole (sassafras)

Coumarin (Touka bean)

Cinnamaldehyde (Cassa oil, oil of cinnamon tree bark)

Vanillan (vanilla beans, tropical orchid)

FIG. 2. Some of the original benzenoid "aromatics."

Other fragrant but nonbenzenoid substances from the sap and tissues of certain plants were also designated as aromatic around 1800. These so-called "essential oils" were typically isolated by ether extraction or steam distillation

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[7] A. Kekulé, *Z. Chem.* 3, 217 (1867).

[8] A. M. Butlerov, *Z. Chem. Pharm.* 5, 297 (1862).

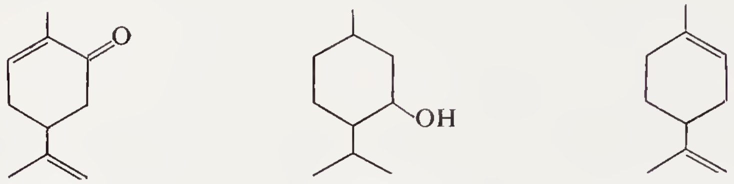
[9a] J. Gillis, *Mededel. Koninkl. Vlaam. Acad. Wetenschap. Belg. Kl. Wetenshap.* **20**, 3 (1958); cited by O. T. Benfey and L. Fikes, *Advan. Chem. Ser.* **61**, 121–122 (1966);

[9b] "Kekulé Centennial." *Advan. Chem. Ser.* **61** (1966).

[10] G. E. Hein, *Advan. Chem. Ser.* **61**, 7–11 (1966).

[11] From the Greek "aleiphar" meaning fat.

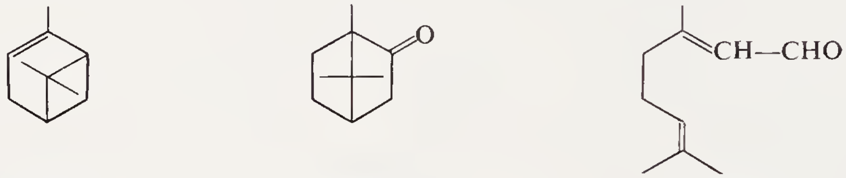
from cloves, roses, lavender, citronella, eucalyptes, peppermint, sandalwood, cedar, turpentine, and similar sources. Structurally, the most important of these compounds are members of the terpene class, hydrocarbons and their oxygenated derivatives formally composed of isoprene units, $(C_5H_8)_n$. A few simple examples are carvone, menthol, limonene, pinene, camphor, and geranial (Fig. 3).



Carvone
(caraway and
spearmint oils)

Menthol
(peppermint oil)

Limonene
(bitter orange, caraway,
and other oils)



Pinene
(turpentine oil,
pine tree)

Camphor
(camphor laurel)

Geranial
(lemongrass oil)

FIG. 3. Some of the original nonbenzenoid "aromatics."

C. THE COMPOSITIONAL CLASSIFICATION OF AROMATIC COMPOUNDS

With the development of accurate combustion analysis (1800–1830), aromatic compounds were catalogued from a compositional point of view. They were thus characterized by their relatively high carbon–hydrogen ratio. Benzene, first detected by Michael Faraday in 1825 as a pyrolysis product of whale oil,[12] was recognized as the compositional parent of the aromatic species.[13] A wide variety of substances from crude petroleum and coal tar subsequently qualified as benzene derivatives. Likewise, the centuries-old and brutal technique of passing petroleum vapors and volatile carbon-rich essential oils over glowing metals provided another rich source for aromatics.[1c] *p*-Cymene (*p*-isopropyltoluene), xylene, and benzoic acid were thus obtained

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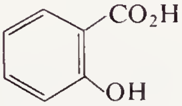
[12] M. Faraday, *Phil. Trans. Roy. Soc. London* p. 440 (1825).

[13] J. Loschmidt, "Chemische Studien I," Private Printing, Vienna (1861). This rare booklet was reprinted by *Ostwalds Klassiker Exakten Wiss.* **190** (1913) [R. Anschütz, ed.].

from camphor or turpentine, *Pinus Martinus* wood, and gum benzoin, respectively. The growing volume of new, unidentified, and always arbitrarily named substances so derived prompted Justus Liebig in 1841 to comment derisively:

> Science has especially within the last few years been enriched with so many bodies of this kind, the products of destructive distillation, that it is much to be wished that the labors of chemists were directed to more really useful ends ... these substances are not encountered in organized nature, they perform no role which is worthy of attention.[14]

Nonetheless, the number of products from dry distillation continued to grow and, naturally enough, chemists were eager to apply the developing structure theory to them. The first such attempt appears to have been made by Couper in his pioneering paper on carbon bonding in 1858.[3a,14a] He represented salicylic acid (**1**) as **2** with two groups of three carbon atoms to which the carboxyl group was attached. Oxygen was considered to have an atomic weight of 8, while atomic organization within each group was unspecified.



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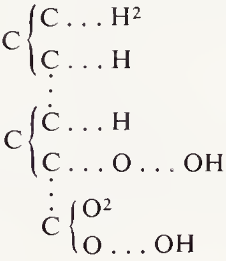
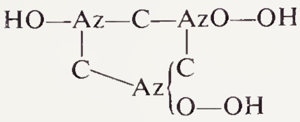


$$\begin{array}{l} C\left\{\begin{array}{l}C\ldots H^{2}\\ C\ldots H\end{array}\right.\\ \quad\;\vdots\\ C\left\{\begin{array}{l}C\ldots H\\ C\ldots O\ldots OH\end{array}\right.\\ \quad\;\vdots\\ \quad\; C\left\{\begin{array}{l}O^{2}\\ O\ldots OH\end{array}\right.\end{array}$$

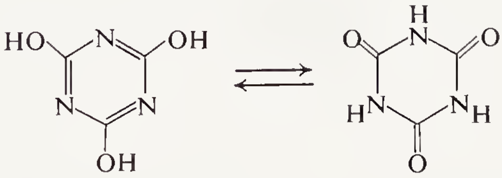
2

Similar structures were shown for mono- and trichlorophosphates of salicylic and phosphosalicylic acid. Couper paid no particular attention to the fact that salicyclic acid is benzenoid. It is of interest that, in the French translation of his full paper[3b] on the structure of carbon compounds, a cyclic structure **3** for cyanuric acid (**4**) is given with no exceptional comment.



$$\begin{array}{l} HO{-}Az{-}C{-}AzO{-}OH\\ \quad\;\, | \qquad\quad\;\; | \\ \quad\;\, C{-}Az\left\{\begin{array}{l}C\\ O{-}OH\end{array}\right.\end{array}$$

3



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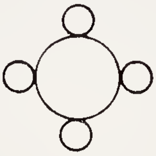
[14] J. Liebig, *Ann.* **38**, 203 (1841).

[14a] A. S. Couper, *Compt. Rend. Acad. Sci.* **46**, 1107 (1858); *Edinburgh New Phil. J.* **8**, 213 (1858). These are French and English translations respectively of the same paper; cf. A. Kekulé, *Ann.* **106**, 132 (1858).

D. JOSEPH LOSCHMIDT: A SEMISTRUCTURAL BASIS FOR AROMATICITY

An unusually imaginative but little publicized effort to come to grips with the theory of chemical structure was made by Joseph Loschmidt in Austria in 1861. In a privately printed book of limited circulation,[13] Loschmidt proposed structures for 368 substances, 121 of which were considered to be aromatic. In the first part of the book, structural formulas for simple acyclic organic compounds were treated. Loschmidt represented carbon atoms as circles ◯, hydrogen atoms as smaller circles ○, oxygen atoms as double circles ◎, and nitrogen atoms as triple circles ⊚ Single bonds were described by tangential spheres, while multiple bonding was depicted by overlapping spheres, the common region of which contained two or three dark lines. Methane, carbon dioxide, and acetylene thus appeared as in **5**, **6**, and **7**. Although he stated that "benzene is to the phenyl series what methane is to the methyl series," Loschmidt was at a loss to describe the unsaturation of the C_6H_6 structure.[15]



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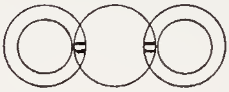

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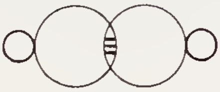

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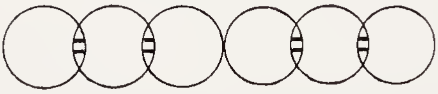

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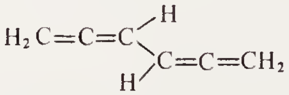
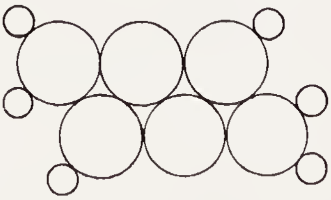


$H_2C{=}C{=}C(H){-}C(H){=}C{=}CH_2$

9

The simplest construct **8** corresponding to bisallene **9** was rejected since benzene, unlike other olefins, was known to resist hydrogenation. Furthermore, dihydro- and tetrahydrobenzenes corresponding to partially saturated **8** were unknown, while substituted benzenes were plentiful. Structure **8** provided no



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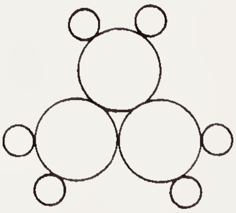
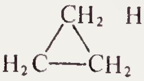
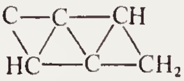


11



12



13

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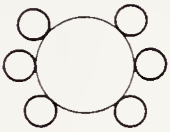
[15] *Ostwalds Klassiker Exakten Wiss.* **190**, 58–60 (1913).

visual clue to these differences. A second structure of layered carbons **10**, analogous to a doubled allyl nucleus **11**, was considered but likewise dropped as unsatisfactory. Although no formal relationship exists, it is interesting to note that Loschmidt's allyl nucleus would correspond in modern structural terms to cyclopropane **12**, whereas **10**, is represented by the unlikely assemblage **13**. It is noteworthy that Couper's earlier formulation of salicylic acid likewise portrayed the phenyl portion of the molecule as a union of allyl-like moieties.

In lieu of further information, Loschmidt admitted his predicament, simply symbolized the Ç_6 nucleus by a large circle, and treated it as a six-position element. Benzene was accordingly assigned structure **14**. This formula clearly suggested a ring of carbon atoms but ignored the fourth carbon valence.



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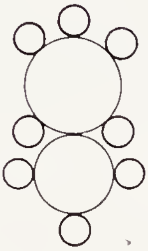

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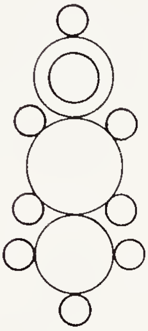

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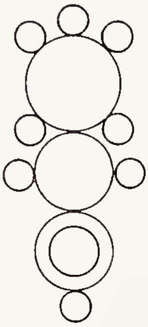

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Nonetheless, a large number of Loschmidt's structures are remarkably similar to those accepted today and were adequate for describing toluene as methyl benzene (**15**) and for explaining the sidechain isomerism of cresol (**16**) and benzyl alcohol (**17**). Loschmidt's contribution was the important recognition that a six-carbon nucleus was a unique feature of aromatic substances. He did not, however, subscribe to the notion that this nucleus contained unsaturated carbon–carbon bonds, as indicated by formulas **10** and **13**. Unfortunately, the chemical world at large did not profit from Loschmidt's speculations. The descriptions of aromatic substances was nonetheless advanced from a compositional basis to a semistructural one.

III. August Kekulé and the Structure of Benzene

A. A STRUCTURAL BASIS FOR AROMATIC CHARACTER

A more penetrating insight into the nature of the phenyl nucleus was provided by August Kekulé in 1865.[16a,b,c,17] Apparently unintentionally,[18] Kekulé offered the first working definition of aromaticity and placed it on a structural basis. In a pair of papers appearing in a French journal,[16a] later republished in German,[16b] and finally appearing in the second volume of his textbook,[16c] he consolidated the known facts concerning aromatic substances. In Kekulé's words:

> (1) All aromatic compounds, even the simplest, are relatively richer in carbon than the corresponding aliphatics.
>
> (2) Numerous homologs exist for aromatic substances as they do for aliphatics.
>
> (3) The simplest aromatic substances contain at least six carbon atoms.
>
> (4) All rearrangement products of aromatic substances belong to the same family. Under vigorous reaction conditions part of the carbon atoms are frequently lost as aliphatic derivatives, but the chief product is always aromatic and contains at least six carbon atoms. When the organic groups are not completely destroyed, the decomposition stops with the formation of the products.
>
> These facts ... justify the assumption that all aromatic compounds contain the same atomic group, or, we may say, a common *nucleus* consisting of six carbon atoms. Within this nucleus a more intimate compact combination of carbon atoms takes place. This explains the high proportion of carbon in aromatic substances. Analogous to compounds of the aliphatic class, additional carbon atoms may be attached to the nucleus. Homologation is thereby explained.[22]

Concerned with the details of the benzene nucleus, Kekulé presumed the existence of two "symmetry rules" for carbon–carbon bonding, one governing aliphatics, the other aromatics [(*a*) and (*b*), respectively].

(*a*) 1/1, 1/1, 1/1, 1/1, etc.
(*b*) 1/1, 2/2, 1/1, 2/2, etc.

A given ratio in the series describes bond multiplicity for each pair of bound carbons. The aromatic core, therefore, was considered formally to consist of a cycle of six carbon atoms with alternating single and double bonds.[23] The six

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[16a] A. Kekulé, *Bull. Soc. Chim.* Paris (3), 98 (1865); *Bull. Acad. Roy. Belg.* **19**, 551 (1865).

[16b] A. Kekulé, *Ann.* **137**, 129 (1866).

[16c] A. Kekulé, "Lehrbuch der organischen Chemie," Vol. 2. Enk, Erlangen, 1866.

[17] All of Kekulé's writings and speeches have been reprinted and collected by his biographer R. Anschütz, "August Kekulé," Vol. II. Verlag Chemie, Berlin, 1929.

[18] Kekulé's intent was to define the structure of those compounds designated in the compositional sense as aromatics.[19] On the contrary he was misunderstood as establishing relatively narrow structural limits for the aromatic species,[20,21] and criticized soundly for it.[20]

[19] A. Kekulé, *Z. Chem.* 3, 214 (1867).

[20] E. Erlenmeyer, *Ann.* **137**, 327 (1866).

[21] R. Fittig, *Ann.* **141**, 129 (1866).

[22] Translation taken in part from W. Baker, *in* "Perspectives in Organic Chemistry" (A. Todd, ed.), p. 28. Wiley (Interscience), New York, 1956.

[23] A. Kekule, *Ber.* **23**, 1302 (1890); Kekulé's delightful and fanciful description of the animated dreams leading to his structure for benzene has been nicely rendered in translation by O. T. Benfey, *J. Chem. Educ.* **35**, 2 (1958).

remaining valences were designated for bonding to atoms external to the six carbon nucleus. Three conceptually equivalent but graphically different symbols (**18**, **19**, **20**) were used to portray these ideas in Kekulé's early papers.[24, 25]

For the parent aromatic, benzene, all express the notion that the six core carbons are chemically equivalent as are the externally oriented six hydrogens. Kekulé considered an alternative triangular arrangement of atoms, **21**, which contains two different kinds of carbon and hydrogen. Hydrogen bonded to a

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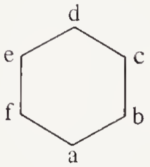

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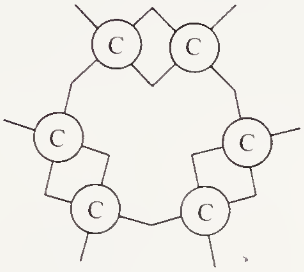

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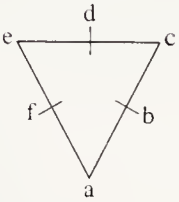

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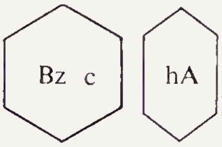
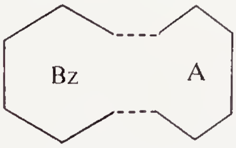
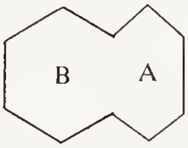
[24] The dots in roll-formula **18** refer to the six available carbon valences, while the arrows indicate bonding between end carbons to give a ring. This symbolism is of the same variety used by Kekulé in his discussion of the structure of carbon compounds.[4] Atoms with different valences were represented as different sizes.

[25] There is some question as to whether the cyclic formula for benzene, particularly the hexagonal form, was entirely original with Kekulé. Anschütz argues that Kekulé never read or discussed Loschmidt's work prior to developing his own theory, but mentions that he was introduced briefly in an offhand fashion to the Loschmidt formulas.[26] Although Anschütz's opinion is difficult to counter, Kekulé's first paper on the benzene theory[16a] footnotes the statement "... a closed chain which contains six free affinities" with a long discussion on the roll-and-ball formula. Kekulé comments that the latter are "preferable to the recently suggested modifications proposed by Loschmidt and Crum Brown." No citations are given. Furthermore Kekulé's classic paper[4] on the tetravalence and chain forming capacity of carbon also contains a revealing and important footnote. He cites a paper of the previous year by A. Laurent. In it the hexagon is used for the first time in print to illustrate a chemical reaction, that between benzoyl chloride (Bz c) and ammonia (hA). (This is probably the first depiction of a transition state as well, albeit an unwitting one.)





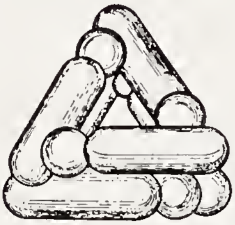


Kekulé had, therefore, previously seen the hexagon in a chemical context.[27]

[26] *Ostwalds Klassiker Exacten Wiss.* **190**, 105 (1913).

[27] O. T. Benfey and L. Fikes, *Advan. Chem. Ser.* **61**, 122 (1966).

corner carbon was positioned external to the triangle, while protons bonded to edge carbons were placed within the figure and thus chemically "less accessible." Kekulé favored **19** over **21**, comparing isomers of known di- and trisubstituted benzenes with those theoretically possible. It is amusing to note that **21** in current structural terms corresponds to all-trans cyclohexatriene, an unknown hydrocarbon with little potential for existence. This brings up a fundamental point. Kekulé at this stage in his thinking made the popular distinction between physical and chemical atoms. The latter represented atoms of the real world, while the former were mental constructs designed to illustrate theoretical and bonding relationships. Thus, structures **18**, **19**, **20**, and **21** employed the physical atoms and were not intended to portray three-dimensional atomic arrangements, but only bond type and number. Nonetheless Kekulé's early architectural training predisposed him to think in spatial terms. Two alternative three-dimensional stacking patterns (**22**, **23**) for the "physical" roll and ball atoms of the benzene formula are found in a footnote of his text.[16c] They express the closed-chain feature of the molecule and anticipate Kekulé's concern for the spatial disposition of atoms.



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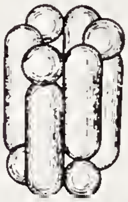

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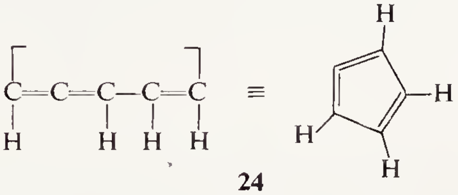
Thus, both Kekulé and Loschmidt saw the benzene nucleus as the basic building block for aromatic substances and both formulated it as a carbocyclic structure. Unlike Loschmidt, however, Kekulé developed a hypothesis which explained not only structural isomerism, homologation, and the chemical properties of mixed aliphatic–aromatic types, but also the nagging question of position isomerism for polysubstituted benzenes. In addition, a plausible proposal concerned with details of atomic relationships for the long recognized six-carbon aromatic unit was presented. The idea of aromaticity consequently advanced from the semistructural exposition of Loschmidt to a thoughtful and partially defined structural thesis as outlined by Kekulé.

B. EMIL ERLENMEYER: A CHEMICAL BASIS FOR AROMATIC CHARACTER

The nuclear six-carbon–six-hydrogen structural basis for aromatic substances was short lived. In the same issue of *Leibig's Annalen der Chemie* that contains the German translation of Kekulé's benzene theory (1866), Emil

Erlenmeyer, though in accord with the benzene structure, attacked the notion that the definition of aromatic compounds could be limited to those with a six-carbon base.[20] In part he was encouraged by an incorrect report of Ludwig Carius claiming the synthesis of an aromatic acid,[28] $C_6H_4O_2$, which required a hydrocarbon base of composition C_5H_4. Kekulé's case of a symmetry-rule device for carbon–carbon bond sequences was taken to its extreme. First, Erlenmeyer generalized the C_6A_6 nucleus to the empirical formula $C_{2n}H_{2n}$, all derivatives of which were supposed to possess an equal number of double and single bonds. Thus, benzene represented the parent substance of only one of a series of aromatics, all of which could be generated in principle by the polymerization of acetylene.[29]

Erlenmeyer next considered aromatic hydrocarbon bases derived from an uneven number of carbon atoms. Specifically, the five-carbon base from Carius' $C_6H_4O_2$ acid was assigned a cyclic allene-like structure **24** from the corresponding symmetry rule: 2/2, 2/2, 1/1, 2/2, 1/1.[30]



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The alternation of single and double bonds was thus seen as an unnecessary requirement for aromatic bases with an unpaired number of carbons. Provisionally, aromatic bases were then defined as "all hydrocarbons in which the number of double bonds is greater than or equal to the number of single bonds." The $C_{2n}H_{2n}$ series as well as several examples from the C_nH_m combination ($n \geqslant 3$ and odd; $m < n$ and even) were cited as candidates. Erlenmeyer explored the other extreme and indicated how any compound containing at least one double bond, that is, any olefin, should also be considered an aromatic base. The absurdity of such a classification was apparent to Erlenmeyer. He saw three alternatives. The least desirable was the broadening of the use of the term aromatic to include alkenes. Favoring the second, he claimed that the specification "aromatic" was unscientific and that this word, the term aliphatic,[31] and

[28] L. Carius, *Ann.* **136**, 336 (1865); **140**, 322 (1866); **148**, 50 (1868). Two other groups also claimed isolation of an acid with composition $C_6H_4O_2$: W. de la Rue and H. Müller, *Ann.* **120**, 339 (1861); A Fröhde, *J. Prakt. Chem.* **80**, 344 (1860).

[29] This appears to be the earliest consideration of cyclobutadiene and cyclooctatetraene as molecular entities, and aromatic ones at that. Initial structural assignments of pyrrole and furan derivatives as cyclobutadienes may have derived from Erlenmeyer's speculations; cf. H. Limpricht, *Ber.* **2**, 211 (1869) and H. Schiff, *Ann.* **6** (Suppl.), 1 (1868).

[30] Once again, it is important to recall that structures were meant to convey only valence relationships; strain, conformation, etc., were concerns that developed later.

[31] The commonly used German term "Fettkorper" has been translated as aliphatic.

the distinction between the two should be dropped. In its stead, Erlenmeyer proposed a rational classification of hydrocarbons based on the rule C_nH_{2n-m} where $m = -1, 0, +1 \ldots n-1$ for each n. For any given number of carbons, variable m thus provides a high, intermediate, and low saturation series.[32] The third and related possibility was quickly adopted by chemists in general and its ramifications are still felt today. In Erlenmeyer's words:

> If the expression "aromatic" is to be given a scientific meaning, it must be applied to all those substances which are related in a *chemical sense* as is the case for the earlier so called aromatic compounds.[33]

The concept of aromaticity consequently became identified with the unique stability of the phenyl group and its distinct preference for reacting by substitution rather than addition. This development can be attributed as much to Erlenmeyer's analysis as to Kekulé's failure to explain why his benzene structure did not visually explain the difference in reactivity between typical unsaturates and the phenyl core. The disposition of the fourth carbon valence for benzene became the focus of a lively controversy, the detailed resolution of which awaited the application of quantum mechanics in the 1930's.

C. PLANAR, HEXAGONAL, NONOSCILLATING BENZENE

For several reasons it is instructive to follow Kekulé's changing views on the benzene problem. By 1867, the concept of unsaturation and its formula expression as double and triple carbon–carbon linkages were relatively well developed. At this time the spatial orientation of atoms in molecules was receiving more attention by Kekulé. In a paper on the structure of mesitylene,[34] predating van't Hoff and Le Bel by 7 years, he suggested the use of tetrahedral carbon models for depicting carbon in varying stages of unsaturation. He noted that although Hofmann's planar models were sufficient for showing single and double bonds, only the tretrahedral version could accommodate triple bonding as well. A careful reading of this paper leaves the impression that Kekulé was equivocal on whether planarity could be attributed to the real benzene molecule, although he recognized that both square planar and tetrahedral carbon could generate a planar benzene ring (in the physical atom sense). In addition, it is clear that the *shape* of the planar figure defined by the twelve atoms of "chemical" benzene, in turn related to carbon–carbon and carbon–hydrogen bond angles and bond lengths, received no explicit attention. In his discussion

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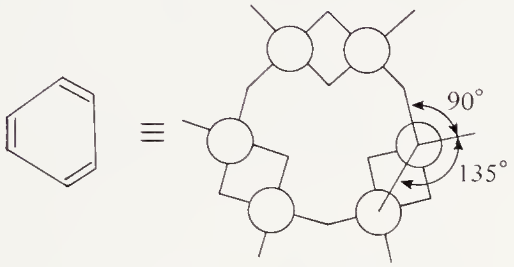
[32] For example, for $n = 6$, $m = -1$ corresponds to normal hexane; $m = 3$, to benzene; and $m = 5$, to 1,3,5-hexatriyne.

[33] E. Erlenmeyer, *Ann.* **137**, 344 (1866); italics added.

[34] A. Kekulé, *Z. Chem.* **3**, 214 (1867).

on the utility of models for picturing atomic bonding relationships, mesitylene (**25**) is printed with square planar carbon, while the application of tetrahedral carbon to the aromatic nucleus is suggested (**26**). In both cases, although the twelve-atom system is planar as mentioned, neither representation furnishes a regular hexagonal superstructure. Carbon–carbon single bonds are longer than carbon–carbon double bonds, while carbon–hydrogen angles are 90° and 135° in **25** and 110° and 130° in **26**. Furthermore, the ring periphery in symbol **25** encompasses more surface area, than the periphery in formula **26**, if carbon valences of the same length are used for the models as proposed by Kekulé.



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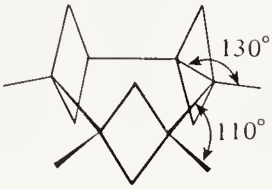

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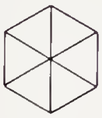
In summary, even though a hexagonal shape for benzene (**19**) was evident in Kekulé's earlier papers and his thinking gradually developed a concern for the third dimension, his reflections of 1867 are vague with respect to the planarity of the "chemical" carbon molecule and completely unexpressed regarding its shape. As we shall see, both are ultimately clarified in a classic paper published in 1872.

Kekulé's first published mention of the uncertainty associated with three alternate olefinic bonds in a six-membered ring appears in a note[35] in 1869 followed by the full paper[36] in 1872. This is his last and most definitive statement on the benzene structure. Attention was drawn to the proposals of Claus



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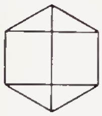

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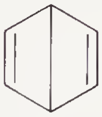

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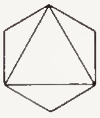

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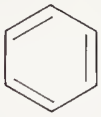

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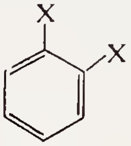
[35] A. Kekulé, *Ber.* **2**, 362 (1869).
[36] A. Kekulé, *Ann.* **162**, 77 (1872).

(**27**), Ladenburg (**28**), Wichelhaus and Stadeler (**29**),[37] the symmetrical figure **30**, and the original cyclohexatriene form **31**. Other formulations were considered to be composites of those shown. Kekulé revealed that symbols **27** and **28** were considered by him for some time but, in the final analysis rejected in favor of **31**. He defended his choice on chemical grounds. Structure **31** best explained the overall chemistry of benzene, acetylene trimerization, the dehydration of three moles of acetone to mesitylene, the formation of hexa-substituted addition products from benzene and halogens, and the relationship of benzene to naphthalene and anthracene. In addition, all structures except **31** led to the assumption that singly bonded carbon is broken in reactions which have no precedent in aliphatic chemistry, while **29** requires the equally facile cleavage of single and double carbon–carbon bonds.

In order to account for the nonexistence of two *ortho*-isomers expected from structure **31** (**32**, **33**), Kekulé made a proposal, which not unlike the fate of *para*-bonded benzene, the so-called "Dewar-structure,"[37] has been misrepresented in the literature and textbooks ever since. Appealing to results of the kinetic molecular theory and leaving the nature of the bonding forces unspecified, Kekulé provisionally equated valence with the relative number of near-neighbor collisions experienced by an atom during a given unit time. For example, a methane carbon was imagined to undergo four collisions with hydrogen while each proton suffered a single impact. Likewise, an acetylene carbon would presumably oscillate four times, colliding with its neighbor carbon three times and hydrogen once, within a given time interval. By applying this novel conception of valence to benzene, Kekulé was able to show that



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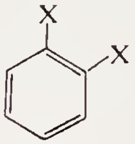

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[37] As has been elaborated by Baker[38] and Wheland[39] the misnamed "Dewar-structure" **29** was never proposed by Dewar as a possible alternative to the Kekulé benzene formula (**31**). In fact Dewar accepted **31** and considered his own work as support for it.[40] Kekulé confirmed this.[36] Dewar's listing of **31** as one of seven formal arrangements of six carbons and six hydrogens has inadvertently associated his name with a proposal, the adoption of which was independently championed by Städeler[41] and Wichelhaus.[42]

[38] W. Baker, *Chem. Britain* **1**, 191 (1965).

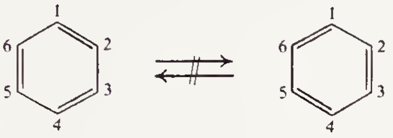
[39] G. W. Wheland, "Advanced Organic Chemistry," pp. 117–118. Wiley, New York, 1960.

[40] J. Dewar, *Proc. Roy. Soc. Edinburgh* **84** (1866–67).

[41] G. Städeler, *J. Prakt. Chem.* **103**, 106 (1868).

[42] H. Wichelhaus, *Ber.* **2**, 197 (1869).

the static structures **34** and **35** are artifacts, the average of which accurately represents the actual benzene molecule. Consider structure **34** and the collisons of C-1. During the first time interval it will collide twice with C-2, once with C-6, and once with hydrogen according to the sequence C-2, C-6, H, C-2. During the second unit of time the sequence is expressed by C-6, C-2, H, C-6, that is, structure **35**. In Kekulé's words[43]:



34 **35**

> The same carbon atom is thus doubly bonded to one of its carbon neighbors in the first time interval and doubly bonded to the other in the second time interval. The simplest average of all collisions of a carbon atom is given by periodic repetition of the sum of the collisions occurring during both time units. The average is: 2, 6, h, 2, 6, 2, h, 6. It is seen that each carbon atom collides equally often with its carbon neighbors, *bearing precisely the same relationship to both of them* (italics added).

That Kekulé is expressing an idea far more subtle than the commonly assumed equilibrium[44] of **34** and **35** follows from the analysis of Gero.[46] Whether any carbon–carbon bond in benzene is single or double depends on the point at which the counting of time is begun. This is illustrated for the C-1—C-2 and C-1—C-6 bonds of **34** and **35** in Fig. 4.

Time sequence 1	C-1—C-2				C-1—C-6				C-1—C-2					
C-1 collides with	C-2	C-6	H	C-2	C-6	C-2	H	C-6	C-2	C-6	H	C-2	C-6	C-2
Time sequence 2		C-1—C-6				C-1—C-2				C-1—C-6				

FIG. 4. Alternate counting sequences for vibrational collisions of C-1 in **34** and **35**. Bonds which are double during a given interval are specified either C-1—C-2 or C-1—C-6.

Clearly, when benzene appears as **34** according to time sequence 1, it appears as **35** according to time sequence 2. Since the start of the timing is arbitrary, it follows that Kekulé's collision hypothesis merely provides for an equivalence of all six carbon atoms and bonds at all times without identifying bonds as

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[43] A. Kekulé, *Ann.* **163**, 88–89 (1872).

[44] Although the notion of equilibrium, under development by C. M. Guldberg and P. Waage from 1864 to 1879,[45] is mentioned once by Kekulé in connection with the stability of the benzene nucleus, it is not invoked in that part of his rather lengthy paper[36] discussing the equivalence of **34** and **35**.

[45] A. J. Ihde, "The Development of Modern Chemistry," p. 408. Harper, New York, 1964.

[46] A. Gero, *J. Chem. Educ.* **31**, 201 (1954).

single or double between a given pair of adjacent carbon atoms at a particular moment. The arbitrariness of the time interval is avoided by doubling the period. Both measure one and two are then equivalent, C-1 colliding with C-2 and C-6 three times each. Obviously neither structure **34** nor **35** was intended by Kekulé in his 1872 paper[36] to completely describe the ground state of the benzene molecule. The average of the two achieves this in addition to attributing equivalent partial single and double bond character to each carbon–carbon bond on the ring. Remarkably, Kekulé's view anticipates the near equivalent electronic description of resonance theory by a little more than half a century.[47] That Kekulé in fact recognized **34** and **35** as approximate descriptive devices for the aromatic nucleus is evident from the following sentence. "If this concept or a similar one should prove correct, it follows that this difference is only apparent but not real."[43]

In accord with the reflections described above, Kekulé's position on the three dimensional structure of benzene was finally clarified. Benzene was depicted as a regular hexagon (**34** and **35**), and explicitly regarded as containing "symmetrical bonds" derived from the "six available affinities equally divided among the six ring carbons."[48] Furthermore, the planarity of the atomic assemblage in the chemical sense is clearly posited:

> It must be assumed that the atoms in a polyatomic molecule are so ordered in space that all attractive forces can be satisfied to the highest possible degree. The ordering of many atoms in a plane was not ruled out but appeared at first to be of little probability. On further reflection, however, one is led to ascribe a greater likelihood to a regular arrangement of the six carbon atoms in space. The thoughts expressed by **34** thus correspond to a planar arrangement as intimated earlier by my suggested use of models.[34,49]

Kekulé's benzene theory was thus completed as was his transformation from the traditional stance of considering atoms only in their imaginary or physical sense.[50]

The final Kekulé benzene structure has been confirmed in all its geometrical aspects by modern spectroscopy[51] although *ortho*-substituted[52] and fused

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[47] All the more remarkable are Kekulé's discourses on the benzene structure when it is realized that the electron's existence was not demonstrated until 25 years later by J. J. Thomson, *Phil. Mag.* **44**, 293 (1897).

[48] A. Kekulé, *Ann.* **162**, 79 (1872).

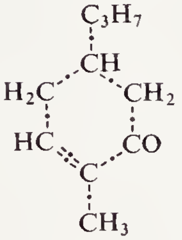
[49] A. Kekulé, *Ber.* **2**, 82 (1869).

[50] For a brief discussion of the unique development of Kekulé's preoccupation with the spatial relationship of atoms see Hein.[10]

[51] X-Ray diffraction: E. G. Cox, *Proc. Roy. Soc.* A**135**, 441 (1932), H. Mark, *Ber.* **57**, 1820 (1929); electron diffraction: L. Pauling and O. Brockman, *J. Chem. Phys.* **2**, 867 (1934); infrared and Raman spectroscopy: W. R. Angus, C. R. Bailey, J. B. Hale, C. K. Ingold, A. H. Leckie, C. G. Raisin, J. W. Thompson, and C. L. Wilson, *J. Chem. Soc.* pp. 912, 915, 925, 931, 941, 955, 966, 971 (1936).

[52] The halogen atoms of *o*-dibromobenzene were shown by electron diffraction to be out of the ring plane by O. Bastiansen and O. Hassel, *Acta Chem. Scand.* **1**, 489 (1947).

derivatives[53] which deviate from planarity for steric reasons are commonly encountered. His pictorial representation **34** has also been generally retained by chemists as most convenient for picturing the aromatic nucleus, though it must be used with the usual reservations. In spite of the historical success of Kekulé's benzene theory and its immediate and profound impact on the development of aromatic chemistry in general and the dye industry in particular,[54] the gross electronic and geometrical structure of benzene has been the subject of considerable debate even into the 1960's (see Fig. 5, footnote *o*). Kekulé himself felt that the final word on the matter would have to be decided by experiment.[35,36] This perhaps explains why he published no further speculations on the matter, and in a series of about forty papers on aromatic substances from 1865 to 1888 the hexagonal figure appears in only nine of those papers. Until 1869 he employed empirical and type formulas for the most part, abandoning the latter around 1870. In a succession of four papers on terpenes in 1873,[55] formulas such as **36**, **37**, and **38** appear without comment and do not appear in subsequent work.



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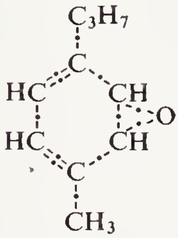

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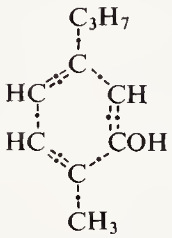

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The detail which stimulated the greatest anxiety about the accuracy of structure **31** and that which eluded Kekulé as well was the failure of this representation to verify the well-known chemical immutability of aromatic compounds and corresponding differences between them and the olefins. Consequently, almost immediately following the appearance of the initial Kekulé paper (1865), alternative formulas were advanced. All three geometrical forms conforming to the symmetry properties of benzene, the hexagon, triangular prism, and octahedron, were offered and subsequently rejected. Some of these are shown in Figs. 5–7. The intriguing story of the various proposals and counterproposals and the puzzles they presented has been told elsewhere.[56]

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[53] C. A. Coulson, *in* "Theoretical Organic Chemistry," p. 49. Butterworths, London, 1959; G. Ferguson and J. M. Robertson, *Advan. Phys. Organ. Chem.* **1**,35 (1963).

[54] D. H. Wilcox, Jr., *Advan. Chem. Ser.* **61**, 24 (1966).

[55] A. Kekulé, *Ber.* **6**, 437, 929, 934, 1087 (1873).

[56] For a particularly lucid and contemporary account up to 1899, see A. Lachmann, "The Spirit of Organic Chemistry," Ch. 3, The MacMillan Co., New York, 1899; V. Schelar, *Advan. Chem. Ser.* **61**, 163 (1966); A. Sementsov, *Advan. Chem. Ser.* **61**, 72 (1966); G. W. Wheland, footnote 39, pp. 55–73, 85–135; C. K. Ingold, "Structure and Mechanism in Organic Chemistry," pp. 156–162. Cornell University Press, New York, 1952.

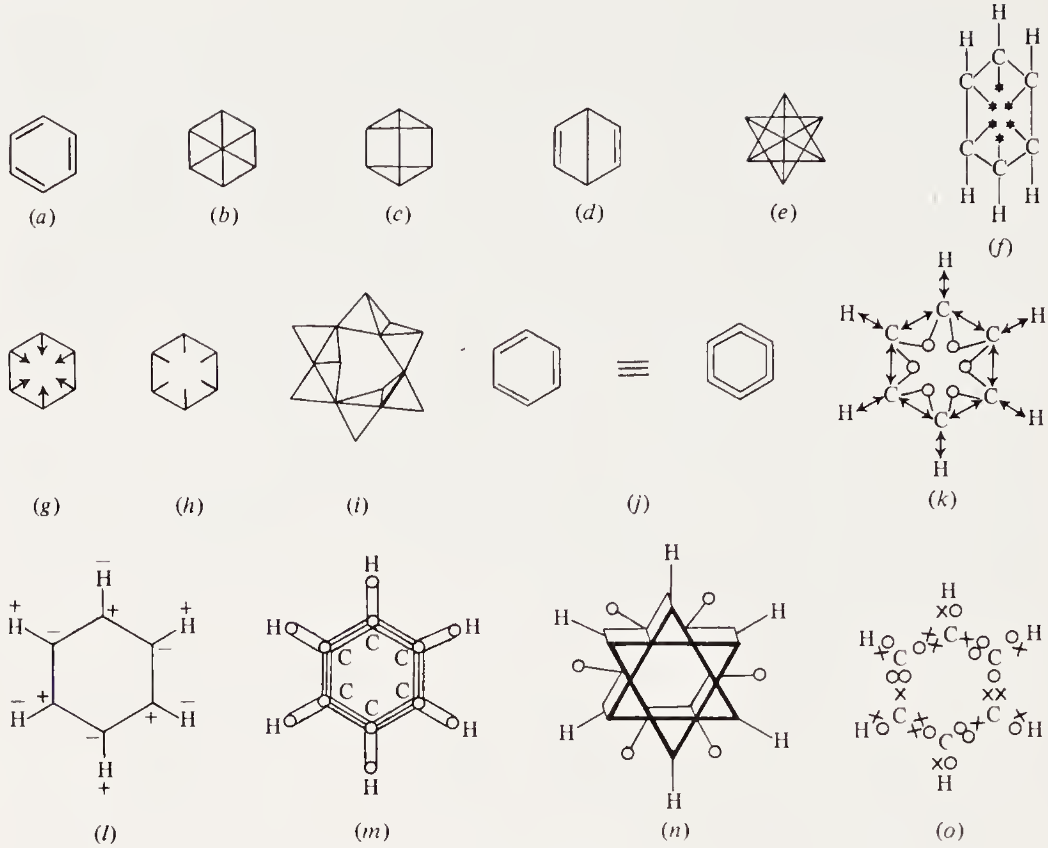


FIG. 5. Proposals for planar benzene.

Key to letters (note chronological order):

(*a*) Kekulé 1865 (see footnotes 35 and 36).

(*b*) A. Claus, "Theoretische Betrachtungen und deren Anwendung zur Systematik der organischen Chemie," p. 208. O. Hollander, Freiberg, 1867; A. Claus, *Ber.* **15**, 1405 (1882); *J. Prakt. Chem.* [2], **37**, 455 (1888).

(*c*) Claus [see (*b*)]; A. Ladenburg, *Ber.* **140**, 272 (1869).

(*d*) Städeler (see footnote 41); Wichelhaus (see footnote 42).

(*e*) Ladenburg [see (*c*)].

(*f*) L. Meyer, "Modern Theorien in der Chemie," 2nd ed., 1872; cited by A. Ihde,[1a] p. 316.

(*g*) H. Armstrong, *J. Chem. Soc.* **51**, 258 (1887).

(*h*) A. Baeyer, *Ann.* **245**, 106 (1888).

(*i*) E. Marsh, *Phil. Mag.* **26**, 426 (1888); cf. C. Graebe, *Ber.* **35**, 526 (1902).

(*j*) J. Thiele, *Ann.* **306**, 87 (1899).

(*k*) H. Kaufmann, *Physik. Z.* **9**, 318 (1908); The symbol ↔ represents a two-electron bond; the symbol ⌒o is a partially dissociated valence electron.

(*l*) H. Fry, *J. Am. Chem. Soc.* **36**, 248 (1914).

(*m*) J. J. Thomson, *Phil. Mag.* **27**, 757 (1914); Each carbon–carbon bond is a three-electron bond.

(*n*) E. C. Crocker, *J. Am. Chem. Soc.* **44**, 1618 (1922); Carbon–carbon bonds are three-electron bonds.

(*o*) J. W. Linnett, *Am. Scientist* **52**, 459 (1964); Carbon–carbon bonds are three-electron bonds; cf. H. Kauffman, "Die Valenzlehre," p. 535. Enke, Stuttgart, 1911.

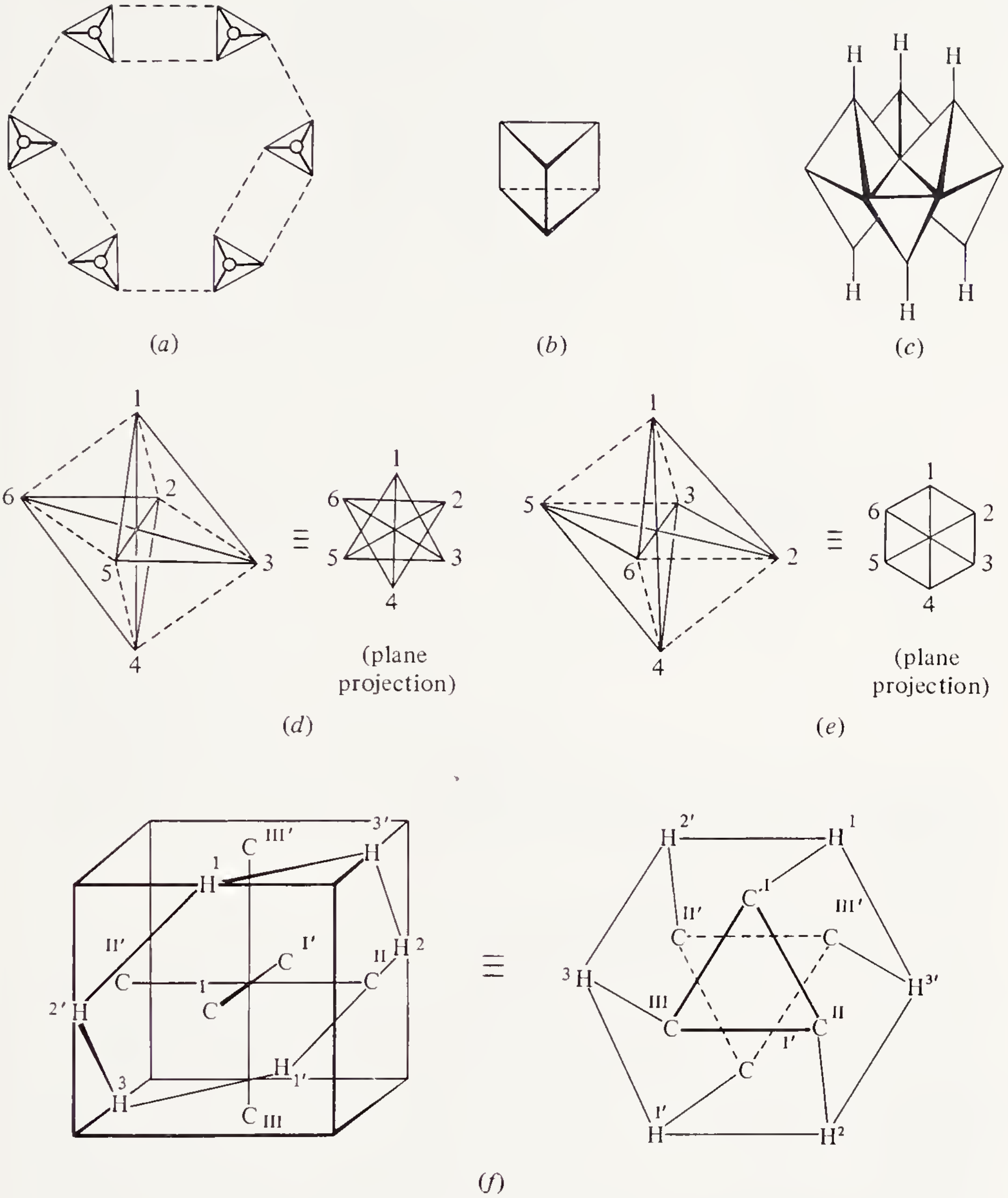


Fig. 6. Proposals for nonplanar benzene.

Key to letters:

(*a*) M. Rosenstiehl, *Bull. Soc. Chim.* Paris **11**, 385 (1869); The small round circles represent hydrogen atoms above the plane of the paper at the apex of the indicated tetrahedra.

(*b*) A. Ladenburg, *Ber.* **140**, 272 (1869).

(*c*) W. Körner, *Giorn. Sci. Nat. Ed. Econ.* **5**, 241 (1869) [abstracted by *J. Chem. Soc.* **29**, 241 (1876)]; *Gaz. Chim. Ital.* **4**, 444 (1874); W. Vaubel, *J. Prakt. Chem.* **44**, 137 (1891); cf. M. L. Huggins, *J. Am. Chem. Soc.* **44**, 1607 (1922).

(*d*) R. Meyer, *Ber.* **15**, 1823 (1882).

(*e*) J. Thomsen, *Ber.* **19**, 2944 (1886).

(*f*) G. Herrmann, *Ber.* **21**, 1949 (1888).

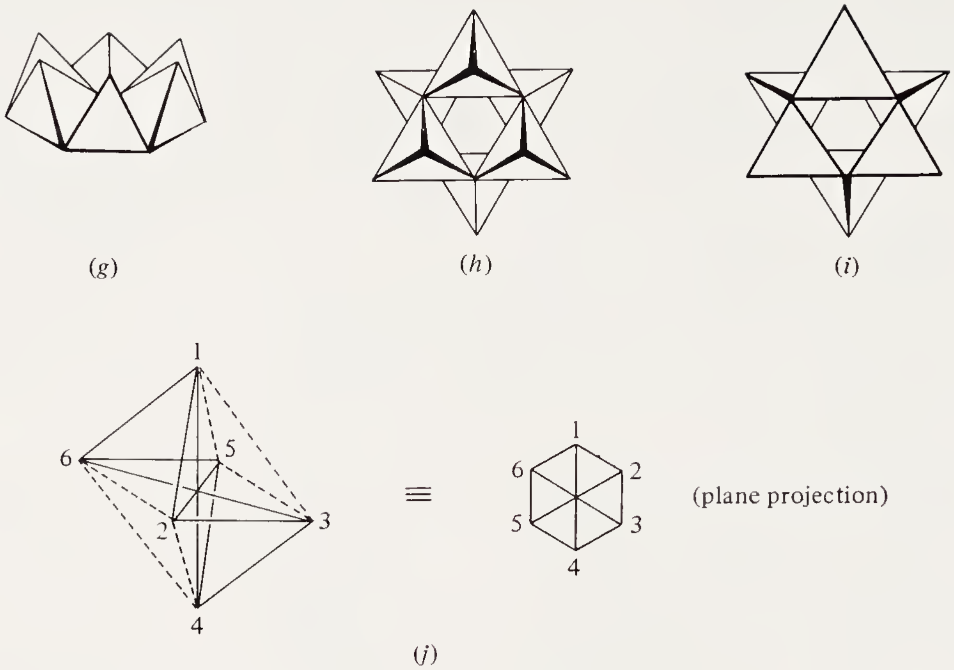


FIG. 6—*continued*

(*g*) E. Marsh, *Phil. Mag.* **26**, 426 (1888); cf. C. Graebe, *Ber.* **35**, 526 (1902); A. Baeyer, *Ann.* **245**, 123 (1888); J. Loschmidt, *Monatsh.* **11**, 28 (1890).

(*h*) H. Sachse, *Ber.* **21**, 2530 (1888); figure taken from V. Schelar, *Advan. Chem. Ser.* **61**, 167 (1966).

(*i*) J. Thiele, *Ann.* **319**, 136 (1901).

(*j*) S. A. Sworn, *Phil. Mag.* **28**, 402, 443 (1889).

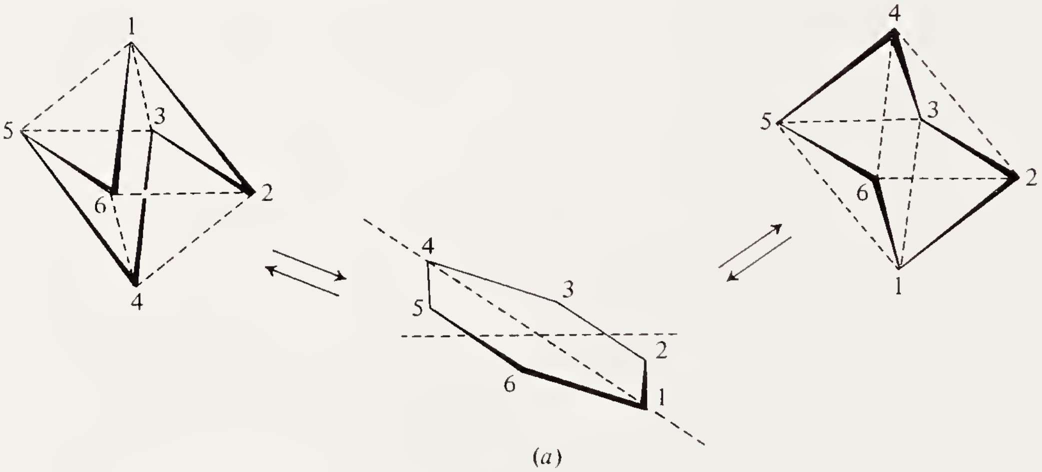
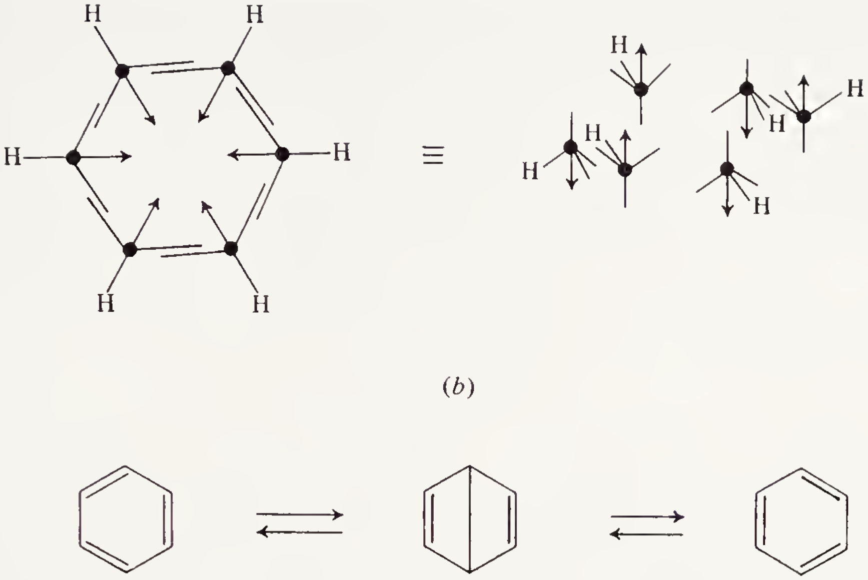


FIG. 7. Proposals for dynamic benzene.

Key to letters:

(*a*) J. N. Collie, *J. Chem. Soc.* **71**, 1013 (1897); **109**, 561 (1916); analogous to the chair–chair interconversion of a distorted cyclohexane.



(*b*)

(*c*)

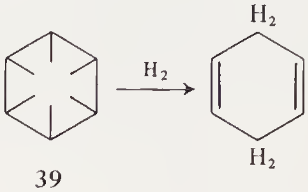
FIG. 7—*continued*

(*b*) A. Weinberg, *Ber.* **52**, 928 (1919).
(*c*) C. K. Ingold, *J. Chem. Soc.* p. 1133 (1922).

IV. Eugen Bamberger and the Hexacentric Theory

The concept of aromatic character survived the preelectron period essentially, unaltered as a chemical criterion. From the mid 1860's to the turn of the century, its base was broadened as annelated benzenes and fully unsaturated heterocycles came to be considered members of the aromatic class. Naturally, the structures proposed for benzene were applied to these systems; the Ladenburg prism, Claus diagonal, Meyer-Baeyer-Armstrong centric, and Kekulé structures proving most popular. However, two noteworthy attempts to identify the unique stability of the aromatic type with a structural feature of the unsaturated cyclic nucleus were made by Eugen Bamberger and Johannes Thiele in 1890 and 1899, respectively. While neither claim successfully encompassed all the known facts and thus never enjoyed full acceptance by chemists, both contain germs of the ideas that have since been generated by the study of wave mechanics. These proposals furthermore enkindled the old idea that aromaticity might find its *raison d'être* in structural terms. Unlike the short-lived carbon cycle criterion for aromatic compounds proferred by Kekulé, the Thiele-Bamberger axioms are concerned with the subtler question of bonding.

Bamberger preferred the ill-defined Meyer-Baeyer-Armstrong centric formula[57–59] (e.g., **39** and **40**) for aromatic substances.



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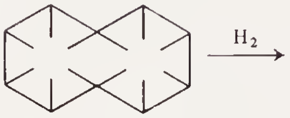

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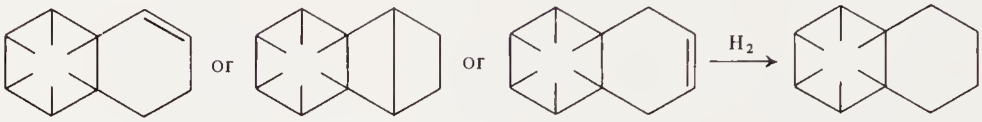

He characterized the central "affinities" or valences as "potential" bonds which were conceived to be held in "a condition of mutual compensation" or equilibrium by unspecified forces analogous to magnetic attraction.[60] The key to aromatic character was thought to be in the assumption that a centric system was possible only if each aromatic ring contained *six* of the potential valences. The transformation of an aromatic substrate into a non-aromatic one was accordingly rationalized as occurring by a perturbation which disrupted the centrally balanced valences. For example, the addition of hydrogen to benzene under the appropriate conditions was formulated as the pairwise saturation of two of these valences with concomitant conversion of all potential bonds into real ones.

Partial hydrogenation of naphthalene, sandwiched between benzenoid and aliphatic systems in chemical behavior, appeared to provide elegant support for this hypothesis. Thus, hydrogen addition at carbons 1, 2, 3, and 4 or at any of the possible pairs not only actuates bonding at these positions but also saturates positions 9 and 10, promoting ring closure to the stable benzene system. Bamberger expressed his views on aromatic character as follows:

> The valences in the centric system are found in a peculiar state which can be characterized as potential bonding. This particular valence condition is responsible for the characteristic "aromatic" properties. Furthermore I believe that Armstrong and Baeyer by introducing this perfect new notion have for the first time provided the essentials for the definition of the "aromatic body." Neither ring formation nor the manner in which the carbon bonds are grouped is responsible for aromatic behavior; only the potential of the valences. This central condition which appears to exist only in a

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[57] L. Meyer, "Modern Theorien in der Chemie," 2nd ed., 1872; cited by A. Ihde,[1a] p. 316.

[58] H. Armstrong, *J. Chem. Soc.* **51**, 258 (1887).

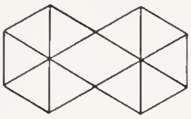
[59] A. Baeyer, *Ann.* **245**, 106 (1888).

[60] E. Bamberger, *Ann.* **257**, 1 (1890).

> system of six reciprocally directed bonding forces, will be destroyed by each equilibrium disturbance which the system experiences.[60]

In later papers: "A centric potential valence system can exist only if hexacentric."[61–63]

To emphasize the necessity for potential bonds in the aromatic nucleus, Bamberger rejected the Claus-type formulation for naphthalene (**41**) since it contained only "actual" bonds.



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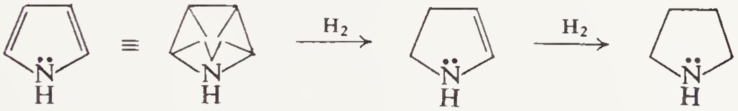
It is not surprising that chemists were unsatisfied with the vague Meyer-Baeyer-Armstrong formulation presented anew in imprecise terminology. Nonetheless Bamberger scored a remarkable but unheralded triumph in the consistent application of his hexacentric principle to five-membered heterocyclic rings. The well-studied chemical behavior of pyrrole (**42**) exhibited two anomalies difficult to rationalize. In the first place, the ring nitrogen is weakly basic, difficult to quaternize, and generally atypical when compared to other amines. Second, the hydrogenation of pyrrole leads in a discontinuous fashion to pyrroline (**43**) and pyrrolidine (**44**) which behave as typical amine derivatives. In this connection Bamberger drew the analogy with heat of hydrogenation studies on benzene and thiophene. The introduction of the first mole of hydrogen proceeds with an unusually high enthalpy value, while addition of the second and third moles corresponds quite closely to that for normal olefins. He expected similar behavior for pyrrole and the chemically related indole system. The natural explanation of these observations for Bamberger rested in attributing the five-membered ring with six potential valences (**42b**). To accommodate the aromaticity of pyrrole in this manner, however, Bamberger was forced to assume a pentacovalent character for nitrogen.[62] This was a bold and innovative assumption since nitrogen was known to be trivalent in amines and tetravelent in its salts, but never pentavalent. Nonetheless, one was able to



42a **42b** **43** **44**

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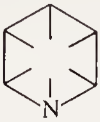
[61] E. Bamberger, *Ann.* **257**, 47–48 (1890).
[62] E. Bamberger, *Ber.* **54**, 1758 (1891).
[63] E. Bamberger, *Ann.* **273**, 373 (1893).

understand why pyridine (**45**) had the basic properties of a tertiary amine while pyrrole was only very weakly basic. The former was considered to be capable of forming a hexavalent group without employing the salt-forming valences of its nitrogen atom, while the latter could do so only by utilizing all its nitrogen valences. Bamberger wrote analogous formulas for the less well-studied systems thiophene (**46**), furan (**47**), imidazole (**48**), selenazole (**49**), thiazole (**50**), and many other similarly constituted heterocycles.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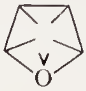
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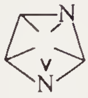
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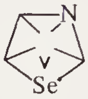
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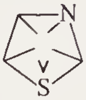
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Again, increased valence was necessitated, sulfur, oxygen, and selenium assuming a value of four. This point proved a serious pitfall for the hexacentric theory. While Kekulé equated vibrational collisions with valence, Bamberger was reduced to identifying valence with the as yet unknown electron. It was left unexplained why the additional central potential valences of nitrogen, sulfur, and oxygen did not show up in the chemistry of nonaromatic derivatives. Also, the magic of "six" in the centric expression never achieved substance beyond the hypothesis stage. These drawbacks, when combined with the uncertainties inherent in the Meyer-Baeyer-Armstrong centric formula, insured the obscurity of Bamberger's suggestions. Nonetheless, Bamberger deserves more credit than is generally afforded him. He recognized the speculative nature and obvious limitations of the hexacentric proposal, but accurately perceived that the known hydrocarbon and heterocycle aromatics were structural relatives in a bonding sense. The stability of different aromatic types was attributed to the sixfold character of the central valence unit, an imaginative idea in accord with current knowledge if electrons are substituted for valences in the Bamberger theory. Thus, the renowned Armit-Robinson "aromatic sextet,"[64] an identical but well-received proposal involving electrons instead of valences, was anticipated by 35 years. If the role of the electron in chemical bonding[65] had been recognized in 1890, the discrepancies in the hexacentric theory would have evaporated and the "rule of six" would certainly be associated with Bamberger's name today.

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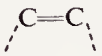
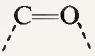
[64] J. W. Armit and R. Robinson, *J. Chem. Soc.* **127**, 1604 (1925).

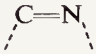
[65] The foundations of modern electronic theory were constructed by G. N. Lewis, *J. Am. Chem. Soc.* **38**, 762 (1916), W. Kössell, *Ann. Physik* **49**, 229 (1916) and I. Langmuir, *J. Am. Chem. Soc.* **41**, 868, 1543 (1919). See also G. N. Lewis, "Valence and the Structure of Atoms and Molecules." Chem. Catalog Co., New York, 1923.

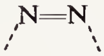
V. Johannes Thiele and the Theory of Partial Valence

The last major preelectronic attempt to explain the stability of the aromatic nucleus was made by Johannes Thiele in 1899. Thiele's thinking began with a rationale for the addition reactions of simple unsaturates.[66] Multiple bonds were attributed a "residual-affinity" or a "partial-valence" making them particularly susceptible to reaction with the appropriate addends. The notion that bonding is not completely developed in unsaturated units was expressed as illustrated, the dotted lines representing the partial bonding capability. The idea was extended to conjugated[67] systems as a way of explaining 1,4-addition.









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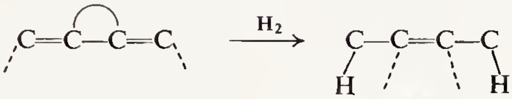

52 **53**

To indicate the reduced addition capacity of the internal sp^2 carbons, expression **51** was modified to **52**. Partial valences are neutralized with the formation of a new but "inactive" double bond. Addition of hydrogen, for example, to the ends of such a system then proceeded to give **53** whereby the "inactive" bond develops partial valences and corresponding olefinic behavior. Thiele subsequently applied this scheme successfully to a host of addition and reduction reactions [66,68] (Fig. 8). A few apparent exceptions to the rule of terminal addition were accepted as 1,4-additions followed by tautomerism. Neatly explained was the fact that only α,β-unsaturated acids are vulnerable to mild reduction, giving β,γ-unsaturated acids. 1,4-Elimination, addition to cross conjugated systems, the acidity of allylic hydrogen, and a number of other phenomena were also accommodated by the partial valence theory.[69]

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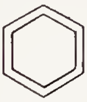

54a **54b**

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[66] J. Thiele, *Ann.* **306**, 87 (1899).

[67] The term "conjugation" was coined by Thiele.[66]

[68] J. Thiele, *Ann.* **308**, 333 (1899); **314**, 298 (1900); **319**, 121 (1901).

[69] It was soon realized that although Thiele's hypothesis could explain 1,4-addition when observed, the presence of conjugated multiple bonds did not require it.[70]

[70] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," pp. 653–654. Cornell Univ. Press, Ithaca, New York.

It should be clear that the chemical stability of benzenoid hydrocarbons could now be elegantly interpreted. The partial valences arising from the three double bonds in Kekulé's symbolism for benzene became completely saturated as pictured by **54a**. More important, Thiele recognized that "the three single bonds cannot be distinguished from the three double bonds. Benzene thus contains six equivalent inactive double bonds."[66] Both the stability and symmetry conditions imposed by the properties of benzene were therefore satisfied and alternately expressed by Thiele with structure **54b**.

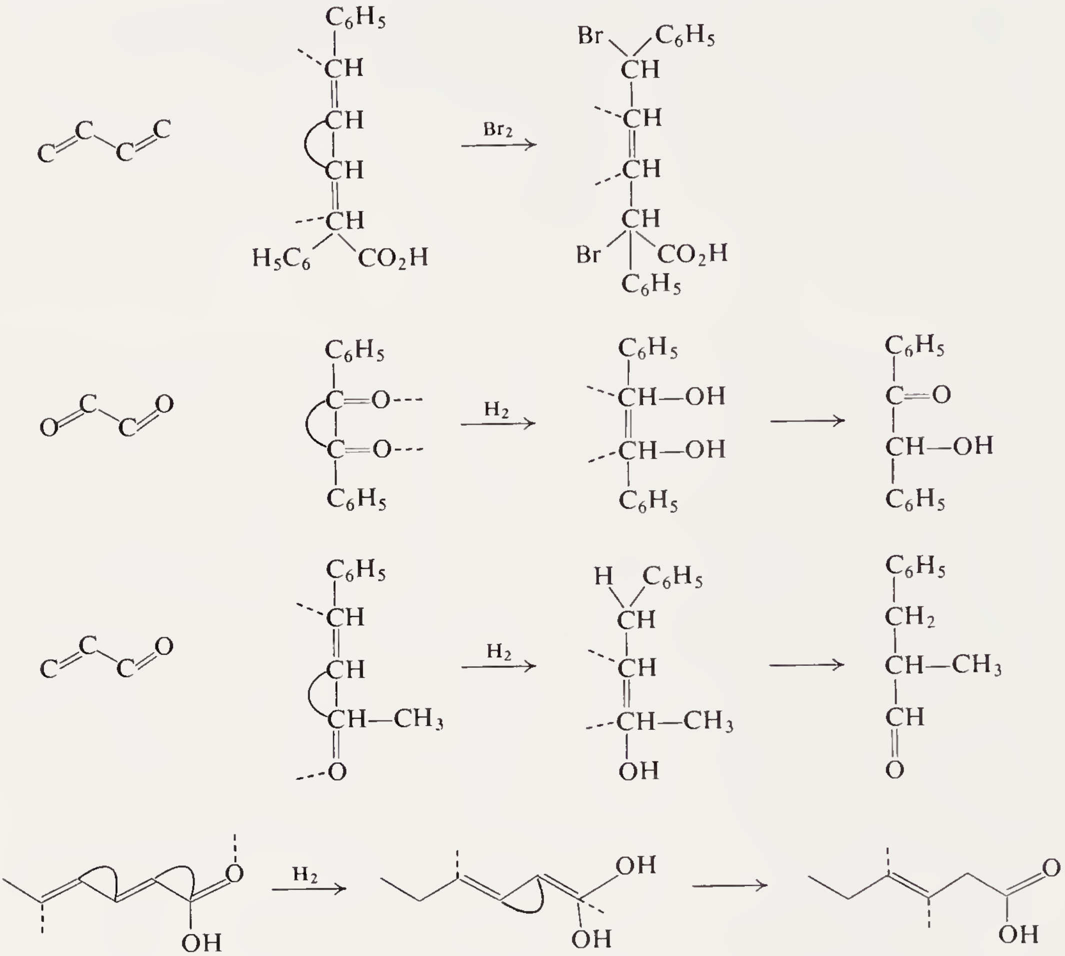
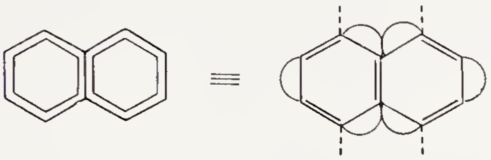


FIG. 8. 1,4-Addition reactions according to Thiele's theory of partial valence.

The preference for α-substitution in naphthalene also found resolution in Thiele's theory. The symmetrical structure **55** revealed that the two bridgehead sp^2 carbons are required to neutralize the partial valences of four α-carbon atoms. A net affinity of 0.5 was consequently assigned to the latter positions, accounting for the prevalence of 1-naphthalene isomers. The 9,10-



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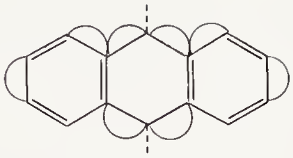
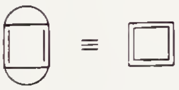


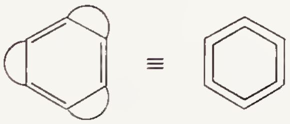
56

reactivity of anthracene (**56**) and other polycyclic aromatics was handled in an analogous fashion. Surprisingly, Thiele made no similar attempt to bring five-membered heterocycles into the family of aromatic substances. He justified this position on the grounds that while polyaza-heterocycles demonstrated benzene-like chemical behavior, the properties of simple monohetero substances, particularly pyrrole and furan, were of dubious aromatic quality.

Obviously the chemical criterion for aromaticity had been firmly established. Thiele interpreted his theory, as Bamberger and Kekulé regarded theirs, as a suitable solution to the question of the unique position of aromatics in the hierarchy of organic substrates. None intended that aromaticity be conceptualized on a structural basis, although Kekulé was misunderstood to have done so.[18] Thiele's hypothesis was initially well received since it provided for the first time an intelligible explanation for aromatic character. That the concepts necessary for understanding conjugated and unconjugated systems, including mono- and polycyclic aromatics, were developed outside the aromatic series, endowed them with exceptional merit. However, Willstätter's group sounded its death knell with their inability to synthesize cyclobutadiene,[71] and the finding that aromatic properties are totally absent in cyclooctatetraene.[72a,b] A fundamental principle of the Thiele hypothesis is that alternating single and double bonds in a cyclic hydrocarbon is a necessary and sufficient condition for aromaticity. Thus, the four- and eight-carbon cycles **57** and **58** along with



57a



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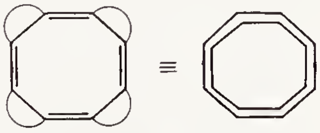
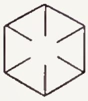


58a

57b



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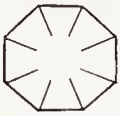

58b

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[71] R. Willstätter and W. von Schmaedel, *Ber.* **39**, 1992 (1905).

[72a] R. Willstätter and E. Waser, *Ber.* **44**, 3423 (1911).

[72b] R. Willstätter and M. Heidelberger, *Ber.* **46**, 517 (1913).

benzene were predicted to stand as the first three members of a $C_{2n}H_{2n}$ ($n = 2, 3, 4 \ldots$) aromatic series. The failure to confirm this prediction caused many supporters of the partial valence theory of Thiele to revert to the Meyer-Armstrong-Baeyer centric symbolism.[72a,73,74]

As evident much earlier, however, acceptance of the centric formula in practice meant only a recognition of the peculiar character of aromatic bonds. In itself the formula had no clear physical significance. The inadequacy of these formulas was aggravated by the fact that, like those of Thiele and Kekulé, they were unable to explain why cyclobutadiene (**57b**) and cyclooctatetraene (**58b**) should differ from benzene. Had Bamberger's identification of an aromatic system with a hexacentric distribution of potential valences been invoked, the puzzle associated with **57** and **58** would have found partial solution.[74]

VI. Summary

The manner in which aromatic compounds were classified up to 1915 changed several times. From 1800 to 1850, with the development of structure theory and accurate analysis, sensory categorization of aromatics gave way to a compositional classification. The initial attempt to place "aromaticity" on a structural basis was made by Loschmidt in 1861. His work was quickly followed in 1865 by the independent and far reaching proposals of Kekulé on the structure of benzene. In the following year, Erlenmeyer undercut the legitimacy of benzene as the structural unit responsible for aromatic behavior. He invoked chemical reactivity as the unifying determinant. Benzene consequently came to be considered the chemical standard by which aromatic behavior was measured, although its molecular and electronic structure took some 60 years to solve. The point of view that stability and reaction by substitution rather than addition is fundamental to the interrelationship of cyclic unsaturates has been persuasive and remains in use today.

Within this context, around the turn of the century Bamberger and Thiele made brilliant intuitive attempts to explain the reactivity of benzenoid and related compounds by exploring the nature of bonding within fully unsaturated

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[73] Centric structures **57b** and **58b** do not appear in Willstätter's work but are found in a comprehensive review on aromatic character by M. E. Vol'pin, *Russ. Chem. Rev.* (*English Transl.*) **29** (3), 129 (1960).

[74] Willstätter discussed the structure of cyclooctatetraene relative to benzene and naphthalene[72a] and considered the symbolism of Kekulé, Meyer-Armstrong-Baeyer, Claus, and Thiele. Likewise Bamberger's hydrogenation studies on naphthalene were cited to justify the aptness of the Meyer-Armstrong-Baeyer formula for benzenoid structures. Bamberger's failure to press the significance of his "hexacentric-axiom," however, is indicated by its absence in Willstätter's discussion.

rings. Both theories were premature, however, since the existence of the electron and its role in chemical bonding was yet to be recognized. Accordingly, the inadequacies of the Bamberger-Thiele postulates were rapidly exposed and the proposals fell into disfavor.

Between 1916 and 1920, Lewis, Langmuir, and Kossel formulated the electronic theory of valence. It was eagerly accepted and widely applied to bonding situations of all types. Shortly thereafter, the advent of quantum mechanics permitted a semiquantitative theoretical evaluation of electron–nucleus and electron–electron interactions. Both valence bond and molecular orbital theories gave satisfactory descriptions of the nature of the bonding in benzene. The latter theory provided additional insight which indicated that the exalted role of benzene as the model for aromaticity was overemphasized. Nonetheless, most chemists continued to acknowledge chemical criteria as central to this question. It is only recently that a revealing set of chemical syntheses and subsequent physical studies have stimulated a reevaluation of the grounds upon which the concept rests. In a later volume of the series these developments will be discussed and the historical survey of aromaticity brought to the present.

2

Biphenylenes

J. W. BARTON

I. Introduction

It is now a little over a quarter of a century since biphenylene (**1**) was first synthesized by Lothrop.[1] It was also obtained accidentally[2] at about the same time. After Lothrop's initial work on the structure of biphenylene,[1,3] only one other paper appeared in the first half of the twentieth century. Since then, however, the increased interest in concepts of aromaticity and related topics has led to the publication of more than 200 papers on biphenylene and its

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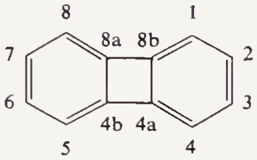
[1] W. C. Lothrop, *J. Am. Chem. Soc.* **63**, 1187 (1941).

[2] W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.* p. 487 (1941); W. S. Rapson, R. G. Shuttleworth, and J. N. van Niekerk, *ibid.* p. 326 (1943).

[3] W. C. Lothrop, *J. Am. Chem. Soc.* **64**, 1698 (1942).

derivatives. The present discussion deals mainly with recent work, as several reviews,[4] including a comprehensive one covering the literature up to 1964,[5] have already appeared.



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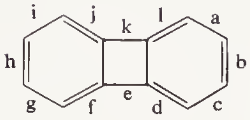


2

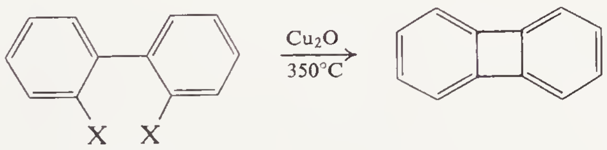
II. Nomenclature

Biphenylene (**1**) can be regarded formally as dibenzocyclobutadiene, but it is perhaps fortunate that this name has never been applied to the compound in view of the complete difference in chemistry of **1** and that of cyclobutadiene.[6] Prior to IUPAC approval of the name biphenylene, it was known as either diphenylene or cyclobutadibenzene. The accepted numbering of the nucleus is shown in **1** and the lettering used for the formulation of annelated derivatives in **2**.

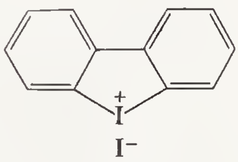
III. Reactions Leading to Biphenylenes

A. From Biphenyls

The most obvious way to produce a biphenylene derivative is by bridging a biphenyl at positions 2 and 2′. Lothrop[1] first accomplished this by heating 2,2′-dibromobiphenyl (**3a**) with cuprous oxide at 350°C and the method, using the diiodo compound **3b**, or the corresponding iodonium salt **4** which isomerizes to **3b** on heating, remains one of the best methods for the preparation.



3a X = Br
3b X = I



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[4] W. Baker and J. F. W. McOmie, *in* "Non-benzenoid Aromatic Compounds" (D. Ginsburg, ed.), Chapter 2. Wiley (Interscience), New York, 1959; J. F. W. McOmie, *Rev. Chim. Acad. Rep. Populaire Roumaine* 7, 1071 (1962).

[5] M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds," Chapters 10 and 11. Academic Press, New York, 1967.

[6] L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Am. Chem. Soc.* 88, 623 (1966).

The reaction bears an obvious similarity to the Ullman biaryl synthesis. Largely as a result of the systematic experiments conducted by Lothrop, it has been assumed that cuprous oxide is the effective dehalogenating agent. However, it has been shown recently[7] that some forms of copper powder are at least as effective as cuprous oxide. Certain samples of cupric oxalate have also given high yields of biphenylene.[8a,b] Many substituted and polycyclic biphenylenes have been synthesized in this manner and the method is of particular value where a derivative cannot be obtained via nuclear substitution into the parent, e.g., 1-nitrobiphenylene.[9] Other recent examples include methoxy,[10] methyl,[11] phenyl,[11] and dibenzo[12a,b] derivatives. Although the yields obtained are often low, the reaction seldom fails, except when a competing reaction predominates as in the reaction of 4-cyanobiphenylene iodonium iodide, which gives 4-iodofluorenone rather than 1-cyanobiphenylene.[13]

Other methods of bridging biphenyl include the treatment of the Grignard reagent from 2,2′-dibromobiphenyl with cupric chloride[2] and the demercuration of biphenylene mercury tetramer,[14] made by treatment of 2,2′-dilithiobiphenyl with mercuric chloride, with metallic silver at 300°C. Such procedures are lengthier and usually offer no advantage over the Lothrop synthesis.

B. By the Dimerization of Arynes

Biphenylenes are produced when arynes are generated under conditions in which they can dimerize. Of the many methods available[15] for the generation of benzyne (**5**) itself, it is found that those which avoid the use of strong nucleophiles and polar solvents give the highest yields of dimer.

The simplest of these methods involves the aprotic diazotization of anthranilic acid[16] to give benzenediazonium-2-carboxylate (**6**), which may then be decomposed into benzyne (**5**), carbon dioxide, and nitrogen by heating in an

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[7] J. C. Salfeld and E. Baume, *Tetrahedron Letters* **28**, 3365 (1966).

[8a] W. Baker, unpublished observations.

[8b] D. W. Lawson, J. F. W. McOmie, and D. E. West, *J. Chem. Soc.* (*C*), p. 2414 (1968).

[9] J. W. Barton and K. E. Whitaker, *J. Chem. Soc.* (*C*), p. 2097 (1967).

[10] J. M. Blatchly, J. F. W. McOmie, and M. L. Watts, *J. Chem. Soc.* p. 5085 (1962); W. Baker, N. J. McLean, and J. F. W. McOmie, *ibid.* p. 922 (1963).

[11] P. R. Constantine, G. E. Hall, C. R. Harrison, J. F. W. McOmie, and R. J. G. Searle, *J. Chem. Soc.* (*C*), p. 1767 (1966).

[12a] J. W. Barton, *J. Chem. Soc.* p. 5161 (1964).

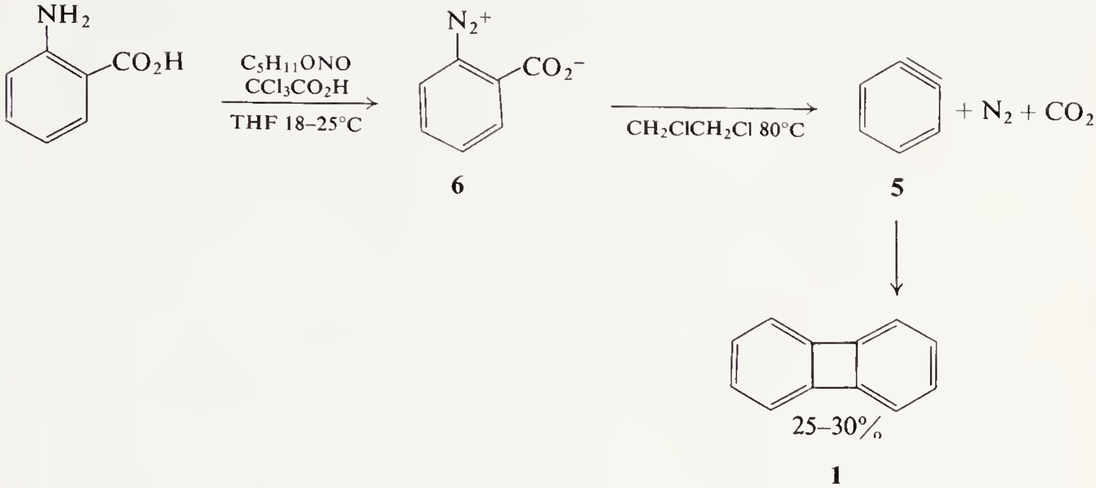
[12b] J. W. Barton, M. A. Rogers, and M. E. Barney, *J. Chem. Soc.* p. 5537 (1965).

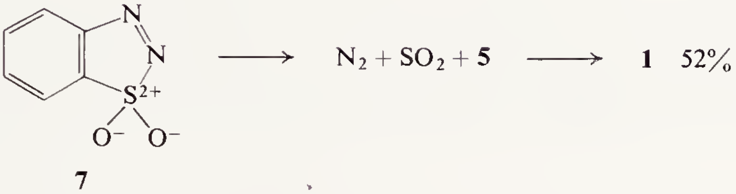
[13] J. W. Barton and S. F. Beresford, unpublished work.

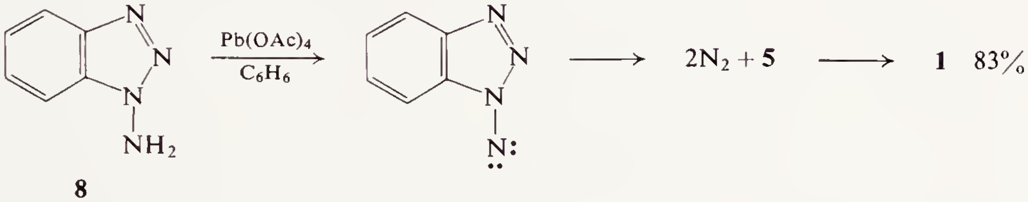
[14] G. Wittig and W. Herwig, *Ber.* **87**, 1511 (1954).

[15] R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Chapter 1. Academic Press, New York, 1967.

[16] L. Friedman and D. F. Lindow, *J. Am. Chem. Soc.* p. 2329 (1968).







inert solvent.[17] Providing that adequate precautions are taken in handling the violently explosive salt **6**,[16] this is probably the best method for preparing relatively small amounts of biphenylene and certain of its derivatives. Apparently, the method fails with nitro and halogenoanthranilic acids.[17]

Benzothiadiazole-1,1-dioxide (**7**) also fragments readily[18] to give benzyne, as does the nitrene produced by lead tetraacetate oxidation of 1-aminobenzotriazole (**8**).[19] The latter reaction gives high yields of biphenylenes, but is limited by the relative inaccessibility of benzo-substituted 1-aminobenzotriazoles. "Crossed" aryne reactions are easily carried out using this procedure,

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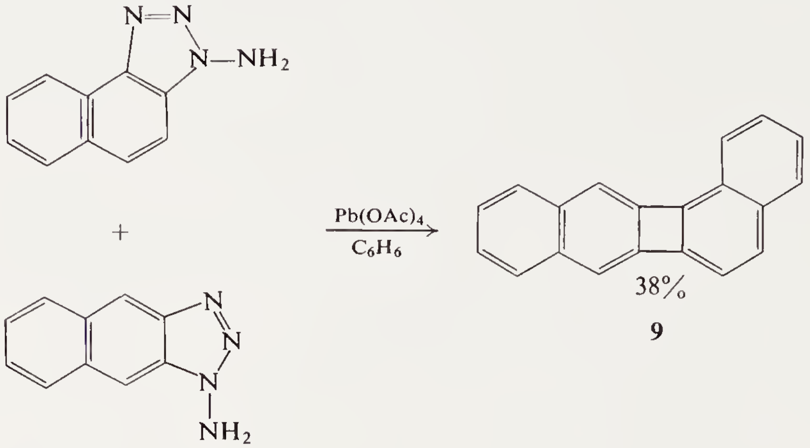
[17] L. Friedman, F. M. Logullo, and A. H. Seitz, *Org. Syn.* (in press).

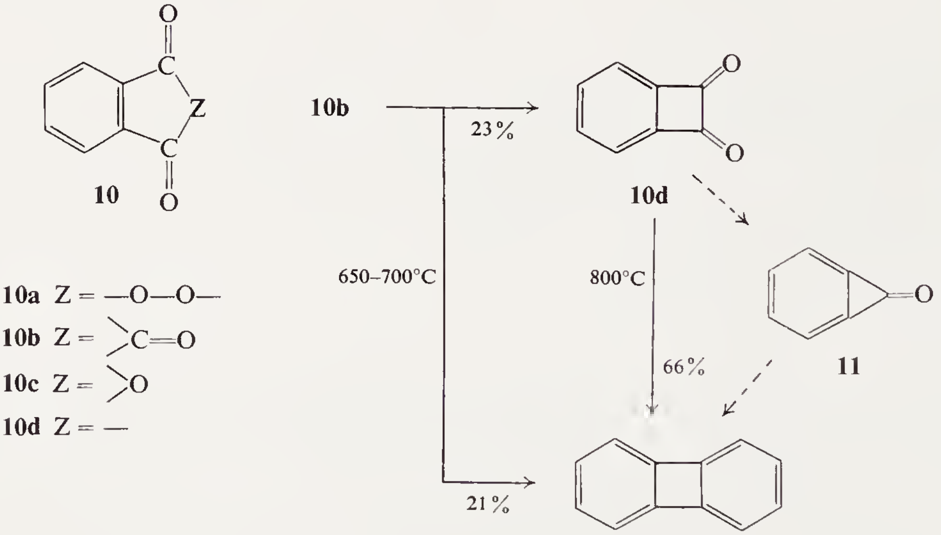
[18] G. Wittig and R. W. Hoffmann, *Ber.* **95**, 2718 (1962).

[19] C. D. Campbell and C. W. Rees, *Chem. Commun.* p. 192 (1965).

and it is valuable for obtaining various benzobiphenylenes which are difficult to prepare by other methods, e.g., dibenzo[a,g]biphenylene (**9**).[20]



Studies of the mass spectra of various 1,2-dicarbonylbenzenes (**10**)[21a–e] indicate that the molecular ions fragment with loss of carbon oxides so that



[20] J. W. Barton and S. A. Jones, *J. Chem. Soc.* (*C*) p. 1276 (1967).

[21a] J. H. Beynon, "Mass Spectrometry and Its Applications to Organic Chemistry," p. 374. Elsevier, Amsterdam, 1960.

[21b] R. F. C. Brown and R. K. Solly, *Australian J. Chem.* **19**, 1045 (1966).

[21c] R. F. C. Brown, D. V. Gardner, J. F. W. McOmie, and R. K. Solly, *Australian J. Chem.* **20**, 139 (1967).

[21d] M. P. Cava, *Chem. Soc. Spec. Publ.* **21**, 163 (1967).

[21e] J. B. Chadwick, D. V. Gardner, and J. F. W. McOmie, unpublished work.

they show a peak of mass/energy = 76 attributable to benzyne. This behavior can be paralleled by prolysis of these compounds in a low pressure nitrogen stream at temperatures in the range 500–850°C, when products derived from benzyne are obtained.

It is reported that phthaloyl peroxide (**10a**) gives biphenylene (27%) at 600°C,[22] while phthalic anhydride (**10c**) gives biphenylene (10–17%) together with traces of other hydrocarbons at rather higher temperatures (800–830°C).[21c] Indanetrione (**10b**) undergoes stepwise loss of carbonyl groups, giving rise first to benzocyclobutene-1,2-dione (**10d**) and then to biphenylene.[21b,d] The unknown benzocyclopropenone, **11**, is possibly involved in the passage of **10d** into biphenylene, but it is not isolable under these conditions. The pyrolysis of phthalic anhydrides has been extended to the synthesis of methyl-,[21c,d] bromo-,[21e] chloro-,[21c,d] and fluorobiphenylenes.[21e] The aryne from tetrabromophthalic anhydride did not survive to dimerize under the reaction conditions (800°C) and only hexabromobenzene (20%) was isolated.[21d] No biphenylenes were obtained from the pyrolysis of 4-benzylphthalic and 4-methoxyphthalic anhydrides,[21c] nor were azabiphenylenes obtained from pyridine-2,3- and pyrazine-2,3-dicarboxylic acid anhydrides.[21d, 23] The latter two compounds show peaks in their mass spectra corresponding to heteroarynes, and products of ring scission of the heteroarynes were found in the pyrolysis experiments.

The formation of biphenylene derivatives in Ullmann reactions of 1,2-dihalides has been observed.[24a–b] Yields are very small unless a nitro group is present in a suitable position to activate one of the halogen atoms.[25a–c] It has been postulated that the reaction involves aryne intermediates rather than a stepwise Ullmann coupling, and a recent study using 1,2-diiodo-3-nitrobenzene supports this.[25c] Thus, the gradual addition of copper powder to this dihalide heated in the absence of solvent gives only the expected biaryl **12**. In *N*,*N*-dimethylformamide (DMF) at 150°C, a mixture of **12** and 1,5-dinitrobiphenylene (**13**) is obtained, with **13** predominating if an excess of copper is present throughout the reaction.

Little is known of the factors which affect aryne dimerization. It has been postulated that benzyne generated by certain methods, e.g., from **8**, may be produced initially in the triplet state and hence may show a greater tendency to

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[22] G. Wittig and H. F. Ebel, *Ann.* **650**, 20 (1961).

[23] R. F. C. Brown, W. D. Crow, and R. K. Solly, *Chem. Ind.* (*London*) p. 343 (1966).

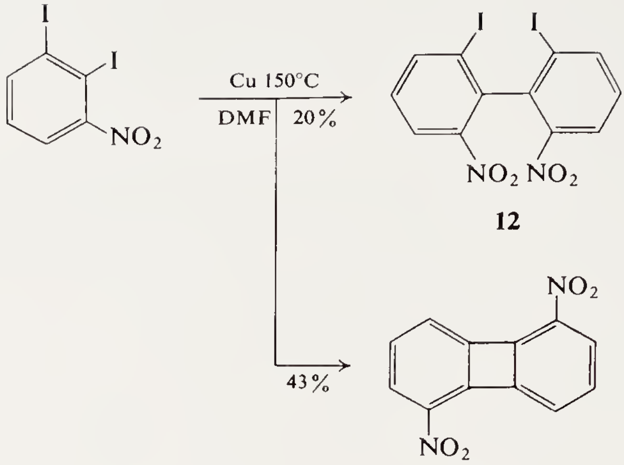
[24a] B. D. Pearson, *Chem. Ind.* (*London*) p. 899 (1960).

[24b] W. Baker, J. W. Barton, J. F. W. McOmie, R. J. Penneck, and M. L. Watts, *J. Chem. Soc.* p. 3986 (1961).

[25a] J. F. Corbett and P. F. Holt, *J. Chem. Soc.* p. 4261 (1961).

[25b] C. R. Harrison, J. F. W. McOmie, J. B. Searle, J. P. Smith, J. O. Jenkins, and J. W. Smith, *J. Chem. Soc.* (*C*) p. 1769 (1966).

[25c] K. Iqbal and R. C. Wilson, *J. Chem. Soc.* (*C*) p. 1690 (1967).

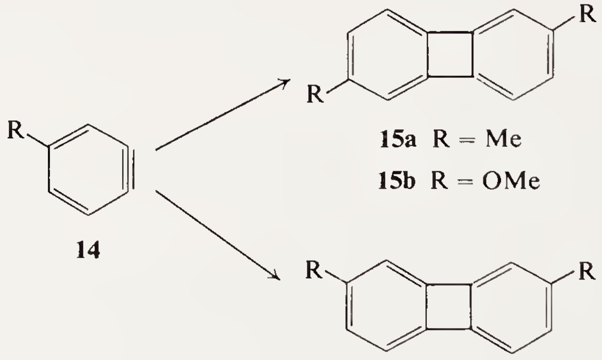


12

13

dimerize than benzyne generated by other methods. Regarding the effect of substituents, it might be expected that any substituent exerting an appreciable polarizing effect on the aryne **14** would increase dimerization to a 2,6-disubstituted biphenylene **15** over that to the 2,7-disubstituted one (**16**), other things being equal. If the substituent is adjacent to the "yne" function, it is not possible to distinguish between steric and polarization effects, and in reactions involving organometallic compounds it may be difficult to determine whether discrete aryne species are involved.

In early studies of the dehalogenation of 3-bromo-4-iodotoluene with magnesium, only 2,6-dimethylbiphenylene (**15a**) was isolated.[26] It was later reported that this isomer was obtained in good yield from the oxidation of 1-amino-5-methylbenzotriazole.[19] More recently, the product from 3-bromo-4-



14

15a R = Me
15b R = OMe

16a R = Me
16b R = OMe

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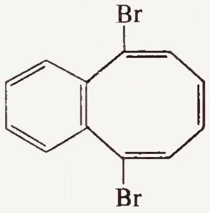
[26] H. Heaney, F. G. Mann, and I. T. Millar, *J. Chem. Soc.* p. 3930 (1957).

iodotoluene has been shown to be a mixture of the isomers **15a** and **16a**, as is that from the thermolysis of 5-methyl-1,2,3-benzothiadiazole-1,1-dioxide.[27] Further studies of the oxidation of 1-amino-5-methylbenzotriazole[28] show that the product is also a mixture of **15a** and **16a** in the estimated ratio of 55:45, and that a similar mixture of isomers, **15b** and **16b**, is obtained from the corresponding methoxy compound (ratio 45:55). Thus, in these two cases there can be little if any orientation of the arynes before dimerization. Concerning reactions in which steric effects may operate, only 1,5-dinitrobiphenylenes have been obtained from the Ullmann type reactions of 2,3-dinitrohalogenobenzenes,[25a–c] while the dimerization of 1,2-naphthalyne from 1-amino-1*H*-naphtho[1,2-d]triazole has given a mixture of dibenzo[a,g]- and dibenzo[a,i]- in the ratio 30:13.[20]

C. From Reduced Biphenylenes and Their Valence Isomers

The reaction of biphenylene with an excess of bromine gives rise to a mixture containing isomeric tetrabromides and hexabromides[29a,b] (Section V,B,2). The partial debromination of any of these compounds with sodium iodide gives 3,8-dibromobenzocyclooctatetraene (**17**), the valence isomer of 4a,8b-dibromo-4a,8b-dihydrobiphenylene (**18**), which can also be obtained by the controlled addition of bromine to biphenylene. On heating in solvents at



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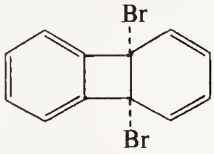

18

temperatures above 100°C, **17** decomposes into a mixture of biphenylene and 2-bromobiphenylene. The latter is formed by substitutive bromination of the biphenylene formed by the bromine split out from the dibromide. Debromination of **17** with zinc dust in acetic acid gives biphenylene together with some benzocyclooctatetraene.[30]

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[27] G. Vargas Nunez, *Bol. Soc. Quim. Peru* **31**, 6 (1965).

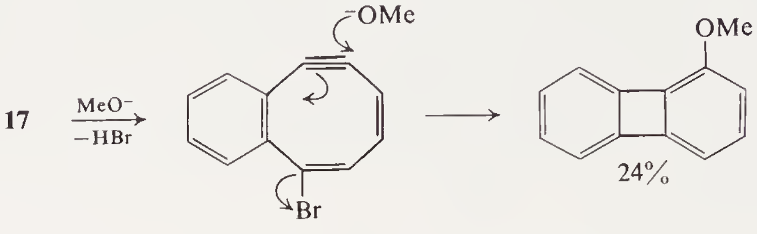
[28] J. W. Barton and C. Comer, unpublished work.

[29a] J. W. Barton, D. E. Henn, K. A. McLauchlan, and J. F. W. McOmie, *J. Chem. Soc.* p. 1622 (1964).

[29b] J. W. Barton and K. E. Whitaker, *J. Chem. Soc.* (*C*) p. 28 (1968).

[30] J. W. Barton, T. A. Chaudri, K. E. Whitaker, and P. Gaskin, unpublished work.

Although the dibromide **17** is unreactive towards nucleophiles, it does react with strong bases. Thus, treatment with sodium methoxide gives some 1-methoxybiphenylene, presumably via a species which may be formally represented as the "yne" **19**.[30] Rather surprisingly, the dibromide **17** reacts



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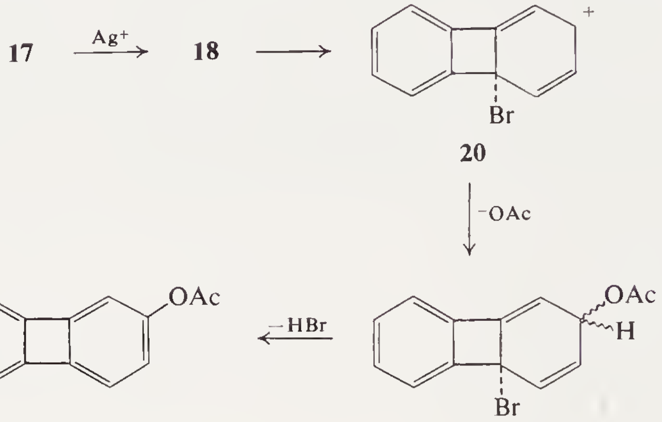

with silver acetate giving 2-acetoxybiphenylene as the main product.[30] The reaction may proceed through the allylic ion **20**, formed via the valence isomer **18**. The corresponding reaction with silver cyanide gives no cyanobiphenylene, while that with silver nitrate gives only traces of 2-nitrobiphenylene.

Bridged tetrahydrobiphenylenes (**21**) result from the reactions of benzocyclobutadiene and its 3-bromo derivative with 1,2,3,4-tetrachloro-5,5′-dimethoxycyclopentadiene.[31] Removal of the ketal bridge from **21b** results in the concomitant loss of hydrogen bromide with the formation of 1,2,3,4-tetrachlorobiphenylene (**22**). The analogous reaction with ketal, **21a**, gives 4,5,6,7-tetrachlorobenzocyclooctatetraene (**23**) rather than its valence isomer 1,2,3,4-tetrachloro-4a,8b-dihydrobiphenylene. A similar sequence, using

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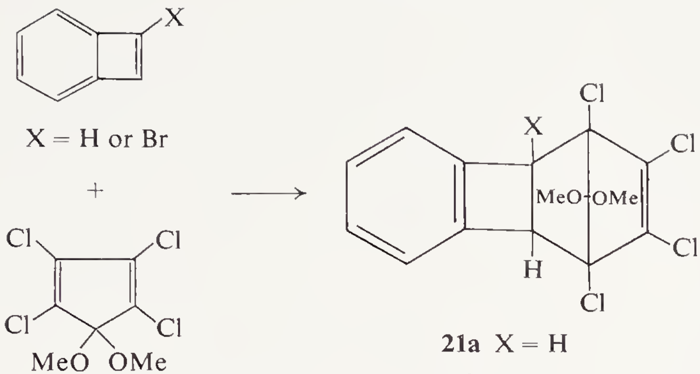
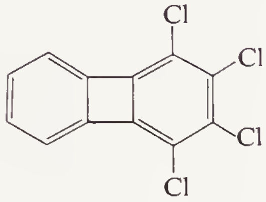
[31] A. J. Boulton and J. F. W. McOmie, *J. Chem. Soc.* p. 2549 (1965).



21a X = H
21b X = Br



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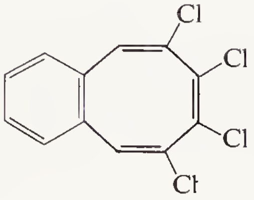

23

diphenylisobenzofuran as the diene, gives 5,10-diphenylbenzo[b]biphenylene in good yield.[32]

When benzocyclobutadiene is generated in the absence of a trapping agent, it undergoes dimerization to 6a,10b-dihydrobenzo[a]biphenylene (**25**),[33a,b] which is readily aromatized to benzo[a]biphenylene by treatment with *N*-bromosuccinimide (NBS). Strong bases bring about the dehydrohalogenation of 1,2-dihalogenobenzocyclobutenes **24** to give monohalogenobenzocyclobutadienes. These give angular dimers, which are then further dehydrohalogenated to the fully aromatic 5-halogenobenzo[a]biphenylene (**26**).[34a,c] This reaction of **24a** with methanolic potassium hydroxide is in fact the first known synthesis of a biphenylene,[34b] although the identity of the product remained unknown for nearly 50 years.

In similar fashion, 3,4-dibromobenzocyclobutadiene (**27**) gives a dimer (**28**) which readily eliminates bromine to give 5,6-dibromobenzo[a]biphenylene (**29**),[35a] together with smaller amounts of 5,10-dibromobenzo[b]biphenylene

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[32] M. P. Cava and R. Polke, *J. Org. Chem.* **27**, 1564 (1962).

[33a] M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.* **79**, 1701 (1957).

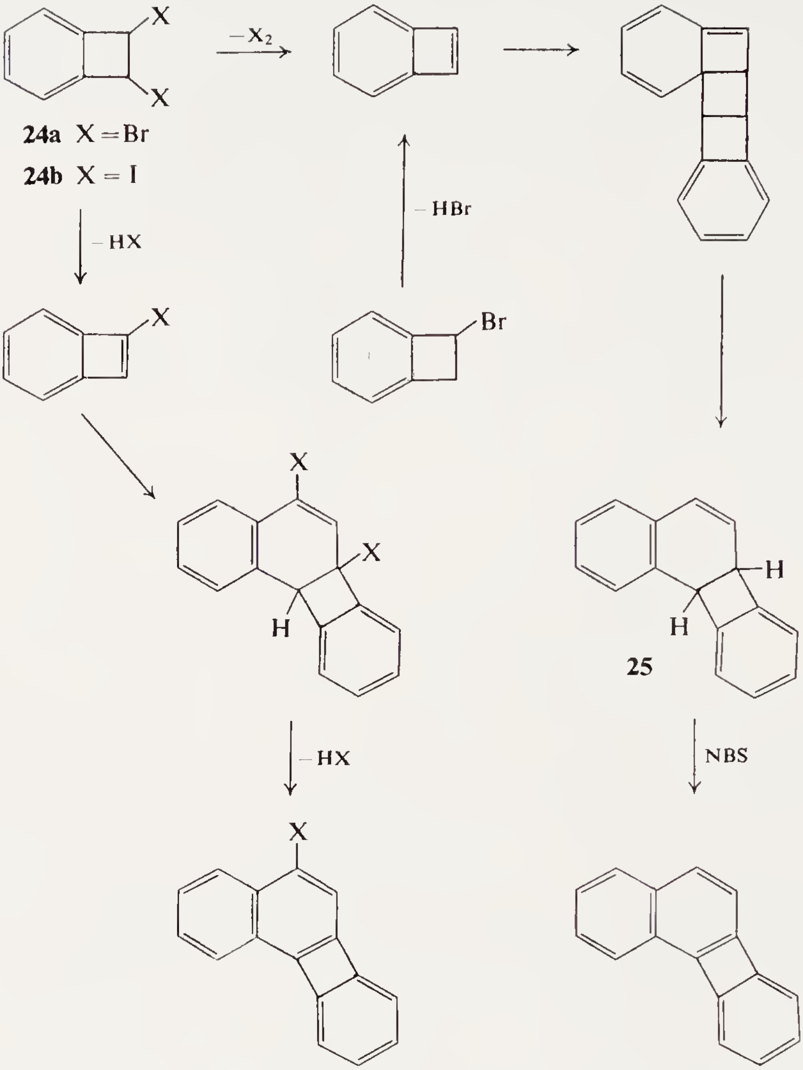
[33b] M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.* **80**, 2255 (1958).

[34a] M. P. Cava and J. F. Stucker, *J. Am. Chem. Soc.* **79**, 1706 (1957).

[34b] H. Finkelstein, Inaugural Dissertation, Strassburg, 1909; *Chem. Ber.* **92**, XXXVII (1959).

[34c] M. P. Cava, K. W. Ratts, and J. F. Stucker, *J. Org. Chem.* **25**, 1101 (1960).

[35a] M. P. Cava and K. Muth, *Tetrahedron Letters* **4**, 140 (1961); *J. Org. Chem.* **27**, 1561 (1962).



24a X = Br
24b X = I

25

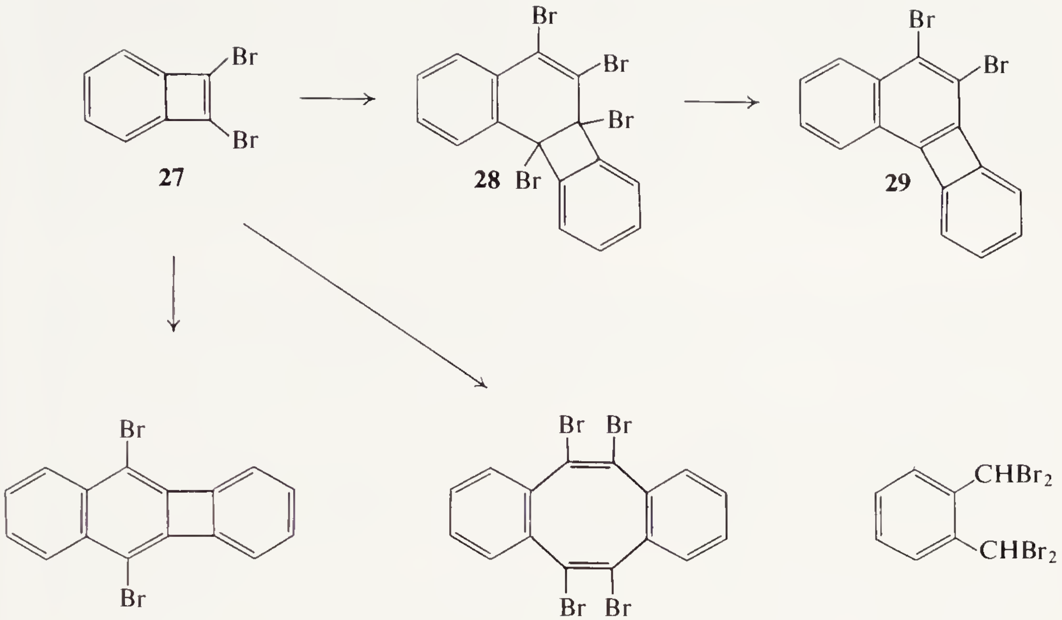
26a X = Br
26b X = I

(**30**), formed by linear dimerization and debromination, and the cyclo-octatetraene derivative **31**.[35b] The treatment of α,α,α′,α′-tetrabromo-*o*-xylene (**32**) with potassium *tert*-butoxide leads directly to a mixture of **29**, **30**, and **31**,[35a, 36a,b] but here the amounts of **30** and **31** are much greater relative to **29**. Thus, it appears that the reaction cannot proceed entirely via 3,4-dibromobenzocyclobutadiene (**27**).

[35b] J. W. Barton and T. A. Chaudri, unpublished work.

[36a] F. R. Jensen and W. E. Coleman, *Tetrahedron Letters* 20, 7 (1959).

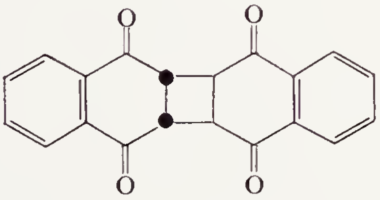
[36b] W. Baker, J. W. Barton, J. F. W. McOmie, and R. J. G. Searle, *J. Chem. Soc.* p. 2633 (1962).



27 **28** **29**

30 **31** **32**

Several of the known photodimers of quinones are the keto tautomers of tetrahydroxybiphenylenes. The naphthalene derivative **33** (*anti* form) is easily tautomerized to **34a** and it may be acetylated and methylated to give **34b** and **34c**, respectively.[37a] It has been reported recently that the more strained *syn* form of this dimer acetylates to **34b** even more readily than the *anti* form.[37b] By contrast, the *syn* dimer of 2,3-dimethyl-1,4-benzoquinone (**35**) can be enolized to the form **36**, with one ring aromatic, and apparently no further.[38, 37a] The



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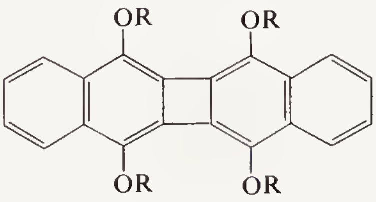
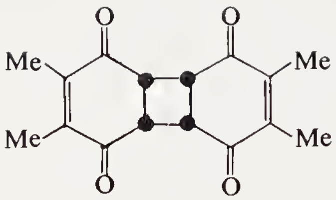


34a R = H
34b R = OAc
34c R = OMe

[37a] J. M. Bruce, *J. Chem. Soc.* p. 2782 (1962).
[37b] J. Dekker, P. J. van Vuuren, and D. P. Venter, *J. Org. Chem.* 33, 464 (1968).
[38] R. C. Cookson, D. A. Cox, and J. Hudec, *J. Chem. Soc.* 1717 (1962).



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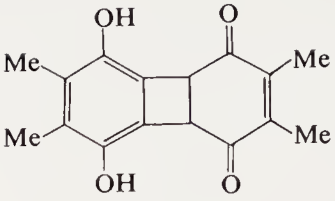

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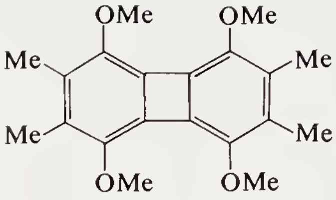

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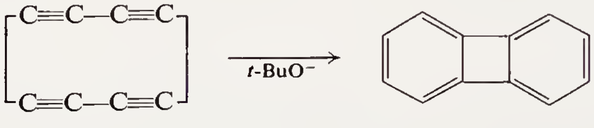
corresponding tetramethoxybiphenylene **37** is known,[8b] but it has not been demethylated.

D. OTHER REACTIONS

An interesting but hardly useful synthesis of the biphenylene nucleus has been achieved starting from acyclic compounds. Glaser coupling of hexa-1,5-diyne has given the unstable cyclic dimer **38** (~9.5% yield), which undergoes base-catalyzed isomerization giving mainly biphenylene (~7.4% overall).[39]



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IV. Properties, Structure, and Stabilities of Biphenylenes

A. PROPERTIES

Biphenylene is a typical tricyclic aromatic hydrocarbon. It crystallizes in long, straw-colored prisms, m.p. 110–111°C, from methanol or light petroleum, and boils at 260°C, below which temperature it is somewhat volatile and sublimes easily, giving off an odor similar to that of biphenyl. While the linearly annelated benzo[b]- and[36a,b] dibenzo[b,h]biphenylenes[40] are also nearly colorless, the angular annelation of rings produces a gradual deepening in color. Thus, the benzo[a]-[41] and dibenzo[a,h]biphenylenes[20] are bright yellow; the dibenzo[a,c]-,[12b] dibenzo[a,g]-[12a] and dibenzo[a,i]-[41] isomers are red. Biphenylene forms molecular complexes with maleic anhydride, tetracyanoethylene, and aromatic polynitro compounds. The complexes of the hydrocarbon and its derivatives with 2,4,7-trinitrofluorenone have a 1 : 1 molecular ratio and are the most useful for characterization purposes.

[39] R. Wolovsky and F. Sondheimer, *J. Am. Chem. Soc.* 87, 5720 (1965).

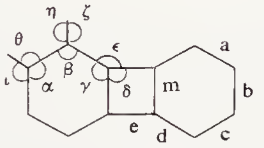
[40] R. F. Curtis and G. Viswanath, *J. Chem. Soc.* p. 1670 (1959).

[41] M. P. Cava and J. F. Stucker, *J. Am. Chem. Soc.* 77, 6022 (1955).

Biphenylene is quite stable and shows no more tendency to undergo addition reactions than do other polycyclic aromatic hydrocarbons in which occur partial bond fixations. Although one might expect the four-membered ring to be considerably strained, it is only in ready catalytic hydrogenation[1] and in reactions conducted at high temperatures (>400°C)[42a,b] that biphenylene shows evidence of this (for estimates of strain energy see Section IV,C).

B. STRUCTURE

Early chemical work on the structure of biphenylene was supported by an electron diffraction study of the vapor[43] and an X-ray crystallographic[44a] study, these serving to confirm its planar tricyclic structure. More recent X-ray studies by Trotter and his co-workers[44b,c] have given precise bond lengths and angles, as shown in **39**. These measurements, supported by chemical evidence,[45] demonstrate the degree of bond fixation in biphenylene. They also show that the main contributor to the resonance hybrid is structure **40**, that the 2–3 bond[b] has the highest bond order, and that the 4a–4b bond[e] has the lowest, the latter being almost as long as a normal single bond. The data also show that it is not possible to apply simple resonance theory in order to deduce the bond orders of biphenylene, since there are considerable differences in



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Bond angles (°)
$\alpha = 122.2 \pm 0.2$
$\beta = 115.2 \pm 0.2$
$\gamma = 122.6 \pm 0.2$
$\delta = 90.0 \pm 0.2$
$\epsilon = 147.4 \pm 0.2$
$\zeta, \eta = 122$
$\theta, \iota = 119$

Bond lengths (Å)
a = 1.423 ± 0.003
b = 1.385 ± 0.004
d = 1.372 ± 0.002
e = 1.514 ± 0.003
m = 1.426 ± 0.003
C—H = 1.06

[42a] L. Friedman and D. F. Lindow, *J. Am. Chem. Soc.* **89**, 1271 (1967); **90**, 2324 (1968).

[42b] L. Friedman and P. W. Rabidean, *J. Org. Chem.* **33**, 451 (1968).

[43] J. Waser and V. Schomaker, *J. Am. Chem. Soc.* **65**, 1451 (1943).

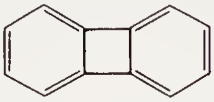
[44a] J. Waser and C. S. Lu, *J. Am. Chem. Soc.* **66**, 2035 (1944).

[44b] T. C. W. Mak and J. Trotter, *J. Chem. Soc.* p. 1 (1962).

[44c] J. K. Fawcett and J. Trotter, *Acta Cryst.* **20**, 87 (1966).

[45] W. Baker, J. F. W. McOmie, D. R. Preston, and V. Rogers, *J. Chem. Soc.* p. 414 (1960).

importance of the five canonical forms, **40–44**. Molecular orbital (MO) calculations of bond order[46a–c] are in good agreement with the observed values.



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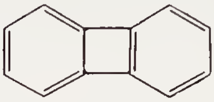

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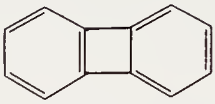

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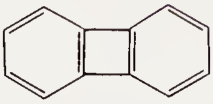

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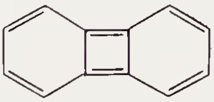

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C. Relative Stabilities

Biphenylene and the linearly annelated benzo[b]-[36a,b] and dibenzo-[b,h]biphenylenes[40] are stable compounds. However, this is not true of the biphenylenes with angularly annelated rings, such as the dibenzo[a,g][12a] and dibenzo[a,i][41] isomers, which behave as highly unsaturated systems. Recently, Dewar and Gleicher,[46b] using two improved MO methods,[47] have calculated the geometrics and resonance energies for these biphenylenes and other polybenzocyclobutadienes. They have shown that there is a correlation between the average bond length of the four-membered ring and the stability of the system; i.e., the compounds with most cyclobutadiene character in the four-membered ring are expected to be the least stable:

dibenzo[b, h] > benzo[b] > –[a, h] > biphenylene > –[a] > –[a, c] > –[a, i] > –[a, g]
Decreasing stability →

This correlation suggests that the cyclobutadiene character of the central ring is low in some of these biphenylenes. There is, however, ample evidence, e.g., from spectra, to show that some exists, i.e., that the compounds are not merely bridged biaryls.

Various estimates have been made of the resonance energy (RE) of biphenylene and of the destabilizing strain energy (SE) in its four-membered ring, most of which have suggested that the latter is the greater. The first estimate of the SE, made by Coulson[48] in 1942, gave a value of the order of 100 kcal/mole, but

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[46a] R. D. Brown, *Trans. Faraday Soc.* **45**, 296 (1949); **46**, 146 (1950).
[46b] M. J. S. Dewar and G. J. Gleicher, *Tetrahedron* **21**, 1817 (1965).
[46c] H. E. Simmons and A. G. Anastassiou, cited in Cava and Mitchell,[5] Chapter 12.
[47] M. J. S. Dewar, *Chem. Soc. Spec. Publ.* **21**, 177 (1967).
[48] C. A. Coulson, *Nature* **150**, 577 (1942).

in view of later treatments of other strained molecules[49] using a "bent-bond concept," this was considered to be too high. An early estimate[46a] placed the total resonance energy at 73 kcal/mole. Springall *et al.*[50a,b] have determined the heat of combustion of biphenylene and compared the so-derived heat of formation with that calculated by the summation of bond energy terms. They obtained a value of 17.1 kcal/mole for net RE[50b] and, by comparison with biphenyl (RE = 81.4 kcal/mole), a value of 64.3 kcal/mole for the SE. The low value of 27.5 kcal for the SE calculated from heats of formation by Dewar and Gleicher[46b] is apparently based on the older combustion data of Springall *et al.*[50a]; use of the value from the later determination leads to a value of 74.2 kcal/mole.

D. SPECTRA

1. *Infrared* (*IR*)

The solid-phase IR spectrum of biphenylene has been recorded by Wittig and Lehmann[51a] and discussed by Curtis and Viswanath,[40] who commented on the following feature. The IR spectra of *o*-disubstituted benzenes such as *o*-xylene and tetralin show an intense C—H bending absorption at 741 cm^{-1}. The attachment of a strained ring brings about splitting of this bond. Thus, indane shows two bands at 752 cm^{-1} and 738 cm^{-1}, while benzocyclobutane shows bands at 781 cm^{-1} and 714 cm^{-1}.[33b] In the IR spectrum of biphenylene, the separation (750 cm^{-1} and 734 cm^{-1}) is greater than in indane but much less than in benzocyclobutene. More recently, a very detailed study of the IR spectra of biphenylene and of perdeuterobiphenylene has been made, and the IR-active vibrational modes assigned.[51b]

2. *Ultraviolet* (*UV*)

The UV spectrum of biphenylene[52a,b,c] shows two main band systems, at 235–260 mμ and 330–370 mμ, and is typical of a polycyclic aromatic hydrocarbon, as opposed to that of a bridged biphenyl. It shows a general resemblance to the spectrum of the corresponding 3-ring, linearly annellated anthracene, while the spectrum of fluorene is much closer to that of biphenyl.

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[49] C. A. Coulson and W. Moffitt, *Phil. Mag.* **40**, 1 (1949).

[50a] R. C. Cass, H. D. Springall, and P. G. Quincey, *J. Chem. Soc.* p. 1188 (1955).

[50b] A. F. Bedford, J. G. Carey, I. T. Millar, C. T. Mortimer, and H. D. Springall, *J. Chem. Soc.* p. 3895 (1962).

[51a] G. Wittig and G. Lehmann, *Ber.* **90**, 875 (1957).

[51b] C. Pecile and B. Lunelli, *J. Chem. Phys.* p. 1336 (1968).

[52a] E. P. Carr, L. W. Pickett, and D. Voris, *J. Am. Chem. Soc.* **63**, 3231 (1941).

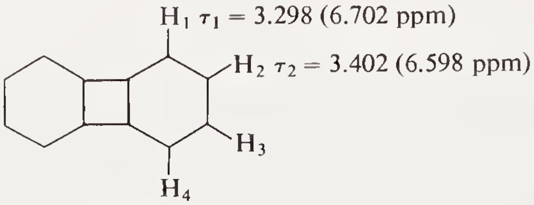
[52b] W. Baker, M. P. V. Boarland, and J. F. W. McOmie, *J. Chem. Soc.* p. 1476 (1954).

[52c] D. G. Farnum, E. R. Atkinson, and W. C. Lothrop, *J. Org. Chem.* **26**, 3024 (1961).

The UV spectra of alkylbiphenylenes are closely similar to that of the parent compound, as are the spectra of 1- and 2-aminobiphenylenes[9,52b] in acid solution. Apart from the usual loss of fine structure, the substitution of a nitro group at position 1 in biphenylene does not modify the spectrum to a great extent,[9] whereas at position 2, the effect is quite marked.[53] On the other hand, substituents such as amino and methoxy cause a pronounced lowering in the intensity of the long-wave portion of the spectrum if present at position 1, but exert little effect if present at position 2.[9,52b]

3. *Proton Magnetic Resonance* (*PMR*)

Cava *et al.*[54] first analyzed the A_2B_2 spectrum shown by biphenylene and assigned the values for chemical shifts and couplings shown in **45**. On the basis



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Coupling constants (cps)
$J_{1,2} = 6.8$
$J_{2,3} = 8.24$
$J_{1,3} = 0.74$
$J_{1,4} = 1.08$

of a planar molecule (**39**) of known geometry having zero ring current in the four-membered ring, they calculated the difference in chemical shift between H-1 and H-2 to be 0.13 ppm as compared with their observed value of 0.104 ppm. Shortly afterwards, Katritzky and Reavill[55] reported similar findings in support of partial bond fixation in the form **40** previously discussed. They assigned the high field side of the A_2B_2 system as due to H-2, 3, 6, 7 by reason of its decrease in intensity on deuteration, which is known to take place more rapidly at position 2 than at position 1.[56a,b] These workers also calculated the expected chemical shifts on the basis of a two ring-current model, obtaining a value of 0.12 ppm for the difference between them. However, they pointed out that the shifts should occur to the low field of the benzene resonance, whereas in fact they are found to the high field of it. They concluded that there is considerable π-electron delocalization in the four-membered ring.

More recently, Figeys[57] has calculated the ring-current effect in biphenylene using the bond length values obtained by Mak and Trotter. His results suggest

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[53] W. Baker, J. W. Barton, and J. F. W. McOmie, *J. Chem. Soc.* p. 2666 (1958).

[54] G. Fraenkel, Y. Asahi, M. J. Mitchell, and M. P. Cava, *Tetrahedron* **20**, 1179 (1964).

[55] A. R. Katritzky and R. E. Reavill, *Rec. Trav. Chim.* **83**, 1230 (1964).

[56a] A. Streitweiser and I. Schwager, *J. Am. Chem. Soc.* **85**, 2855 (1963).

[56b] J. M. Blatchly and R. Taylor, *J. Chem. Soc.* p. 4641 (1964).

[57] H. P. Figeys, *Chem. Commun.* p. 495 (1967).

that the two six-membered rings have comparatively small ring currents (+0.563) while the four-membered ring has a large paramagnetic ring current (−1.028) (benzene = +1.0). The corresponding calculated chemical shifts of H-1 and H-2, 6.662 ppm and 6.756 ppm, respectively, agree well with the observed values but are in the reverse order to the assignments made by the previous workers. The fact that H-1 is known to be more acidic than H-2[58] is more in keeping with the findings of Katritzky and Reavill. However, NMR data from some specifically labeled deuterobiphenylenes[59] has provided evidence in support of Figeys work.[57]

Regarding the relationship between bond order and vicinal proton coupling constant, the values obtained for biphenylene fit into the linear relationship found for other six-membered ring compounds.[60a,b]

4. *Mass Spectrum*

The mass spectrum of biphenylene has been analyzed by Friedman and Lindow.[42a] Taking into account data obtained from thermal reactions (Section V,B) they conclude that fragmentation to give benzyne is not an important process and that the ion with mass/energy = 152 probably consists mainly of radical ions with the four-membered ring opened, rather than intact parent ions.

5. *Other Spectra*

The electronic, fluorescence, and phosphorescence spectra of biphenylene have been studied, as have the electron spin resonance spectra of the positive and negative radical ions (for discussion and references, see Simmons and Anastassiou[46c]). It has been reported that the radical anion disproportionates into biphenylene and its dianion[61a] (a $4n + 2$ π-electron system), but further work has shown the amount of disproportionation to be very small[61b]

$$2H^- \overset{K}{\rightleftharpoons} H^0 + H^{2-} \quad K < 1.5 \times 10^{-2} \text{ (cf., Hush and Rowlands}^{61c}\text{)}$$

V. Chemical Reactions of Biphenylenes

A. SUBSTITUTION REACTIONS

The reactivity of biphenylene has been investigated using molecular orbital

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[58] A. Streitweiser, G. R. Ziegler, P. C. Mowery, A. Lewis, and R. G. Lawler, *J. Am. Chem. Soc.* **90**, 1357 (1968).

[59] B. E. Ayres, J. B. Chadwick, H. P. Figeys, J. F. W. McOmie, and R. H. Martin, unpublished work.

[60a] N. Jonathan, S. Gordon, and B. P. Dailey, *J. Chem. Phys.* 36, 2443 (1962).

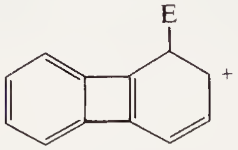
[60b] W. B. Smith, W. H. Watson, and S. Chiranjeeri, *J. Am. Chem. Soc.* **89**, 1438 (1967).

[61a] N. L. Bauld and D. Banks, *J. Am. Chem. Soc.* **87**, 128 (1965).

[61b] R. Waack, M. A. Doran, and P. West, *J. Am. Chem. Soc.* **87**, 5508 (1965).

[61c] N. S. Hush and J. R. Rowlands, *Mol. Phys.* **6**, 317 (1963).

methods and has been assessed in various terms.[46c] The most recent predictions, based on localization energies, are that position 2 should be the more reactive towards electrophiles, nucleophiles, and radicals, even though the free valence is slightly higher at position 1 than at position 2. More simply, inspection of the main contributors to the Wheland intermediates, formed by the addition of an attacking species to biphenylene, leads to the conclusion that position 2 is likely to be the more reactive. For example, the addition of an electrophile at positions 1 and 2 gives rise to Wheland intermediates which are hybrids of the ions **46–48** and **49–51**, respectively. On the assumption that canonical forms with the most cyclobutadiene character in the four-membered ring are the least stable (Section IV,C), then the two forms **46** and **48** are relatively more energy-rich for 1-substitution compared with (**51**) for 2-substitution. Thus the Wheland intermediate for 2-substitution is likely to be the more stable.



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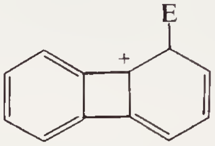

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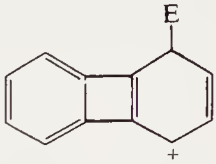

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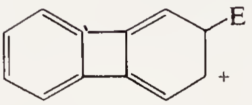

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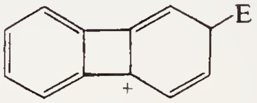

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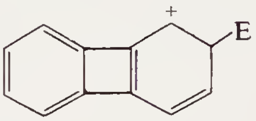

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Recently, Streitweiser and his co-workers[58] have drawn attention to the fact that hydrocarbons which have an aryl position adjacent to a fused, strained ring show enhanced acidity but reduced reactivity towards electrophiles at this position. Position 1 in biphenylene is an example of this; in protodetritiation experiments with lithium cyclohexylamide in cyclohexylamine at 50°C, it is found to be 79 times as reactive as position 2. As a consequence of this enhanced acidity biphenylene undergoes hydrogen metal exchange with *n*-butyl lithium almost exclusively at position 1.[62] The resulting 1-biphenylenyl lithium is a key intermediate for the synthesis of several 1-substituted biphenylenes[62] (Fig. 1).

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[62] A. J. Boulton, J. B. Chadwick, C. R. Harrison, and J. F. W. McOmie, *J. Chem. Soc.* (*C*) p. 328 (1968).

[63] J. W. Barton, J. B. Chadwick, and J. F. W. McOmie, unpublished work.

[64] W. Baker, J. W. Barton, and J. F. W. McOmie, *J. Chem. Soc.* p. 2658 (1958).

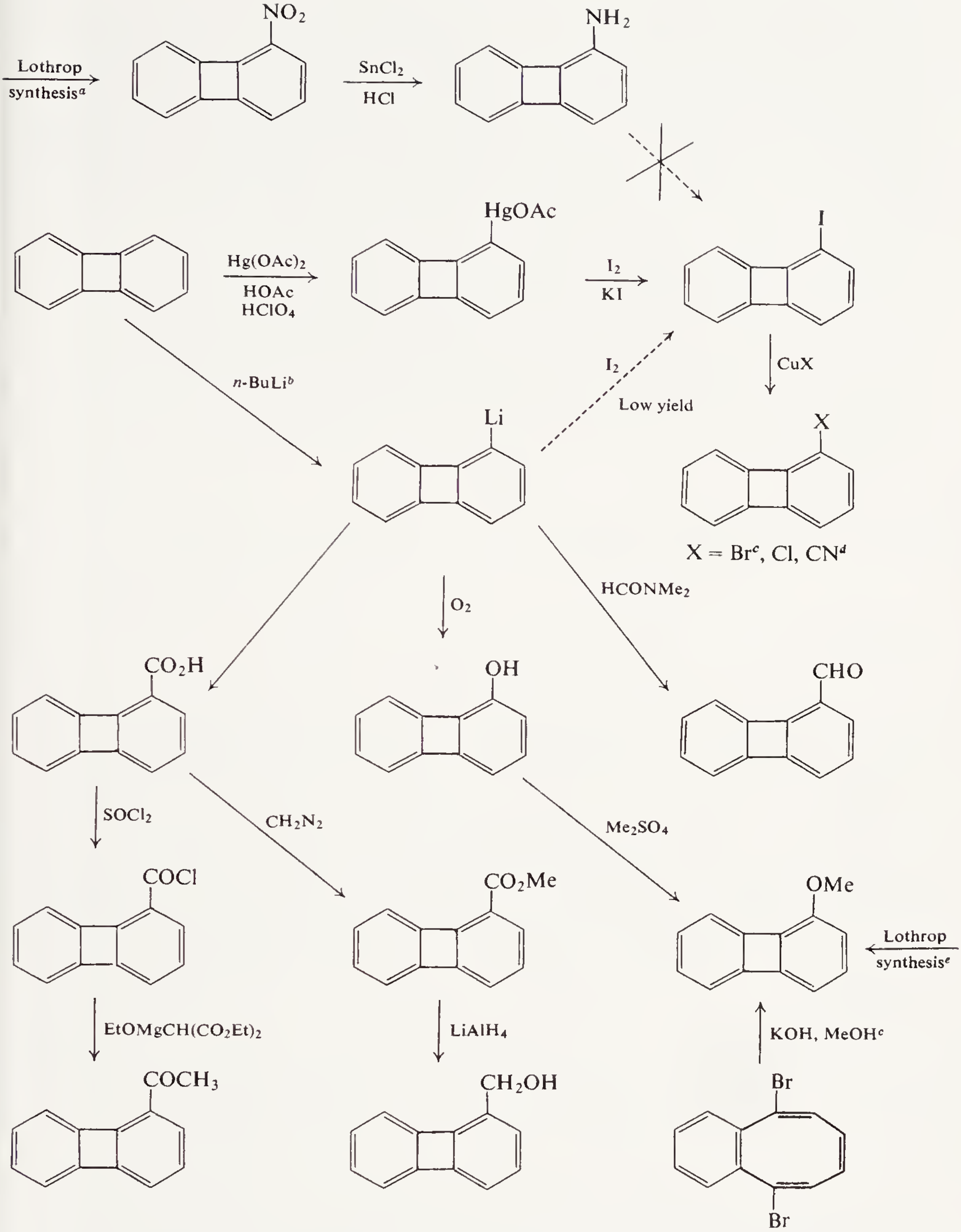

FIG. 1. Synthetic routes to 1-substituted biphenylenes. References: (*a*) Barton and Whitaker[9] (*b*) Boulton *et al.*[62] (*c*) Barton and Whitaker[29b] (*d*) Barton *et al.*[63] (*e*) Baker *et al.*[64]

1. Electrophilic Substitution

Streitweiser and Schwager[56a] first investigated the relative rates of substitution at positions 1 and 2 of biphenylene by tritiodeprotonation in trifluoroacetic acid–70% perchloric acid (96.9:3.1 by volume) at 25°C, obtaining a value of $k_2/k_1 = 64$. Shortly afterwards, Blatchly and Taylor[56b] obtained a value of $k_2/k_1 = 135$ from experiments conducted in anhydrous trifluoroacetic acid at 70°C. Both of these values are considerably greater than the relative rate predicted from localization energies ($k_2/k_1 \sim 4$).

It has been reported recently that complete deuteration of biphenylene can be achieved using sufficiently strenuous acidic (or basic) conditions.[65]

Only 2-substituted biphenylenes have been isolated in qualitative studies of acylation,[52b,53,36b] halogenation,[53] and nitration.[53] The 2-acetyl derivative is a

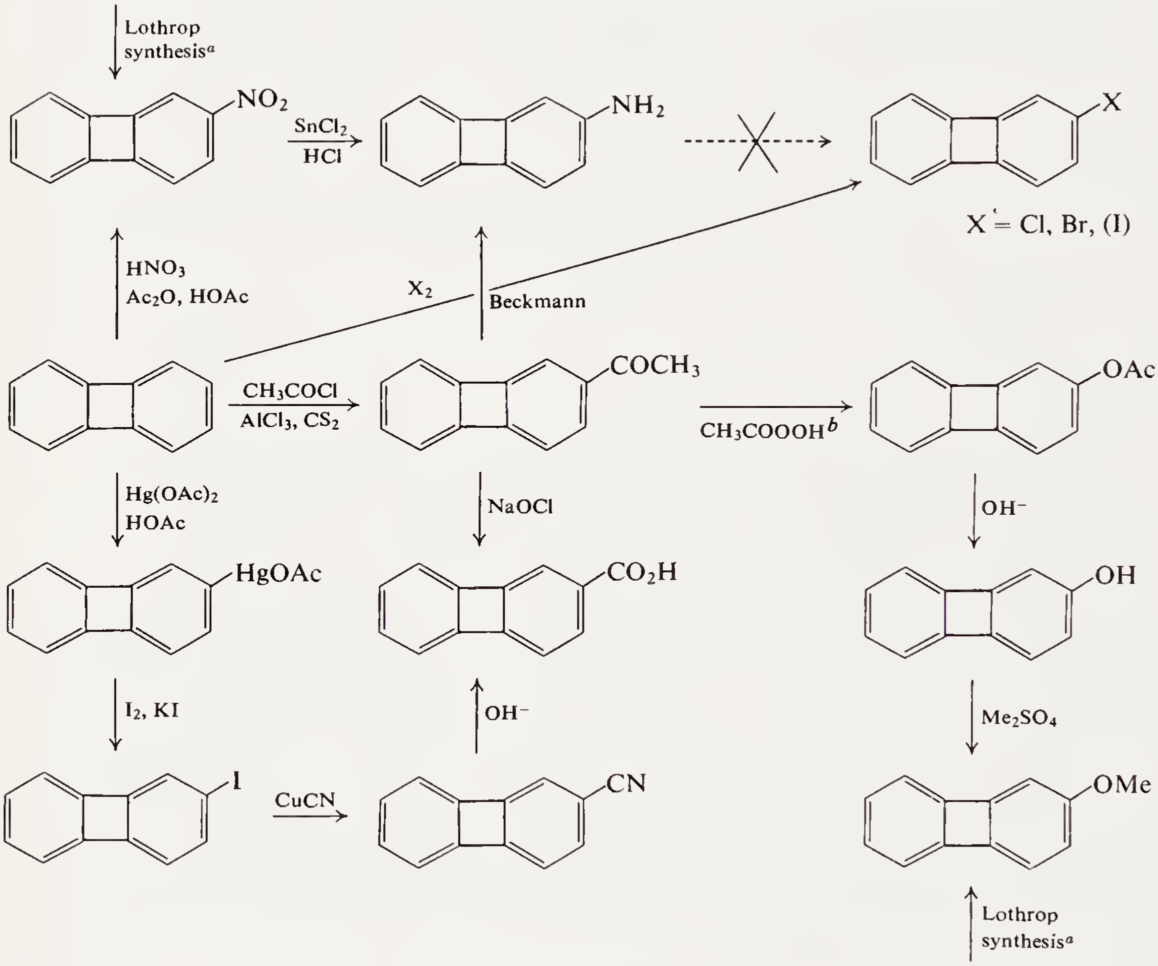

FIG. 2. Synthetic routes to 2-substituted biphenylenes.[52b, 53] References: (*a*) Baker *et al.*[64] (*b*) Blatchly *et al.*[66]

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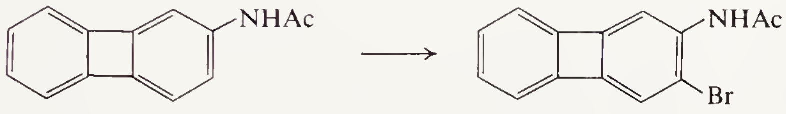
[65] B. Lunelli and C. Pecile, *Can. J. Chem.* 46, 391 (1968).

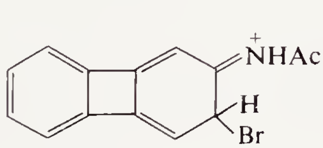
[66] J. M. Blatchly, D. V. Gardner, and J. F. W. McOmie, *J. Chem. Soc.* (*C*) p. 272 (1967).

key intermediate for the preparation of many compounds of the 2 series (Fig. 2). Nitration has given only low yields of 2-nitrobiphenylene (20–25 %) owing to a competing addition reaction (Section V,B,2). Mercuration in acetic acid, where a simple electrophilic substitution is by no means clear cut, gives rise to a mixture of 1- and 2-acetoxymercuribiphenylenes,[29b] the latter predominating. This reaction is markedly accelerated by the addition of perchloric acid, and, by reason of its reversibility, eventual buildup of the 1 isomer occurs. For synthetic purposes, the mercuration reaction is useful, as it can lead to halides of either the 1 or 2 series, which are not available from the corresponding amines by the Sandmeyer reaction (Figs. 1 and 2).

Electrophilic substitution in some biphenylene derivatives has also been studied. In the case of a biphenylene having a strongly activating substituent at position 2, it has been well established that further substitution occurs at position 3,[45,67a,b] e.g., **52**–**53**. This orientation was first predicted by Longuet-Higgins[68] who calculated the electron availability at the various ring positions in the carbanion formed from 2-methylbiphenylene. Inspection of the resonance contributors of the ion formed on addition of a bromine cation at position 3 in 2-acetamidobiphenylene (**52**) leads to the same result. It is apparent that the most favorable contributing form is **54** with the double bonds in the substituted ring exocyclic to the four-membered ring and the positive charge on nitrogen. There is no corresponding form for attack at position 1 and thus **55**, for the reasons given above, would be much less favorable. Where the substituent is less strongly activating, e.g., ethyl, some



52 **53**



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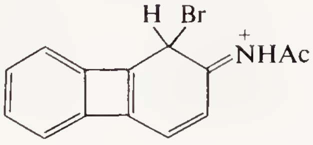

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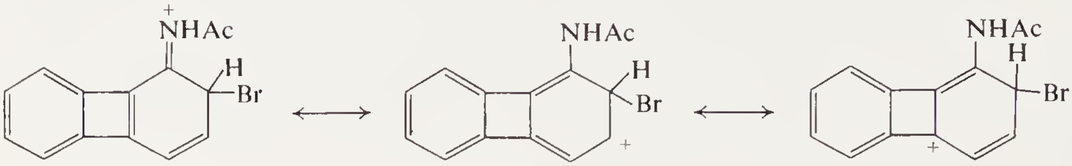
[67a] H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta* **44**, 1985 (1961).

[67b] J. M. Blatchly, D. V. Gardner, J. F. W. McOmie, and M. L. Watts, *J. Chem. Soc.* (*C*) p. 1545 (1968).

[68] H. C. Longuet-Higgins, *Chem. Soc. Tilden Lecture*, *Proc. Chem. Soc.* p. 157 (1957).

substitution also occurs in the other ring at positions 6 and 7.[69] Further bromination of 2-bromobiphenylene, in which the substituent is deactivating but *ortho* or *para* directing, probably follows similar lines as mixtures of dibromobiphenylenes[29b] and, under strenuous conditions, 2,3,6,7-tetrabromobiphenylene[59] have been obtained.

In the corresponding case of a biphenylene having a strongly activating substituent at position 1, attack by an electrophile might be expected to take place at position 2 (or 4). However, it appears that none of the contributors to

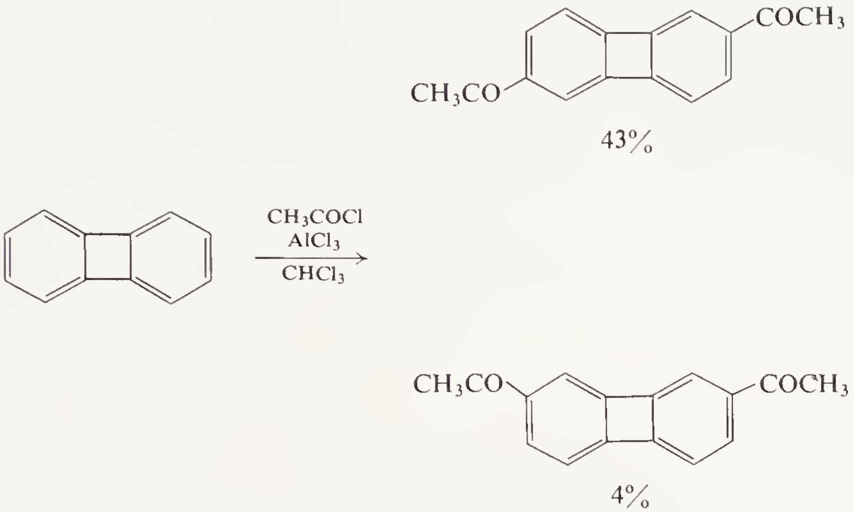


56 **57** **58**

the resulting ion **56–58** would be particularly favorable, i.e., activation of the ring is likely to be abnormally low. Consideration of the electron distribution in the carbanion from 1-methylbiphenylene[70] leads to a similar conclusion and one finds the highest charge density at the bridge position (**8b**), suggesting that addition may predominate with compounds of this type. A clear-cut example has yet to be recorded. It has been found that 1-hydroxybiphenylene does not undergo normal diazo coupling[62] as does the 2 isomer[71] and that the Fries migration reaction of 1-acetoxybiphenylene gives only traces of a product which may be 2-acetyl-1-hydroxybiphenylene.[62] Preliminary experiments on the bromination of 1-acetamidobiphenylene[72] indicate that the reaction takes place very much less readily than with the 2 isomer. A mixture of addition and substitution products is formed and, in one of the latter, the bromine has entered the unsubstituted ring.

Acylation[53,73] and nitration[53] studies have shown that, if a deactivating *meta* directing substituent is present at position 2, then further substitution takes place in the unsubstituted ring, mainly at position 6 and to a minor extent at position 7. Cava and Mitchell[5] have extended the arguments involving Wheland intermediates to show that the 6-position is preferred. Disulfonation of biphenylene occurs readily,[52b] but the orientation of the product has not been determined.

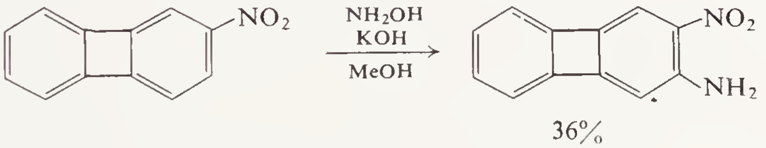
[69] D. V. Gardner and J. F. W. McOmie, unpublished work.
[70] D. R. Preston, Ph.D. Thesis, Univ. of Bristol, 1960.
[71] J. M. Blatchly, J. F. W. McOmie, and S. D. Thatte, *J. Chem. Soc.* p. 5090 (1962).
[72] J. W. Barton, unpublished work.
[73] J. M. Blatchly, A. J. Boulton, and J. F. W. McOmie, *J. Chem. Soc.* p. 4930 (1965).



+ 2-acetylbiphenylene 13% (Blatchly *et al.*[73])

2. *Nucleophilic Substitution*

Nucleophilic substitution in biphenylene should not take place readily and no example is known. By comparison with other polycyclic hydrocarbons,[74] methylation should occur to some extent with the carbanion from dimethyl sulfoxide. When a nitro group is present, the naphthalene nucleus becomes susceptible to nucleophilic amination in positions *ortho* and *para* to this substituent.[75] This is also the case with 2-nitrobiphenylene, which undergoes attack at position 3 to give **56**.[76] 1-Nitrobiphenylene, on the other hand, does not react under these conditions. It appears that this situation parallels the low reactivity towards electrophilic attack of biphenylenes with an activating substituent at position 1.



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[74] P. A. Argabright, J. E. Hofmann, and A. Schreisheim, *J. Org. Chem.* **30**, 3233 (1965); H. Nozaki, Y. Yamamoto, and R. Noyori, *Tetrahedron Letters* **11**, 1123 (1966); G. A. Russell and S. A. Weiner, *J. Org. Chem.* **31**, 248 (1966).

[75] J. Sauer and R. Huisgen, *Angew Chem.* **8**, 294 (1960).

[76] J. W. Barton and K. E. Whitaker, unpublished work.

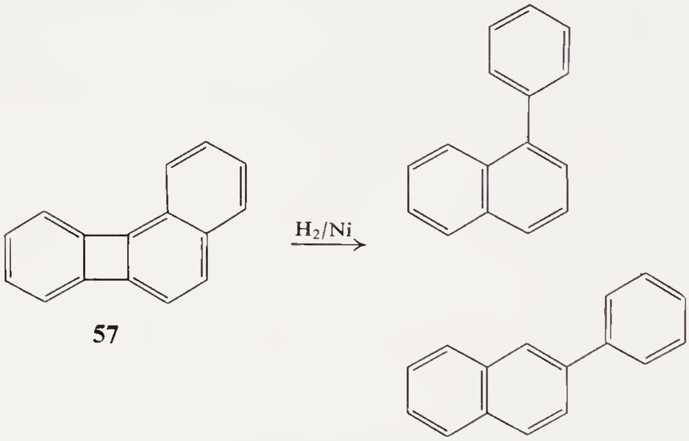
3. *Homolytic Substitution*

Early work showed that biphenylene reacts with lead tetraacetate in acetic acid, giving low yields of 2-acetoxybiphenylene.[52b,64] More recently, Dickerman *et al.*[77] have shown that phenylation occurs at both positions in biphenylene. A relative rate of $k_1/k_2 = 7/22$ was obtained. This is in better agreement with the value calculated from localization energies than are the findings for hydrogen exchange. It was also concluded that biphenylene has "normal" reactivity in homolytic phenylation as compared with naphthalene and phenanthrene.

B. ADDITION REACTIONS

1. *With Rupture of the Four-Membered Ring*

When Lothrop discovered biphenylene he observed that it was reduced to biphenyl with hydrogen and a hot copper catalyst.[1] This reductive ring opening, which is a characteristic of biphenylene and its derivatives, does in fact occur under very mild conditions.[40] Warming an ethanolic solution of the compound with active Raney nickel is usually sufficient to promote it. The reaction has proved useful in confirming structures, e.g., **57**,[41] although with some unsymmetrical biphenylenes, the scission is selective and gives predominantly one of the two possible biaryls.[20,41] Surprisingly, biphenylenes are not cleaved by other reagent–catalyst combinations, such as hydrazine–palladium,[4] nor by metal–acid reductions such as the Clemmensen.[52b] Reduction of biphenylene using metal–amine systems gives mainly biphenyl and its reduction products,[52b,78] according to the vigor of the reaction. For example, lithium in



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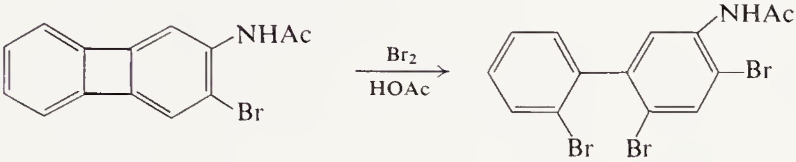
[77] S. C. Dickerman, N. Milstein, and J. F. W. McOmie, *J. Am. Chem. Soc.* **87**, 5522 (1965).

[78] J. W. Barton and D. J. Walsh, unpublished work.

ethylamine–diethylamine 1 : 4 at 0°C gives biphenyl (85 %), together with small amounts of 1-phenylcyclohexene and a tetrahydrobiphenylene.[78]

The addition of bromine to certain biphenylene derivatives, e.g., **53**, occurs with opening of the 4a–4b bond,[45, 79] but with the parent hydrocarbon this has not been observed as the addition occurs by other modes (Section V,B,2).



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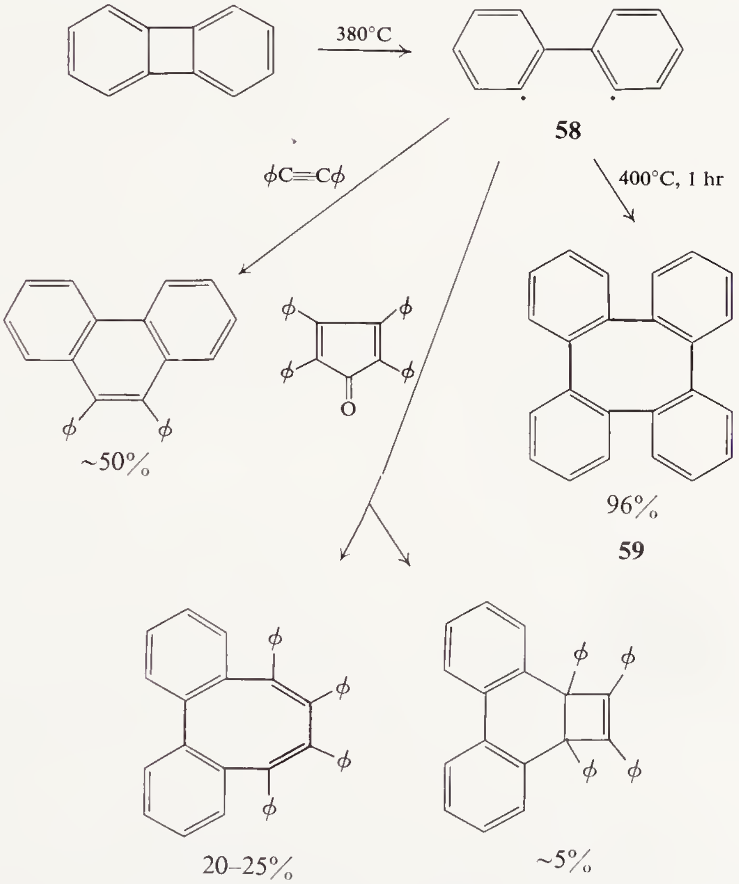
Friedman and his co-workers[42a, b] have studied the reactions of biphenylene at temperatures in excess of 380°C. Under these conditions, the diradical **58** is formed which then dimerizes to tetraphenylene (**59**) unless it is trapped by suitable electron-rich systems. Transition metal carbonyl complexes also



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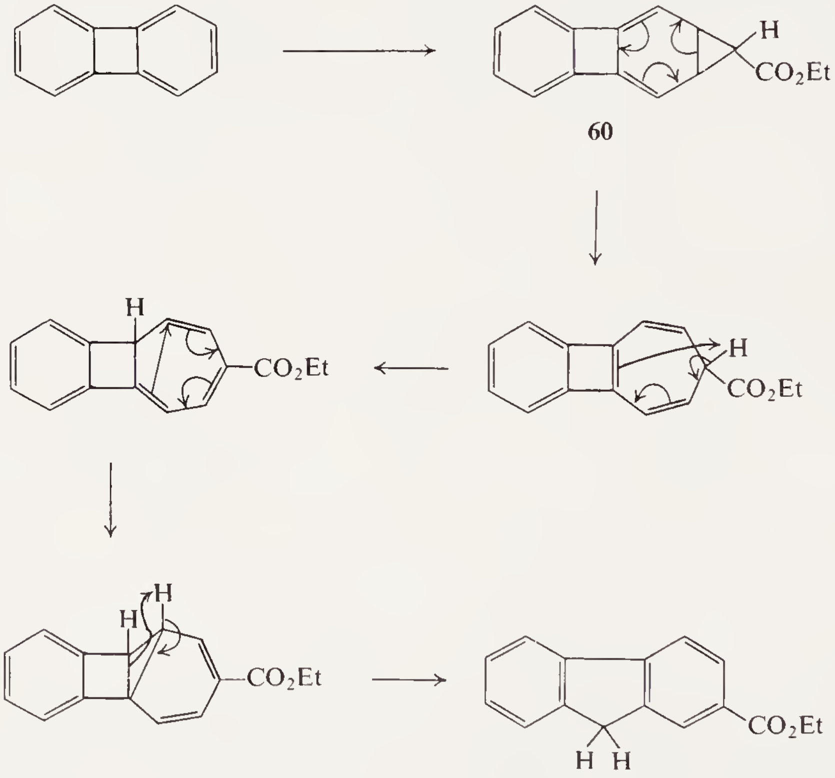
[79] W. Baker, N. J. McLean, and J. F. W. McOmie, *J. Chem. Soc.* p. 1067 (1964).

promote reactions of this type. When biphenylene is heated at 100°C with bistriphenylphosphine nickel dicarbonyl a small yield of tetraphenylene is obtained,[80] while with chromium hexacarbonyl at 255°C, a carbonyl insertion reaction gives rise to some fluorenone and its reduction products.[81]

2. *Additions to the Six-Membered Rings*

The bond length data and molecular orbital studies suggest that the 2–3 bond in biphenylene has the highest bond order. However, only one example of addition at this site has been recorded. Baker *et al.*[52b] reacted biphenylene with ethyl diazoacetate and obtained, after hydrolysis, a low yield of a carboxylic acid which was different from fluorene-9-carboxylic acid the product which would have arisen by insertion at the 4a–4b bond. A reinvestigation of the reaction by Kende and MacGregor[82] showed the product to be the ethyl ester of fluorene-2-carboxylic acid (**61**), apparently formed by addition of carbethoxycarbene across the 2–3 bond to give **60**, followed by a series of tautomerizations.



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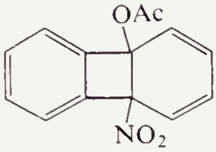
[80] J. Chatt, R. G. Guy, and H. R. Watson, *J. Chem. Soc.* p. 2332 (1961).
[81] E. R. Atkinson, P. L. Levine, and T. E. Dickelman, *Chem. Ind.* p. 934 (1964).
[82] A. S. Kende and P. T. MacGregor, *J. Am. Chem. Soc.* **86**, 2088 (1964).

Other additions to a six-membered ring of biphenylene have been observed, several of which involve the ring junction 4a–8b bond. Nitration in acetic anhydride gives mainly 3-acetoxy-8-nitrobenzocyclooctatetraene (**63a**),[83] the valence tautomer of the dihydrobiphenylene **62**. Additions of nitrosyl formate and chloride give the analogous products **63b** and **63c**, rather than nitroso compounds.



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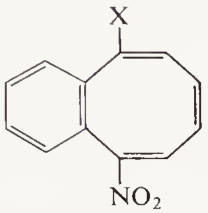

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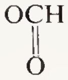
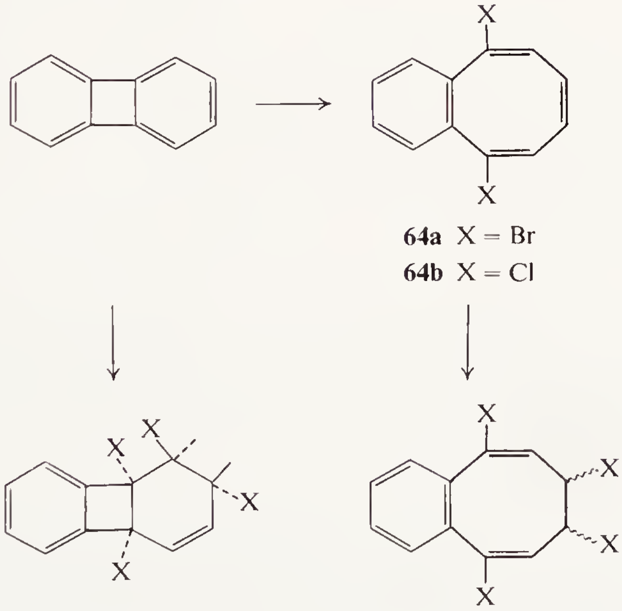
63a X = OAc

63b X = 
$OCH(=O)$

63c X = Cl



64a X = Br
64b X = Cl

66a X = Br
66b X = Cl

65a X = *trans*-Br
65b X = *cis*-Cl

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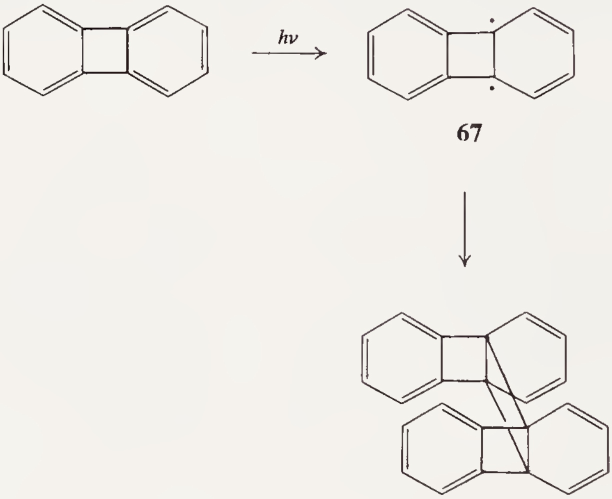
[83] J. W. Barton and K. E. Whitaker, *J. Chem. Soc.* (*C*) p. 1663 (1968).

Halogenations in the absence of a carrier are very complex. Bromination gives some of the benzocyclooctatetraene derivative **64a**[29b] which readily undergoes a further addition to give the tetrabromide **65a**. Another tetrabromide, **66a**, has also been isolated together with the two hexabromides formed from it by further addition of bromine. A dibromide precursor of **66a** has not been found, but it appears likely that, in this series, the initial attack takes place at position 2 of biphenylene, as in electrophilic substitution. Whereas in nitration the addition of nitronium acetate to biphenylene is presumably ionic in character, the bromine addition is catalyzed by light and the reactions are to some extent homolytic. Additions of molecular chlorine give similar mixtures[76] of tetrachlorides, including **65b** and **66b**, and hexachlorides, while the reaction of biphenylene with sulfuryl chloride gives a low yield of 3,8-dichlorobenzocyclooctatetraene, together with a mixture of chlorobiphenylenes.

Recently a photodimer (**68**) of biphenylene has been reported,[84] in which coupling has occurred at positions 4a and 8b in both molecules, presumably via the diradical species **67**.



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Biphenylenes in which the cyclobutadiene character of the four-membered ring is higher than in the parent, i.e., angularly annelated benzologs, show an increased tendency to add bromine across the ring junction. For example, 5-bromobenzo[a]biphenylene gives 5,6a,10b-tribromo-6a,10b-dihydrobenzo-[a]biphenylene (**69**) as the initial product.[35a] As valence tautomerization is not a

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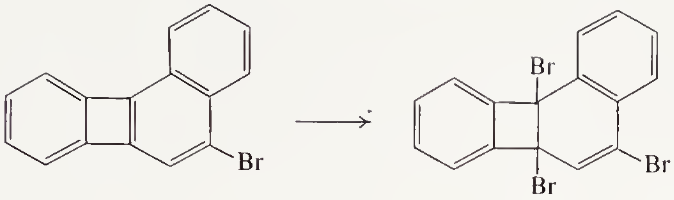
[84] N. L. Goldman and R. A. Ruden, *Tetrahedron Letters* **36**, 3951 (1968).



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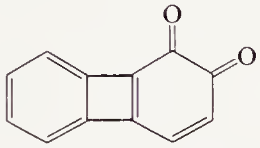
favorable process in this compound, further addition of bromine occurs at the nonaromatic 5–6 double bond.[36b]

VI. Quinones of Biphenylene

Six quinones of biphenylene are possible, three with the carbonyl groups confined to one ring and three extended quinones:



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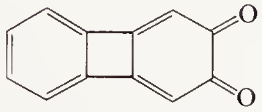

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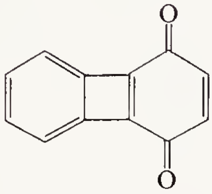

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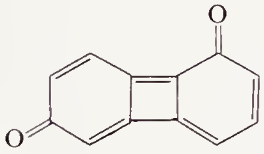

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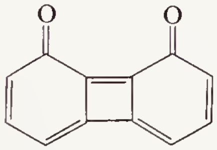

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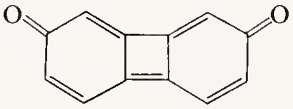

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From what is known of the bond structure of biphenylene, it might be expected that the 2,3-quinone, **71**, in which all the formal double bonds can be exocyclic to the four-membered ring, would prove to be the most stable. A molecular orbital study[85] has given the following order of relative stability:

$$\mathbf{71} > \mathbf{72} > \mathbf{70} > \mathbf{74} > \mathbf{73} > \mathbf{75}$$

Biphenylene-2,3-quinone (**71**) is, in fact, the only one of these parent quinones which has been reported.[71] It is prepared by standard methods, either by the oxidation of 2-amino-3-hydroxybiphenylene with chromic acid or by the direct

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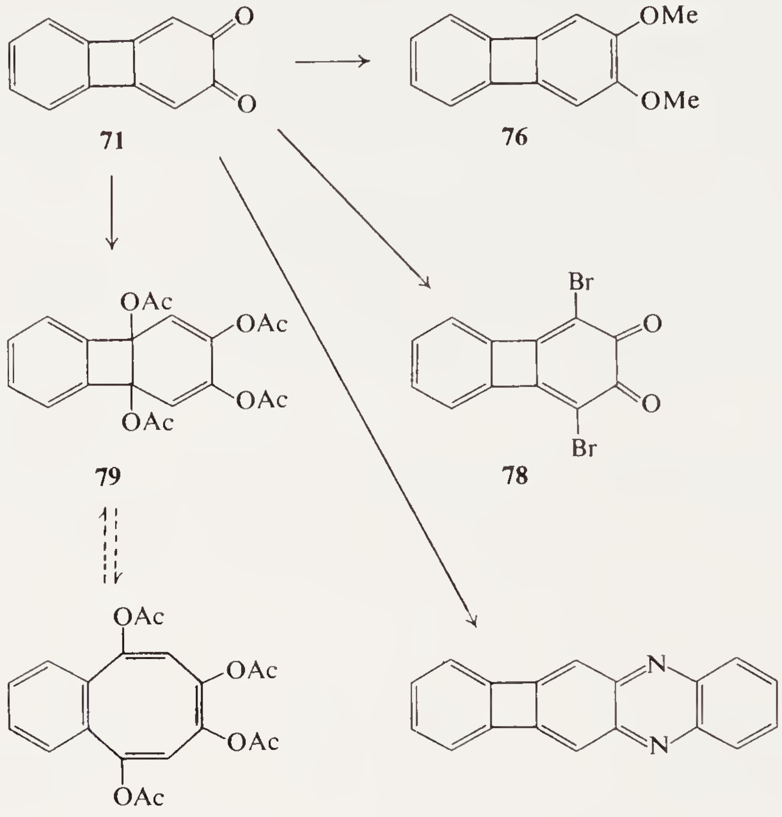
[85] H. R. Schweizer, *Helv. Chim. Acta.* **45**, 1934 (1962).

oxidation of 2-hydroxybiphenylene with Teuber's reagent (potassium nitrosodisulfonate). The latter reaction was unsuccessful when applied to 1-hydroxybiphenylene in order to obtain **70** or **72**.[62] Biphenylene-2,3-quinone is very stable and it exhibits most of the reactions characteristic of an ortho-



80 **77**

quinone. It undergoes reductive methylation to give 2,3-dimethoxybiphenylene (**76**), forms the quinoxaline **77** with *o*-phenylene diamine, and is brominated at the positions adjacent to the carbonyl groups to give **78**. Abnormal behavior is observed under Thiele acetylation conditions: the quinone adds two molecules of acetic anhydride forming what is either the tetraacetoxy dihydrobiphenylene **79** or its valence tautomer **80**.

Several methoxylated derivatives of biphenylene-2,3-quinone are known, and a tetramethoxy derivative of the extended 2,7-quinone **75** has also been reported.[79] Since the theoretical study finds the 2,7-quinone to be the least stable, it seems probable that highly substituted derivatives of the other quinones, **70**, **72**, **73**, and **74**, can be prepared, even if the parent quinones are unstable.

3

The Cyclodecapentaene Problem

T. L. Burkoth and E. E. van Tamelen

I. Introduction

A. CYCLODECAPENTAENE[1a] AS A NONBENZENOID AROMATIC

Soon after the structure of benzene was proposed by Kekulé[1b] in 1865, chemists began to suspect that this C_6H_6 hydrocarbon might not be unique in

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[1a] Throughout this chapter, unless otherwise specified, the term cyclodecapentaene will be used to designate cyclodeca-1,3,5,7,9-pentaene without regard to stereochemistry or electronic configuration.

[1b] A. Kekulé, *Bull. Soc. Chim. France* 3, 98 (1865); *Ann.* **137**, 129 (1866).

its properties, but rather the first-discovered member in a series of cyclic, conjugated polyenes similarly endowed with stability. The synthesis of the next higher vinylog, cyclooctatetraene, was undertaken in order to test this hypothesis and was achieved by Willstätter and Waser[2] in 1911. To the dismay of many, this homolog exhibited chemical reactivity like that expected of a linear polyene. Obliged on this account to regard benzene as a special case, early chemists developed various explanations for its uniqueness. One of these featured the "aromatic sextet" of electrons, a popular concept which was called upon to rationalize the inordinate stability of the formal triene, including the tendency to retain its structural type during reaction. In 1932, Hückel,[3] employing a quantum mechanical approach, developed a theoretical treatment which downgraded the so-called "aromatic sextet" from its exalted position of uniqueness, and repositioned it as one member of a series of structures expected to be stable by virtue of a closed shell of $4n + 2$ π-electrons. Hückel's theory (or, since its gain in currency, Hückel's rule) was stated to be valid only for monocyclic polyolefins which were fully conjugated. The extent to which Hückel's rule has succeeded in permitting predictions of aromaticity or the absence thereof is now general knowledge. The purpose of this chapter is to describe how the most simple vinylog of benzene for which Hückel predicted aromatic stability, cyclodecapentaene, has resisted the varied synthetic attempts of organic chemists for over 35 years and only recently and somewhat reluctantly yielded significant data relating to its nature.

B. PROBLEMS POSED BY THE CYCLODECAPENTAENE SYSTEM

Reported synthetic approaches to either parent or substituted cyclodecapentaenes are many and varied. The failure of such preparative attempts focused attention on factors other than the closed shell of 10 π-electrons. In this case, approximate coplanarity, necessary for proper orbital overlap to insure maximal electron delocalization, gives rise to bond angle strain and/or nonbonded atomic repulsion in the interior of the carbocyclic structure. It was never certain whether the amount of energy involved in such factors was large enough to counterbalance the energy of stabilization due to aromaticity. That it might be, however, was indicated by the general tendency of medium-ring polyenes to undergo facile skeletal rearrangements and transannular reactions to relieve this strain. Furthermore, cyclodecapentaene, hypothetically, can exist in various cis–trans modifications, for example isomers **1**, **2**, and **3**. The impact of this complicating factor becomes evident when one tries to predict the nature or properties of cyclodecapentaene. Its importance would be most readily

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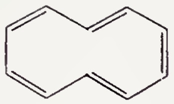
[2] R. Willstätter and E. Waser, *Ber.* **44**, 3423 (1911).

[3] E. Hückel, *Z. Phyzik* **70**, 204 (1931); **78**, 628 (1932); "Grundzüge der Theorie ungesättigter und aromatischer Verbindungen." Verlag Chemie, Berlin, 1938.



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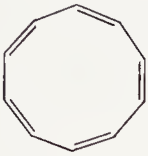

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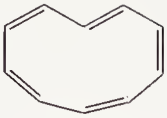

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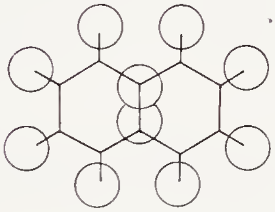
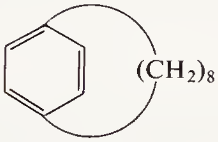
apparent when, at the conclusion of a synthesis that is ambiguous with respect to geometric isomerism, an attempt is made to interpret physical data. A critical inspection of synthetic approaches to cyclodecapentaene readily engenders appreciation for the special problems of synthesis and structure of this molecule.

C. The Problem of Steric Destabilization

In 1952, Mislow[4] predicted stabilities for the annulenes on the basis of anticipated geometry, assigned through the use of accepted van der Waals' radii, bond lengths, and angles. In his analysis of cyclodecapentaene ([10]annulene), Mislow chose to treat the cis,trans,cis,cis,trans isomer **1** (**1**′). In this



1′



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model, strong interaction of the internal 1,6 hydrogen atoms demands distortion from planarity. In fact, Mislow concluded from similar treatment of the higher annulenes that the first in the series capable of achieving planarity and thus aromatic stabilization would be [30]annulene. Several investigators have almost arbitrarily discounted this difficulty with cyclodecapentaene.[5,6] More recently, Baker[7] called attention to several groups of compounds, specifically, benzenes and fused benzenoid aromatics, either substituted with bulky groups or bridged so as to preclude coplanarity of the aromatic portions,

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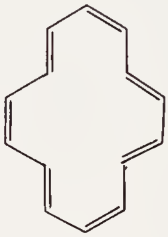
[4] K. Mislow, *J. Chem. Phys.* **20**, 1489 (1952).

[5] G. B. Bachman and R. I. Hoaglin, *J. Org. Chem.* **8**, 301 (1943).

[6] G. M. LeClercq, Ph. D. Thesis, Univ. of Washington, 1956 [*Dissertation Abstr.* **17**, 747 (1957)].

[7] W. Baker and J. F. W. McOmie, *in* "Non-benzenoid Aromatic Compounds," p. 477 ff. Wiley (Interscience), New York, 1959.

which indicate that considerable aromatic stability can be retained even though nuclear atoms are forced out of plane. The actual magnitude of the distortion which an aromatic nucleus can accommodate is not known. However, in an extreme case, the benzene nucleus in [8]paracyclophane (**4**)[8] tolerated a distortion calculated to be 20° from a planar configuration and yet retained aromaticity, i.e., a magnetically induced ring current was detectable by nuclear magnetic resonance (NMR) spectroscopy (see Section I,E). It is generally accepted that the loss of resonance energy is directly related to the distortion from planarity, and this case indicates that a significant degree of distortion can be tolerated. A case which serves to lessen the apprehension generated by Mislow's geometric analysis is the synthesis of [14]annulene (**5**)[9] by Sondheimer and Gaoni (see Section II,E). This species, shown by means of X-ray crystallography to have the geometry treated by Mislow, exhibits NMR behavior indicative of aromaticity (Section I, E). The steric strain of cyclodecapentaene, although expected to be greater than that of [14]annulene, might similarly be tolerated if aromatic stabilization is sufficiently great.



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D. The Problem of Angle-Strain Destabilization

Another geometric isomer of cyclodecapentaene which deserves consideration is the all-cis isomer, **2**. In this case, the severe nonbonded interaction of hydrogen atoms interior to the ring is avoided, but significant in-plane distortion of bond angles is generated. Quantitative theoretical treatment of the energy expense involved in this distortion is precluded, because the increase of the carbon–carbon bond angle in this polyene from the strainless 120° to the 144° of a regular decagon is far too great a perturbation to permit simple treatment using spectrally derived bending-force constants for double bonds.[10] There are, however, two cases for comparison which can serve to place the

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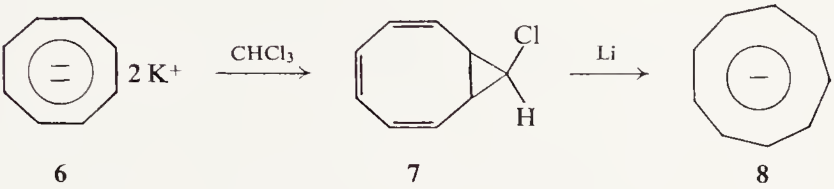
[8] D. J. Cram, C. S. Montgomery, and G. R. Knox, *J. Am. Chem. Soc.* **83**, 515 (1966).

[9] F. Sondheimer, *Proc. Roy. Soc.* **A297**, 173 (1967) and references therein.

[10] F. H. Westheimer, *in* "Steric Effects in Organic Chemistry" (M. S. Newman, ed.), p. 524. Wiley, New York, 1956.

all-cis isomer of cyclodecapentaene in context. The cyclooctatetraene dianion (**6**), prepared by Katz[11] by treating cyclooctatetraene with two equivalents of potassium metal, is aromatic. In this planar, monocyclic, and necessarily all-cis 10 π-electron dianion, the bond angles have been distorted in becoming 135°.



Moreover, Katz and Garratt[12] and LaLancette and Benson[13] report that treating the dianion with chloroform affords 9-chlorobicyclo[6.1.0]nona-2,4,6-triene (**7**), from which the cyclononatetraenyl anion (**8**) can be generated by means of metallic lithium. In this anion, also a 10 π-electron species, the bond angles have been opened to 140°, a distortion of magnitude similar to that in the all-cis isomer of cyclodecapentaene. As in the previous case, the anion **8** exhibits physical properties (see Section I, E) characteristic of an aromatic, all-cis, planar species. Comparison of the accepted energies of stabilization due to resonance[14] and the bond angle distortion for the three species being compared (Table I) is not straightforward. It must be kept in mind that there is a change in the number of angles being distorted and that the function which describes the energy expense of angle distortion is not a linear one. Although

TABLE I

COMPARISON OF RESONANCE STABILIZATION AND ANGLE DISTORTION

Species	Resonance stabilization (kcal/mole)	Angle distortion from 120° (°)
Cyclooctatetraene dianion (**6**)	67	15
Cyclononatetraene anion (**8**)	27	20
Cyclodecapentaene (**2**)	55	24

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[11] T. J. Katz, *J. Am. Chem. Soc.* **82**, 3784 (1960); H. P. Fritz and H. Keller, *Ber.* **95**, 158 (1962).

[12] T. J. Katz and P. J. Garratt, *J. Am. Chem. Soc.* **86**, 5194 (1964).

[13] E. A. LaLancette and R. E. Benson, *J. Am. Chem. Soc.* **85**, 2853 (1963).

[14] A. Streitweiser, Jr. and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Vol. I, p. 84. Pergamon, Oxford, 1965.

both of these factors disfavor the cyclodecapentaene structure, the superficial strain energy of all-cis cyclodecapentaene is not insurmountable. Unfortunately, no attempt has apparently been made to solve the cyclodecapentaene geometry and conformation problem mathematically by maximizing orbital overlap while minimizing angle strain and nonbonded repulsion.

E. The Problem of Criteria for Aromaticity

The problem of functionally defining the term "aromatic" becomes apparent in the series of annulenes predicted to exhibit this quality by Hückel's rule. This matter becomes critical in the case of cyclodecapentaene. The historical designation "aromatic," arising from the characteristic odor of the first compounds of this group, was gradually altered in meaning until it finally referred to the reduced chemical reactivity of such compounds. It is now generally accepted that mere chemical considerations are not valid. Both theoretical understanding of the features of an aromatic system and modern transition-state theory lead to the conclusion that chemical reactivity is only indicative of transition-state energies. Moreover, in order to specify a moiety as "aromatic," probes which can detect resonance phenomena in the ground state are necessary. Fortunately, several such probes are available to the chemist, although their use is not without both technical difficulty and interpretative ambiguity.

Determination of the energy content of a substance by means of calorimetry is one method of detecting increased stability due to a ground-state resonance phenomenon. Unfortunately, this technique usually involves considerable error and is fraught with experimental restrictions. X-ray crystallographic analysis as a measurement of interatomic distances (or, more appropriately here, bond lengths) has been employed to specify the nature of the bonding. Comparison is made between normal ethylenic linkages and those in benzene. Clearly, this technique is limited in that only crystalline, relatively stable species can be inspected. There is another serious limitation in the field of the annulenes, in that the criterion for a ground-state resonance phenomenon, namely the lack of bond length alternation, is predicted to fail for large ring polyenes.[15] In fact, [18]annulene, a compound predicted and shown to be aromatic, exhibits a peculiar variation in bond length.[9]

A more general probe for the ground-state resonance phenomena of aromaticity is nuclear magnetic resonance (NMR) spectroscopy. A functional definition of aromaticity is not without complications; but, in general, a

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[15] See for example: H. C. Longuet-Higgins and L. Salem, *Proc. Roy. Soc.* **A251**, 472 (1959); **A257**, 445 (1960); M. J. S. Dewar and G. J. Gleicher, *J. Am. Chem. Soc.* **87**, 685 (1965); G. O. Hultgren, Ph. D. Thesis, California Inst. of Technol., 1966 [*Dissertation Abstr.* **27B** (3), 755 (1966)].

moiety can be regarded as aromatic if it can sustain an externally induced magnetic field, as revealed by a predictable change in chemical shift of incorporated nuclei bearing a certain geometric relationship to each other. For example [14]annulene (**5**) is regarded as aromatic by Sondheimer and coworkers on the basis of NMR data.[9] This annulene showed the chemical reactivity and general instability expected of an extended linear polyene. At room temperature, the hydrocarbon exhibited an NMR spectrum also indicative of a nonaromatic polyene, exhibiting the singlet vinyl proton resonances at 6.07 and 5.58 δ of the two equilibrating conformers. At low temperatures, however, the equilibration of the high-field isomer was prevented, and an aromatic ring current was detected from an upfield shift of the four protons interior to the ring to 0.0 δ and a downfield shift of the 10 external protons to 7.6 δ. Likewise, the aromatic nature of cyclooctatetraene dianion (**6**)[11] and cyclononatetraene anion (**8**)[12,13] was shown by NMR. These ionic species, moreover, having singlet resonances at 5.7 and 6.9 δ, respectively, demonstrate that another anisotropic effect, in this case the formal charge on each carbon, might mask the effect of the aromatic moiety. The effect of incipient charge on the chemical shift is opposite to that of a magnetically induced ring current. If it is possible to rule out such special effects on chemical shifts as an unexpected anisotropy or a nonadvantageous rate of equilibration, NMR serves as the most powerful tool for detection of aromaticity in the annulene series.

II. Synthetic Approaches to Cyclodecapentaene

Many investigators have attempted syntheses of cyclodecapentaenes. In some cases, the attempted routes led quickly to an impasse, and as a result the published reports take the form of very preliminary work with model compounds. It will never be known how much of the published investigation of the chemistry of medium ring alkenes was originally directed toward the synthesis of cyclodecapentaene and, while failing in this respect, succeeded in leading to other worthwhile avenues of research. In any case, it is instructive to review those investigations which are claimed as approaches to cyclodecapentaene or its derivatives. This review, when conducted by grouping syntheses arbitrarily according to type, is enlightening with regard to the cyclodecapentaene system, including its possible precursors and modes of decomposition.

A. ACETYLENE POLYMERIZATION

Polymerization of acetylene units is perhaps conceptually the most simple method of generating the annulenes. In 1948, Reppe *et al.*[16] reported that a high-pressure nickel cyanide-catalyzed polymerization of acetylene yielded a

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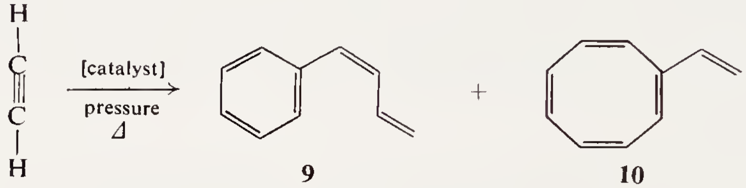
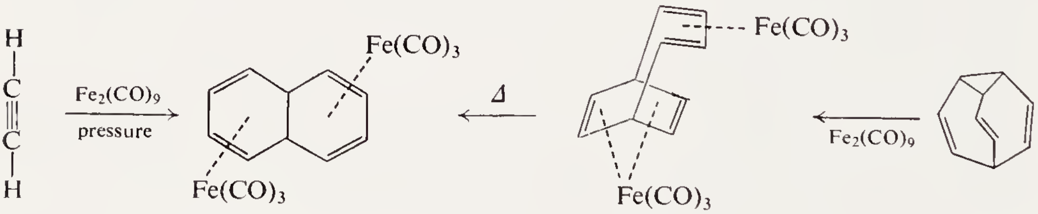
[16] V. W. Reppe, O. Schlichting, and H. Meister, *Ann.* **560**, 93 (1948).

plethora of products, including two oligomers of the empirical formula $C_{10}H_{10}$—one orange, the other yellow. Both isomers were reduced catalytically to $C_{10}H_{20}$ species. Reinvestigation of both compounds, believed by Reppe and his colleagues to be two forms of cyclodecapentaene, was undertaken independently in three laboratories. Cope and Fenton,[17] Craig and Larrabee,[18] and Withey[19] were in agreement in identifying the $C_{10}H_{10}$ oligomers as *cis*-1-phenylbuta-1,3-diene (**9**) and vinylcyclooctatetraene (**10**).

In light of recent studies involving other transition metal catalysts for the polymerization of olefins via complexes with geometries so prescribed that specific oligomerizations are favored,[20] one might anticipate many new efforts in this area. In fact, only one experiment is reported which may bear on the acetylene-polymerization approach to cyclodecapentaene. Weiss *et al.*[21] performed a high-pressure acetylene polymerization in the presence of iron enneacarbonyl and diiron dodecacarbonyl. Of the many products formed, one, isolated in trace quantity, was shown to have the empirical formula $C_{10}H_{10}Fe_2(CO)_6$. On the basis of its NMR spectrum the compound was tentatively assigned the structure **11**, a 9,10-dihydronaphthalene diiron hexacarbonyl of unspecified stereochemistry at the ring juncture. The identical



9 **10**



11 **12** **13**

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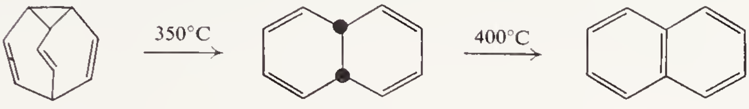
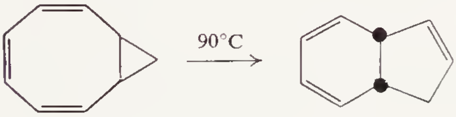
[17] A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.* 73, 1195 (1951).
[18] L. E. Craig and C. E. Larrabee, *J. Am. Chem. Soc.* 73, 1191 (1951).
[19] D. W. Withey, *J. Chem. Soc.* p. 1930 (1952).
[20] For example, G. Wilke, *Angew. Chem. Intern. Ed. Engl.* **2**, 105 (1963).
[21] E. Weiss, W. Hübel, and R. Merenyi, *Ber.* **95**, 1155 (1962).

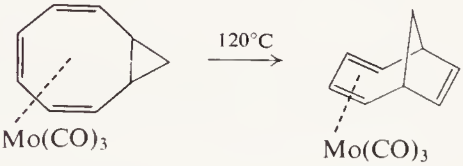
complex has been isolated by Schrauzer *et al.*[22] as a result of pyrolysis of the iron carbonyl complex **12**, in turn generated by treatment of bullvalene (**13**) with iron enneacarbonyl in benzene at reflux. Since this latter study, in the authors' description, has permitted isolation of intermediates in the known conversion of bullvalene to naphthalene,[23] and is in agreement with the more recent observation by Doering and Rosenthal[24] of the stepwise transformation **13** → **14** → **15** in the hydrocarbon series, it is reasonable to suggest that the stereochemistry of the complex **11** is cis, as in **14**. Observations described in Section II, H, 2, identifying *cis*-9,10-dihydronaphthalene (**14**) as the product of thermal rearrangement of cyclodecapentaene,[25] lead one to suspect that the iron carbonylacetylene polymerization may have involved a transient cyclodecapentaene, either free or complexed, as a progenitor of the dihydronaphthalene complex **11**. Caution should be exercised in employing this type of thinking, for, although the rearrangement of the parent hydrocarbon and the metal carbonyl complex is perfectly parallel to bullvalene–dihydronaphthalene system, this need not always be the case. Grimme,[26] in studying the thermal rearrangement of the bicyclic triene **16** and its molybdenum tricarbonyl complex **18**, uncovered an example of disparity in this analogous case. Thus, triene **16** is observed to undergo rearrangement to 8,9-dihydroindene (**17**) upon being heated. The complex **18** of this triene, however, rearranges at a



13 **14** **15**



16 **17**



18 **19**

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[22] G. N. Schrauzer, P. Glockner, and R. Merenyi, *Angew. Chem. Intern. Ed. Engl.* **3**, 509 (1964).

[23] G. Schröder, *Ber.* **97**, 3140 (1964).

[24] W. von E. Doering and J. W. Rosenthal, *J. Am. Chem. Soc.* **88**, 2078 (1966); *Tetrahedron Letters*, p. 349 (1967).

[25] E. E. van Tamelen and T. L. Burkoth, *J. Am. Chem. Soc.* **89**, 151 (1967).

[26] W. Grimme, *Ber.* **100**, 113 (1967).

slightly higher temperature to the complex **19** of bicyclo[4.2.1]nona-2,4,7-triene.

B. GENERATION OF UNSATURATION IN A PREFORMED RING

Another general route to cyclodecapentaene is one involving the generation of unsaturation in a preformed 10-membered carbocycle by either catalytic or other stepwise chemical means. The first of these possibilities was inspected by Prelog *et al.*,[27] who dehydrogenated eight medium-ring cycloalkanes (C_9–C_{18}). Several examples are shown in Fig. 1. The resulting hydrocarbon products point to the tendency of the unsaturated medium-ring intermediates to react in a transannular sense to produce fused, mainly benzenoid, aromatic species. In a similar study Prelog and Schenker[28] treated various functionalized cyclodecanes **21a–e** with a mixture of alumina and palladium-on-charcoal at 350°C.

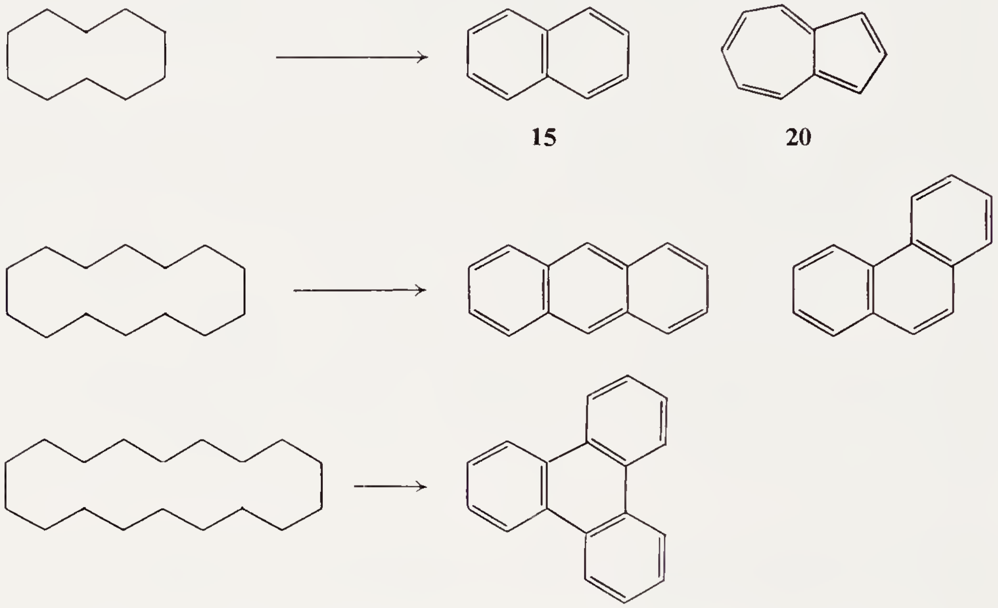
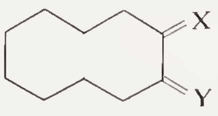


FIG. 1. Examples of dehydrogenation of medium-ring cycloalkanes.



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	21a	**21b**	**21c**	**21d**	**21e**
X:	H, OH	O	O	H, OH	O
Y:	H_2	H_2	H, OH	H, OH	O

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[27] V. Prelog, V. Boarland, and S. Polyak, *Helv. Chim. Acta* **38**, 434 (1955).

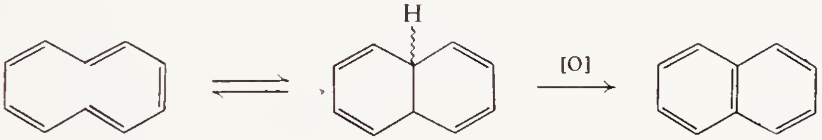
[28] V. Prelog and K. Schenker, *Helv. Chim. Acta* **36**, 1181 (1953).

As in the dehydrogenation of cyclodecane above, azulene (**20**) was a minor product, while naphthalene (**15**) was produced in major amount. This work was likewise cited as evidence for the greater stability of benzenoid species, and, in conjunction with the precedents provided by Alder[29] in the cyclonona-1,3,5-triene system **22**–**23** and by Cope[31] in the cycloocta-1,3,5-triene system **24**–**25**, led Prelog[30] to postulate that a major difficulty in the synthesis of cyclodecapentaene would be valence bond isomerization. Cope[31] defined valence bond isomerization or valency tautomerism to be a reversible isomerization

22 **23**

24 **25**

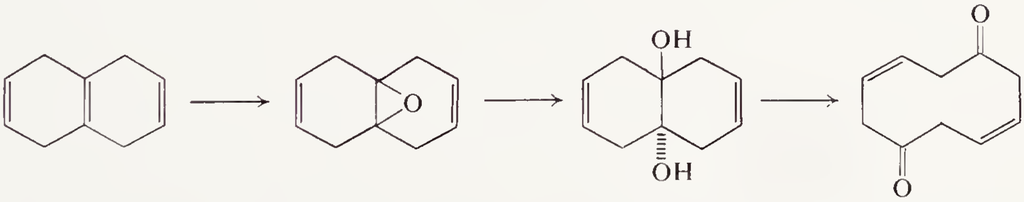
such as **22** $\rightleftharpoons$ **23**. He stated: "Only electronic displacements corresponding to interconversion of double and single bonds occur in the isomerization, with the corresponding changes in bond angles and distances." In keeping with this definition, Prelog suggested that cyclodecapentaene (**1**) could isomerize by



1 **26** **15**

ring closure to a 9,10-dihydronaphthalene (**26**) and then, in some manner, be oxidized to the very stable naphthalene (**15**).

Stepwise chemical generation of unsaturation best characterizes the classical approach to cyclodecapolyenes of Grob and Schiess.[32] The so-called isotetralin **27** was converted to the diene epoxide **28**, which was opened to the



27 **28** **29** **30**

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[29] K. Alder and H. A. Dortmann, *Ber.* **87**, 1492, 1905 (1941).

[30] V. Prelog, *in* "Perspectives in Organic Chemistry" (A. Todd, ed.), p. 127. Wiley (Interscience), New York, 1956.

[31] A. C. Cope, A. C. Haven, Jr., F. L. Ramp, and E. R. Trumbull, *J. Am. Chem. Soc.* **74**, 4867 (1952).

[32] C. A. Grob and P. W. Schiess, *Helv. Chim. Acta* **47**, 558 (1964).

trans-dihydroxydiene **29**. This species was cleaved in high yield to the dienedione **30** by means of lead tetraacetate. The diketone **30** served as precursor to 1,6-bisdimethylaminocyclodeca-*cis*-*cis*-3,8-diene (**31**) via its bisoxime derivative. The diamine **31** was subjected to the conditions of the Hoffman and Cope eliminations (Fig. 2) after being converted to the necessary bisquaternary

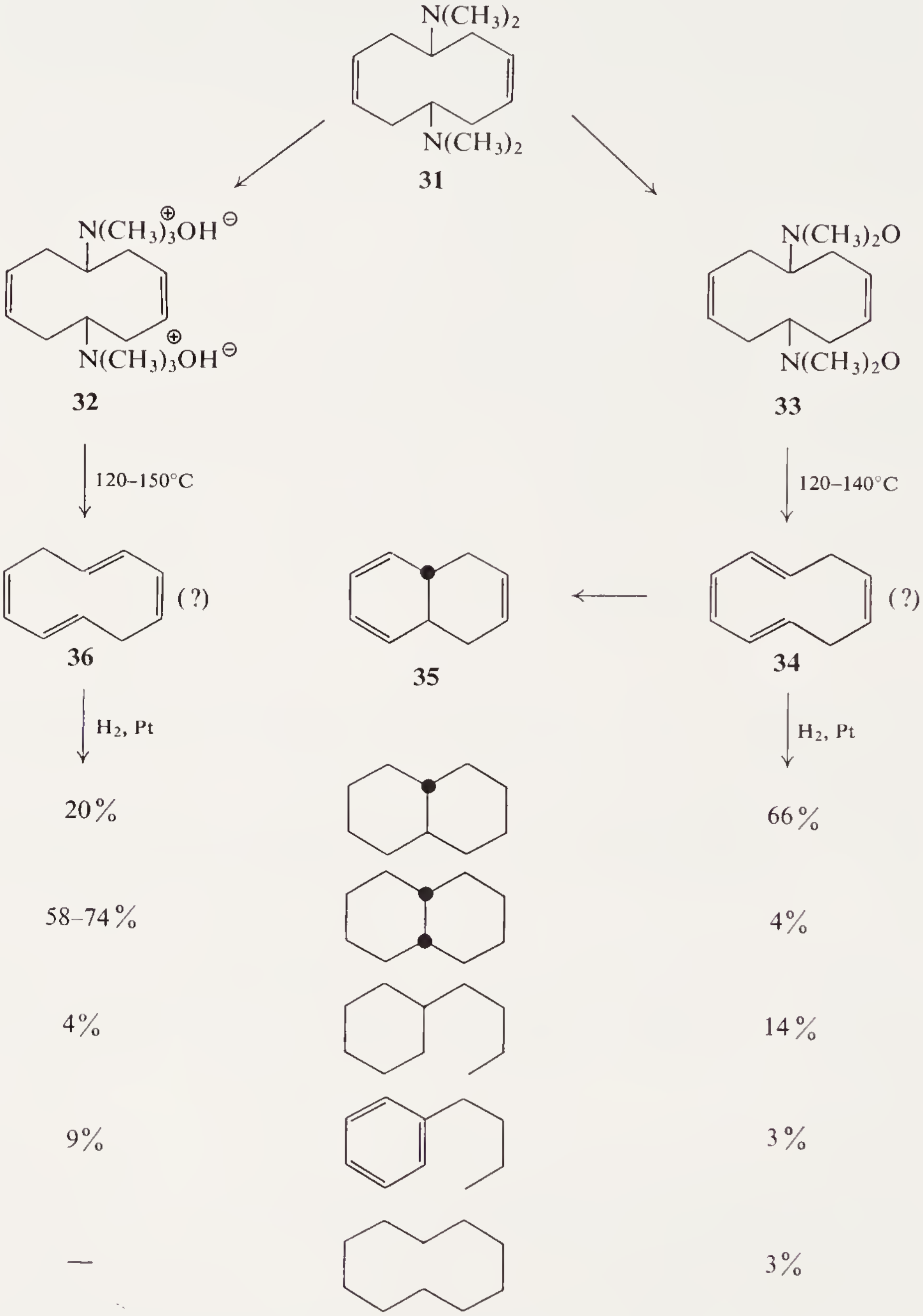
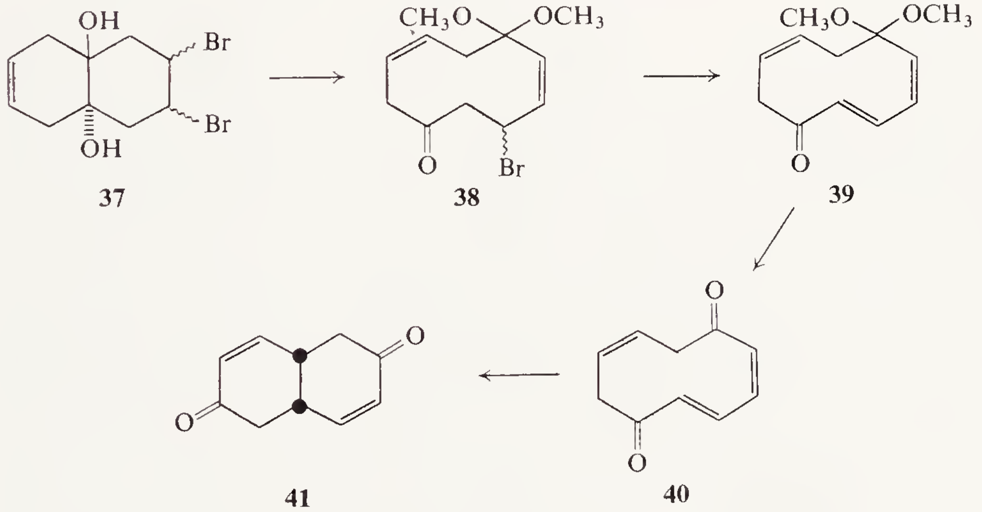


Fig. 2. Diamine (**31**) subjected to conditions of Hoffman and Cope eliminations.

ammonium hydroxide **32** and bis-*N*-oxide **33** derivatives, respectively. In each case cyclodecatetraene isomers, apparently unstable, are postulated as shown. For example, from the pyrolysis of the bis-*N*-oxide **33** a cyclodecatetraene valence bond isomer, *trans*-1,4,9,10-tetrahydronaphthalene (**35**), was isolated; but in both cases the stereochemistry of the presumed intermediary cyclodecatetraenes is only inferred from knowledge of the mechanisms of the two types of elimination. This inference is partially substantiated by analysis of the products of catalytic hydrogenation. The preponderance of the decalins among the reduction products, along with the apparently facile valence bond isomerization to the triene **35**, seem to give the synthetic difficulty anticipated by Prelog considerable basis in fact.

Another attempt to generate a cyclodecapentaene by stepwise increase of the unsaturation in a 10-membered ring was made by Sondheimer and Mulligan.[33] Starting with the bicyclic diene diol **29** of Grob and Schiess by monobromination to **37**, they found that cleavage with lead tetraacetate in methanol under reflux afforded the ketal **38**, a product of elimination. Basic alumina promoted further elimination to the trieneone ketal **39**, which was readily hydrolyzed in acidic, aqueous acetone to the triene dione **40**, formally a keto enol tautomer of 1,6-dihydroxycyclodeca-1,3,5,7,9-pentaene. The severe distortion of the 10-membered ring in this dione is attested to by the lack of change in the ultraviolet spectrum ($\lambda_{max} = 257$ mμ) upon generation of **40** from **39**. Attempts to secure a species of the cyclodecapentaene type, specifically the bisenol acetate or the dichloride, were unsuccessful. Treatment of the



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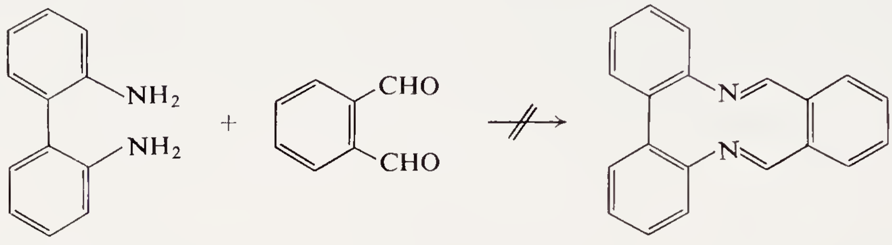
[33] P. J. Mulligan and F. Sondheimer, *J. Am. Chem. Soc.* **89**, 7118 (1967).

trienedione **40** with acid at slightly elevated temperatures afforded the cis bicyclic dienedione **41**.

C. Approaches to Heteroatomic Substituted Species

Avoidance of the serious difficulty of nonbonded hydrogen repulsion interior to the carbocyclic skeleton of cyclodecapentaene was apparently considered of prime importance in the synthetic designs of Noller and Blood.[34] They report that inspection of Fischer-Hirschfelder as well as Briegleb molecular models draws one to the conclusion that planarity is possible in 1,6-diazacyclodecapentaene. Their synthetic attempts based on this belief were not fruitful, however, as the reaction of 2,2′-diaminobiphenyl (**42**) with *o*-phthalaldehyde (**43**), even under conditions of extreme dilution, led to linear polymers and tars rather than the desired species, **44**. In another attempt, the action of phosphorus oxychloride in *N*-benzylidene-*N*-acetyl-2,2-diaminobiphenyl **45** led to the amidine **47** rather than the desired methyltribenzodiazacyclodecapentaene **46**.



42 **43** **44**

Interest in such heteroatomic substituted cyclodecapentaenes led to the reinvestigation of some early work by Diels and Alder.[35] In several papers (1932–1934), these authors reported the reaction of dimethyl acetylenedicarboxylate with pyridines and also quinolines. To these potential valence bond isomers of azacyclodecapentaene—one reportedly "labile," the other "stable," —Diels and Alder tentatively assigned the structures **48** and **49**, respectively. Reinvestigation, undertaken independently by Acheson and Taylor[36] as well as by van Tamelen *et al.*,[37] led to reassignment of structure **49** to the "labile" isomer, and **50** (by the latter group) to the "stable" isomer, to which **49** rearranged. The latter investigators interpreted NMR studies in specifically ruling out an azacyclodecapentaene structure.

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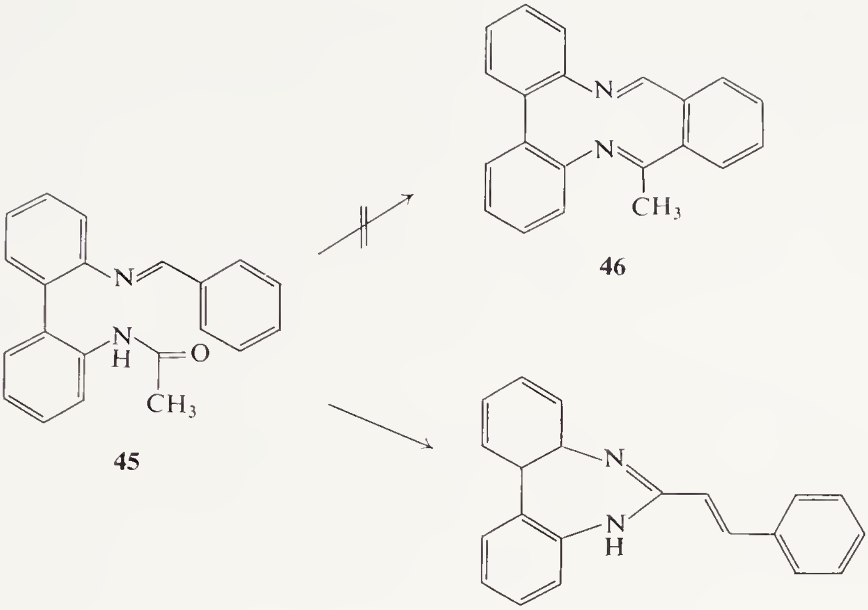
[34] A. E. Blood and C. R. Noller, *J. Org. Chem.* **22**, 873 (1957).

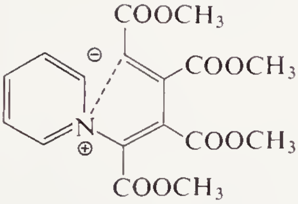
[35] O. Diels and K. Alder, *Ann. Chem.* **498**, 16 (1932); **505**, 103 (1933); **510**, 87 (1934).

[36] R. M. Acheson and G. A. Taylor, *Proc. Chem. Soc.* p. 186 (1959).

[37] E. E. van Tamelen, P. E. Aldrich, P. Bender, and G. Miller, *Proc. Chem. Soc.* p. 309 (1959).



45 **46** **47**



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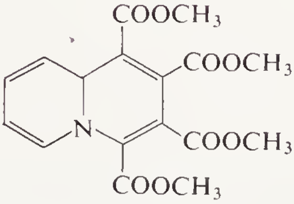

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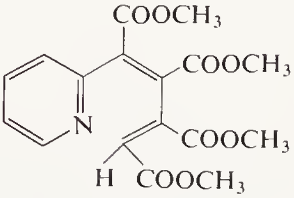

50

A proposal bearing on the possibility of eliminating internal hydrogen repulsion by substituting heteroatoms in a 1,6 relationship had been made 10 years earlier. Sworski[38] predicted that 1,2,6,7-didehydrocyclodecapentaene

51

(**51**) could exist as a planar, fully conjugated cyclic structure. This cyclic polyene has a π system of 10 coplanar electrons and could formally assume a

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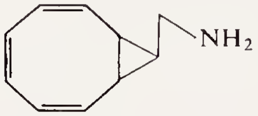
[38] T. J. Sworski, *J. Chem. Phys.* **16**, 550 (1948).

geometry which is strainless with respect to both bond length and bond angles. The reason that the validity of the prediction was not established experimentally by synthesis may be that the internal repulsion by the filled electron orbitals of the acetylene and cumulene moieties, which have lobes in the plane of the carbocycle, is comparable to internal hydrogen repulsion. The same argument may be advanced to explain the failure to realize by synthesis the azacyclodecapentaenes **44** and **46**, in which the unshared electron pair on nitrogen would be interior to the 10-membered ring.

D. RING EXPANSION

Application of the general synthetic approach of ring expansion to the task of generation of cyclodecapentaenes, potential precursors, or closely related species has been reported by several research groups. In a classical attempt, Champion[39] prepared the cyclopropylcarbinyl amine **52** by elaboration of the adduct of carboethoxycarbene and cyclooctatetraene. His work in this series seemed plagued by the now well-documented rearrangement[40a–e] of 9-substituted bicyclo[6.1.0]nona-2,4,6-trienes (**53**) to 8,9-dihydroindene derivatives (**54**), another example of the tendency of medium-ring polyenes to react in a transannular fashion. It is clear, however, that upon treatment of the bicyclic amine **52** with aqueous nitrous acid under conditions for the Demjanov rearrangement, no ring expansion, in the desired sense, occurred.



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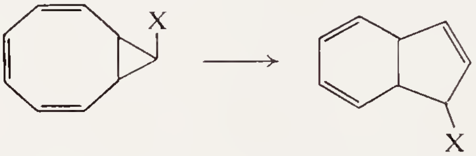

53 **54**

At Stanford, a closely analogous experimental approach was inspected.[41] An attempt to form the cation **56**[42] by solvolysis of the bicyclic tosylate **55**

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[39] W. C. Champion, Ph. D. Thesis, Cornell University, 1958 [*Dissertation Abstr.* **19**, 3122 (1959)].

[40a] E. Vogel and H. Kiefer, *Angew. Chem.* **73**, 548 (1961).

[40b] E. Vogel, W. Wiedemann, H. Kiefer, and W. F. Harrison, *Tetrahedron Letters* p. 673 (1963).

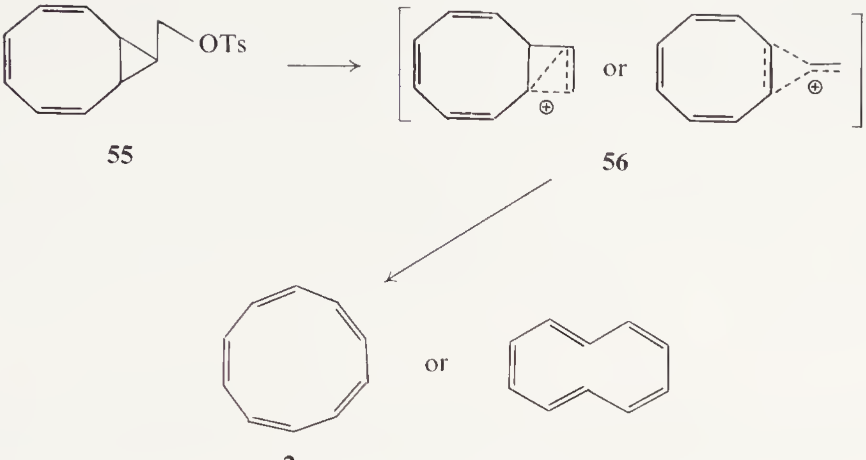
[40c] K. F. Bangert and V. Boekelheide, *J. Am. Chem. Soc.* **86**, 905 (1964).

[40d] K. F. Bangert and V. Boekelheide, *J. Am. Chem. Soc.* **86**, 1159 (1964).

[40e] T. L. Burkoth, *J. Org. Chem.* **31**, 4259 (1966).

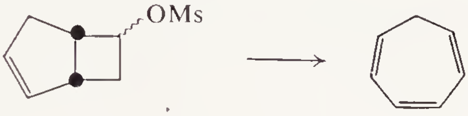
[41] T. L. Burkoth, Ph. D. Thesis, Stanford University, 1967.

[42] P. von R. Schleyer and G. W. Van Dine, *J. Am. Chem. Soc.* **88**, 2321 (1966).



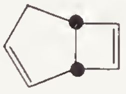
55 **56** **2** **1**

was prompted by a precedent provided by Dryden.[43] This investigator prepared cycloheptatriene (**58**) in good yield by solvolysis of the bicyclic mesylate



57 **58**

57. The solvolysis was accomplished under distillative conditions, however, and the author has not considered or ruled out solvolytic formation of the bicyclic diene **59** followed by thermally induced valence bond isomerization to cycloheptatriene. It was considered likely that, through use of polar aprotic



59

media, the conditions for solvolysis could be made less severe and more propitious for elimination, thereby permitting generation of a cyclodecapentaene species. When 9-hydroxymethylbicyclo[6.1.0]nona-2,4,6-triene tosylate (**55**) was dissolved in the anhydrous system dimethylformamide saturated with lithium perchlorate and containing potassium carbonate, and stirred under nitrogen for 2 hours at room temperature, the maximum amount of

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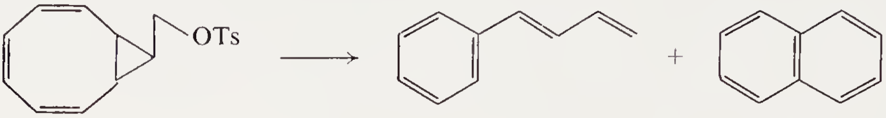
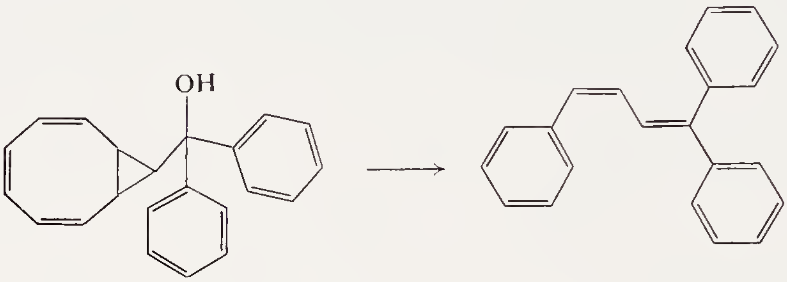
[43] H. L. Dryden, Jr., *J. Am. Chem. Soc.* 76, 2841 (1954); H. L. Dryden, Jr. and B. E. Burgert, *ibid.* 77, 5633 (1955).

solvolytic elimination was observed. The unexceptional products *trans*-1-phenylbuta-1,3-diene (**60**) (30%) and naphthalene (**15**) (10%) were produced, the balance of products having alcohol functional groups. This result is in essential agreement with work by Bangert and Boekelheide,[40d] who reported the cationic rearrangement of the diphenylbicyclo[6.1.0]alcohol (**61**) through the agency of fluoroboric acid. These investigators isolated 1,1,4-triphenylbuta-1,3-diene (**62**) in 80% yield. In this case, due to the highly activated tertiary alcohol, a carbonium ion of the desired type was surely formed. It can be reasoned, therefore, by comparison of reaction products in the two experiments, that the solvolytic ring expansion route to cyclodecapentaene has been adequately tested and shown to fail.

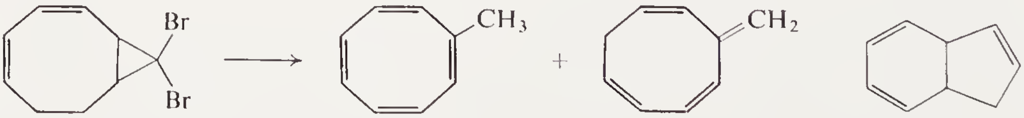


55 **60** **15**



61 **62**

Cortez,[44] in some preliminary experiments designed to generate medium-ring polyenes by a ring-expansion method, treated the adduct **63** of dibromocarbene and cycloocta-1,3,5-triene with strong base. Isolation of the hydrocarbon products **64**, **65**, and **66** with no indication of ring expansion discouraged further investigation of this method.



63 **64** **65** **66**

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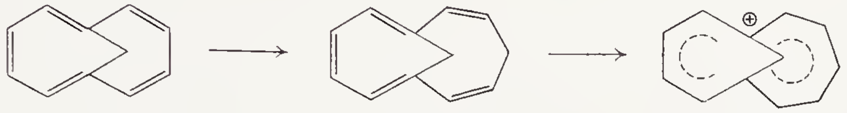
[44] H. V. Cortez, Ph. D. Thesis, Univ. of Texas, 1964 [*Dissertation Abstr.* **25**, 2754 (1964)].

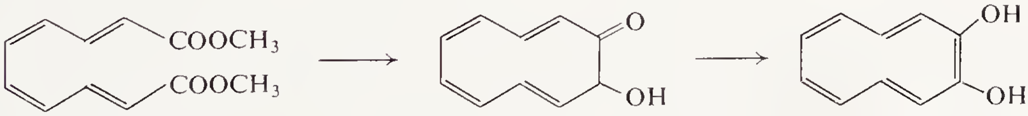
Several more promising examples of carbenoid ring-expansion routes to cyclodecapentaene have been reported. In an extension of the principle involved in the synthesis of cyclononatetraene anion (**8**) from the cyclooctatetraene dianion (**6**), as mentioned in Section I, D, preliminary attempts to ring expand the cyclononatetraene anion in a similar fashion have been made by Katz and co-workers. To date the results have been unpromising.[45] Success in another series by Vogel *et al.*[46] makes the continuing efforts along these lines seem worthwhile. Vogel ring expanded the aromatic 1,6-methanocyclodecapentaene **67**. Thus treatment of **67** with diazomethane in the presence of copper(I) chloride furnished the bicyclic pentaene **68**, which afforded the 10 π-electron cation **69** upon treatment with triphenylmethyl tetrafluoroborate.



67 **68** **69**

E. Ring Closure

The general approach of ring closure has also been employed in several attempts to synthesize a cyclodecapentaene. LeClercq[6] favored a scheme involving a very powerful method for producing medium-to-large carbocyclic systems, the acyloin condensation. His goal was preparation of the tetraene diester **70**, and—by means of the acyloin reaction—production of the tetraene acyloin **71**. The acyloin **71** might then undergo enol tautomerization to **72** or be converted to the parent cyclodecapentaene by a stepwise chemical transformation. Model studies with the more readily obtainable *cis,cis*-dimethylmuconate **73** yielded only the geometrically isomerized *trans,trans*-diene diester



70 **71** **72**

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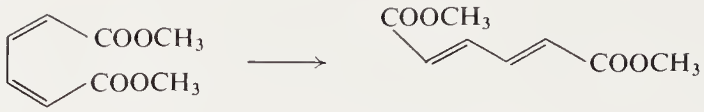
[45] T. J. Katz, private communication.

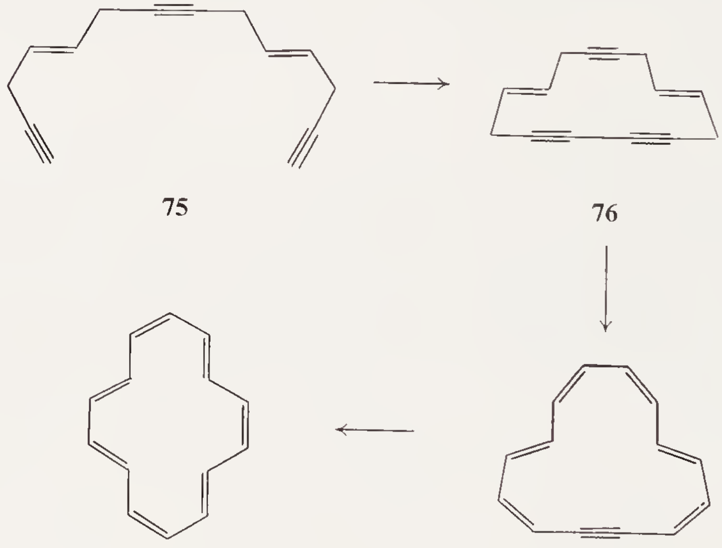
[46] W. Grimme, H. Hoffmann, and E. Vogel, *Angew. Intern. Ed. Engl.* **4**, 354 (1965).



73 **74**

74, isomerization presumably being much faster than acyloin condensation, and therefore precluding it.

Sondheimer and his co-workers have successfully applied several methods of acetylene coupling in ring-closure approaches to the annulenes.[9] As the result of notable effort in this area, this group can boast syntheses of [12]-, [14]-, [16]-, [18]-, [20]-, [24]-, and [30]annulene as well as 16 dehydroannulenes! One illustrative example of their work is the synthesis of [14]annulene (**5**) (see Sections I,C and I,E). In this synthesis the linear C_{14}-dienetriyne **75** was treated with copper(II) acetate in pyridine to effect an acetylene coupling-type ring closure, generating the highly unsaturated carbocycle **76** in 2% yield. This material could be rearranged by means of potassium tertiary butoxide in tertiary butanol to a monodehydro[14]annulene shown to have the structure **77**. Partial hydrogenation of this species on calcium carbonate afforded [14]-annulene in 30% yield. The C_{10} series, however, has resisted attempts modeled after those syntheses so rewarding in the larger ring systems. A recent report[47]



75 **76** **5** **77**

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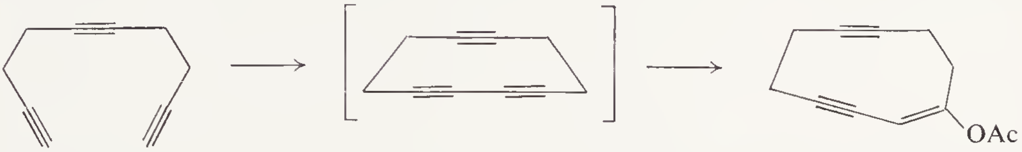
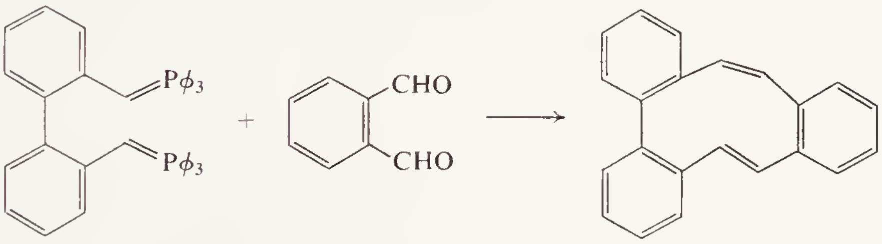
[47] R. Wolovsky and F. Sondheimer, *J. Am. Chem. Soc.* **88**, 1525 (1966).

was made of an acetylene coupling which may ultimately provide an entrance into this system. Treatment of 1,5,9-decatriyne (**78**) with pyridine and copper(II) acetate apparently gave rise to the cyclic triyne **79** as an unstable intermediate which rapidly added the elements of acetic acid to give the enol acetate **80** and its positional isomer. Sondheimer describes the two enol acetates as "the most highly unsaturated unbridged 10-membered ring compounds known and appear to be useful intermediates for the synthesis of [10]annulene and its derivatives."



78 **79** **80**

Recently Sondheimer has employed the Wittig reaction to fabricate two annelated cyclodecapentaenes by a coupling variety of ring closure. With Grohmann[48] he reported the synthesis of mono *trans*-1,2:3,4:7,8-tribenz[10]-annulene (**82**) in 15% yield by generation of the bisylide **81** in the presence of *o*-phthalaldehyde. The same product could be obtained, albeit in reduced yield, when the reverse-functionalized compounds were reacted. The tribenzocyclodecapentaene **82** was reasonably stable in the solid state but gradually decomposed in solution or when exposed to light and air. It rearranged thermally to 9,10-dihydro-1,2:3,4-dibenzanthracene **84** via disrotatory closure to an intermediate *o*-xylylene derivative **83** which could be trapped by virtue of its



81 **82**

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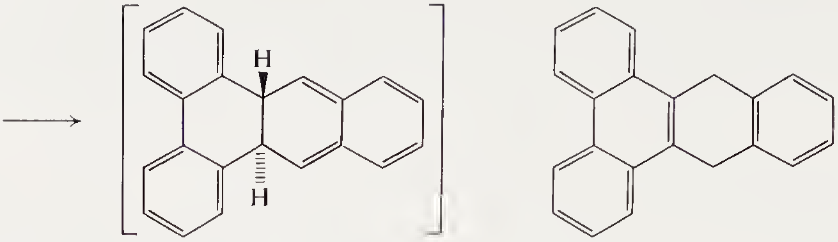
[48] K. Grohmann and F. Sondheimer, *J. Am. Chem. Soc.* **89**, 7119 (1967).

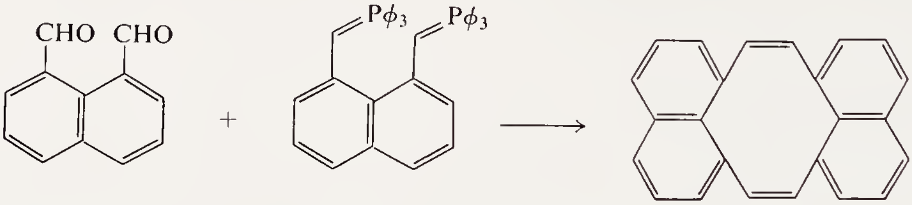
82



83 **84**

Diels-Alder reactivity with maleic anhydride. The mono-trans configuration of cyclodecapentaene **82** was assigned by virtue of a 17 cps vinyl coupling constant in the NMR spectrum as well as the infrared absorption at 958 cm^{-1}, also characteristic of a trans linkage. Moreover, the NMR spectrum was considered too complex to fit the di-trans isomer. Substantiation for this assignment was found in spectra properties of the Diels-Alder adduct which indicate a trans ring fusion. Thermally induced electrocyclic ring closure of a mono-trans species **82** would be expected to occur in a disrotatory fashion to afford a trans fused system. The unexpected stability of this cyclodecapentaene is presumed due to the necessity of disrupting the cyclic delocalization of a benzene ring during this latter isomerization.

Along similar lines, Sondheimer and Mitchell[49] report a Wittig reaction of 1,8-naphthalene dicarboxaldehyde (**85**) with the bisylide **86** to afford a mixture



85 **86** **87**

of substances from which the very interesting dinaphth[10]annulene **87** can be isolated in crystalline form in 2% yield. This bis annelated cyclodecapentaene **87** is not stable, but initially cyclizes with attendant hydrogen shifts to 7,14-dihydrozethrene (**88**). This isomerization is followed by facile air oxidation to the parent zethrene (**89**). The NMR spectrum of **87** exhibits a multiplet at 7.9–7.0 δ (14 H), a singlet at 3.49 δ (1 H), and a doublet ($J = 7$ cps) at 3.40 δ (1 H). This spectrum is not interpretable at present. A considerable effect on the spectrum was observed upon change of solvent but no temperature dependence was detected. Cis stereochemistry about the double bonds was

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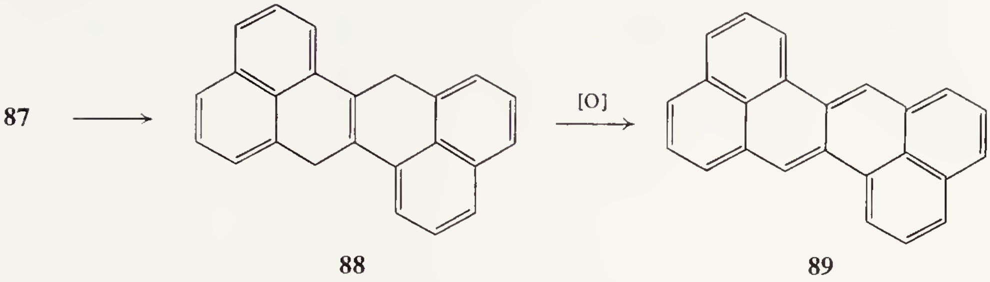
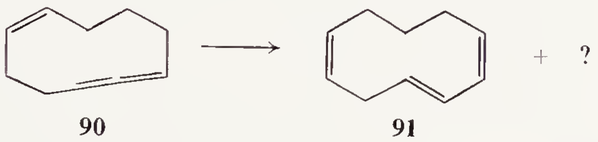
[49] R. H. Mitchell and F. Sondheimer, *J. Am. Chem. Soc.* **90**, 530 (1968).



assigned on the basis of only a very weak infrared band at 968 cm^{-1}. Sondheimer reasons from the data in hand that "it [**87**] is a nonplanar molecule and that it does not represent an annelated delocalized 10 π-electron system."

F. Isomerization of Cyclic Allenes or Acetylenes

Inherent in any synthetic use of intermediates gained by acetylene coupling or ring closure at a similar oxidation level is the problem of isomerizing and/or partially reducing triple bonds. Synthetic elaboration of the interesting enol acetate intermediates (**80**) would necessarily include operations of this type at some stage. In fact, a general approach to cyclodecapentaene synthesis might depend on the transformation of a 10-membered carbocycle already incorporating a sufficient degree of unsaturation in the form of acetylene or allene linkages. Cortez,[44] in early stages of work directed to this end, was able to isomerize the allene **90** to *cis,trans,cis*-cyclodeca-1,3,6-triene (**91**) accompanied by another hydrocarbon unisolable by reason of its instability.



Another potential intermediate for this general scheme was prepared by Grohmann and Sondheimer.[50] The dienedione **30**, first produced by Grob and Schiess (Section II,B), is found to undergo reactions in a transannular sense under the most mild of conditions. Treatment with phosphorus pentachloride, however, provides the three monocyclic chloroalkenes **92**, **93**, and **94** in reasonable yield, in additon to traces of a trichloroazulene of undetermined

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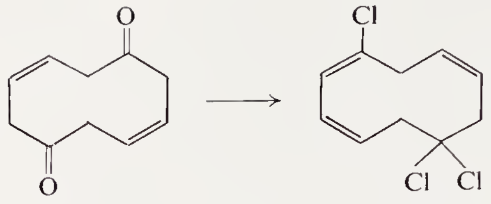
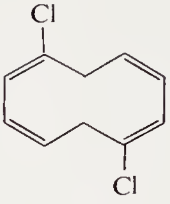
[50] K. Grohmann and F. Sondheimer, *Tetrahedron Letters*, p. 3121 (1967).



30 **92**



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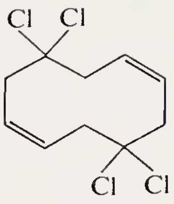
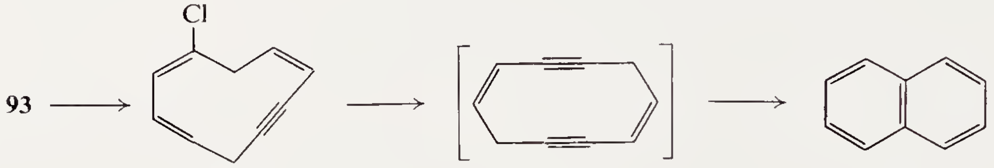
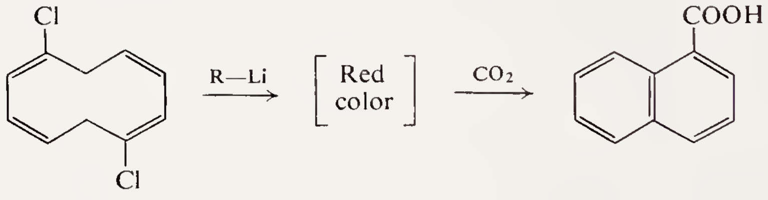


94

structure. The dichlorotetraene **93** was shown to have tetra-cis stereochemistry by X-ray crystallographic analysis. Removal of the elements of HCl by treatment of **93** with lithium diisopropylamide resulted in all *cis*-1-chlorocyclodeca-1,3,8-triene-6-yne (**95**). Attempts to effect dehydrochlorination of trieneyne **95** led to the production of naphthalene. Mechanistic speculation rests on the dienediyne **96** as a likely intermediate, but no supporting evidence is available. In contrast, treatment of dichlorotetraene **93** with butyllithium induced a deep-red color which was not explained. Carboxylation of a solution of the red material afforded naphthalene-1-carboxylic acid (**97**) in 78% yield.



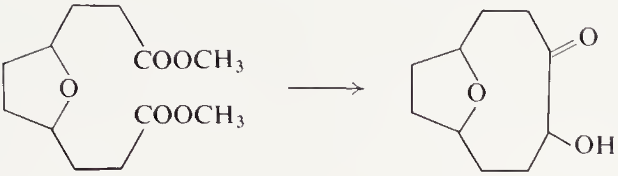
95 **96** **15**



93 **97**

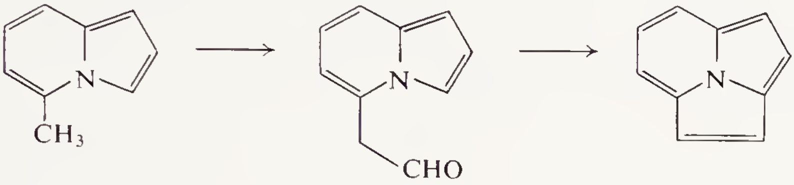
G. Formation of Bridged Species

Several investigators have acted on the possibility that a cyclodecapentaene containing a carbon or heteroatom bridge would be more easily secured and/or would possess greater stability than the parent monocycle. An early example is found in the work of LeClercq[6] (see Section II,E). In an effort to avoid the problem of double-bond isomerization in the acyloin ring closure of unsaturated diesters **70** and **73**, this investigator chose to bridge the system with oxygen.



98 **99**

However, cyclization studies were apparently discontinued despite the successful ring closure of a model saturated diester (**98**–**99**). In 1958, Boekelheide and Windgassen[51] synthesized the parent (**102**) of a new class of aromatic compounds to which they applied the trivial name cycl[3.2.2]azine. Treatment of 5-methylpyrrocoline (**100**) with butyllithium followed by dimethylformamide afforded the pyrrocoline aldehyde **101.** This intermediate underwent cyclodehydration in hot glacial acetic acid to yield the desired product **102**. Although cycl[3.2.2]azine is formally a cyclodecapentaene bridged by nitrogen, both its chemical behavior[52] and properties, as predicted by molecular orbital calculations,[53] expose it as a distinct aromatic species for which the description "bridged cyclodecapentaene" is not apt. Much like naphthalene in odor and ease of sublimation, the cyclazine is a yellow, fluorescent compound stable to heat, light, and air. It exhibits no basicity! Reactions of this compound are best characterized as aromatic substitutions. Molecular orbital calculations, which have permitted successful prediction of the sites of chemical reactivity, suggest a delocalization energy of $\sim 5\ \beta$. In contrast, the cyclodecapentaene periphery is predicted to be stabilized by a factor of $2.9\ \beta$.



100 **101** **102**

In 1964, this concept of a bridged species led to the preparation of the first stable cyclodecapentaene derivatives. Vogel and Roth[54] concluded that a 1,6-methane bridged 10-membered cyclic polyene could exist in an almost planar, strainless conformation by virtue of the absence of the normally

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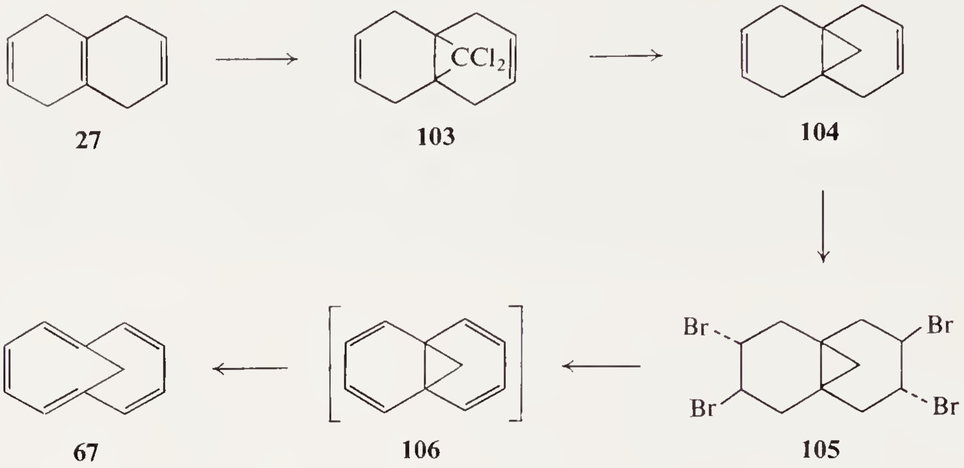
[51] V. Boekelheide and R. J. Windgassen, Jr., *J. Am. Chem. Soc.* **80**, 2020 (1958).

[52] V. Boekelheide and T. Small, *J. Am. Chem. Soc.* **83**, 462 (1961).

[53] R. J. Windgassen, Jr., W. H. Saunders, and V. Boekelheide, *J. Am. Chem. Soc.* **81**, 1459 (1959).

[54] E. Vogel and H. D. Roth, *Angew. Chem. Intern. Ed. Engl.* 3, 228 (1964).

interfering internal 1,6-hydrogens. A straightforward synthetic sequence (**27** → **103** → **104** → **105** → **67**) beginning with (*a*) the addition of dichlorocarbene to isotetralin (**27**), followed by (*b*) reductive removal of chlorine with sodium in ammonia, (*c*) bromination, and then (*d*) dehydrobromination with



27 **103** **104**

67 **106** **105**

aqueous base, led not to the tetraene **106** but directly to the aromatic species **67**. Both chemical behavior and physical data constitute evidence for the aromaticity of the bridged cyclodecapentaene. The hydrocarbon exhibits no tendency to polymerize and does not react with maleic anhydride in boiling benzene.[55] Its treatment with electrophilic reagents affords products of mono- and disubstitution (an addition–elimination mechanism seems to be involved in some cases).[55] For example, Vogel and Böll observed nitration in the usual fashion to give the yellow mononitro aromatic species **107** as well as the orange dinitro compound **108**. Other bridged cyclodecapentaenes have been prepared.[56] Vogel *et al.*[57] as well as Sondheimer and Shani[64] have described compounds of structure **109** where X is NH, NAc, or O. It is also reported that when X is quaternary nitrogen, pyrolysis gives naphthalene;[58] and that alcohol **109** (X = CHOH) loses carbon monoxide under conditions of mild oxidation, also to yield naphthalene[59] The compound **109** where X is $C{=}CH_2$ has also

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[55] E. Vogel and W. A. Böll, *Angew. Chem. Intern. Ed. Engl.* **3**, 642 (1964); E. Vogel, W. Grimme, and S. Korte, *Tetrahedron Letters*, p. 3625 (1965).

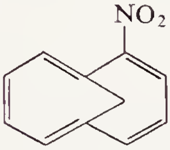
[56] E. Vogel, W. Schröck, and W. A. Böll, *Angew. Chem. Intern. Ed. Engl.* **5**, 732 (1966).

[57] E. Vogel, M. Biskup, W. Pretzer, and W. A. Böll, *Angew. Chem. Intern. Ed. Engl.* **3**, 642 (1964); E. Vogel, W. Pretzer, and W. A. Böll, *Tetrahedron Letters*, p. 3613 (1965).

[58] E. Vogel, Seminar, Stanford University, 1966.

[59] E. Vogel, F. Weyres, H. Lepper, and V. Rautenstrauch, *Angew. Chem. Intern. Ed. Engl.* **5**, 732 (1966).

been prepared.[59] According to physical criteria (ultraviolet,[60] NMR,[61] electron spin resonance spectroscopy,[62] and dipole measurements[63]), all of the above bridged species are aromatic. The hydrocarbon **67**, for example, has ultraviolet maxima at 256, 259, and 298 mμ ($\epsilon = 68,000$, 63,000, and 6200), incompatible with the tetraene precursor **106**. The conjugated system of double bonds in **67** clearly indicates the ability to sustain a ring current induced by an external magnetic field. The proton chemical shifts, the result of diamagnetic anisotropy about a strong ring current, are 6.8–7.5 δ (8 H, A_2B_2 multiplet) and -0.5 δ (2 H, singlet). Testimony to the great stability of such bridged cyclodecapentaenes is given by the fact that Sondheimer and Shani[64] prepared 1,6-oxidocyclodecapentaene (**109**, X = O) inadvertently in connection with a projected synthesis of the quinone vinylog **110**. Further indication of this stability is found in the preparation of the chromium carbonyl complex of 16-methanocyclodecapentaene[65]: photolysis of appropriate starting materials for 86 hours affords product, for which NMR evidence suggests full 10 π-electron aromaticity.[66] The size of the bridge appears to be a prime factor in determining the stabilization of a bridged cyclodecapentaene. Bloomfield and Quinlin[67] prepared the furano bridged tetraene **112**, and found it to be stable with respect to its aromatic valence bond isomer. Likewise, the bridged anhydride **113** prepared by Vogel *et al.*[68] was noted not to isomerize upon



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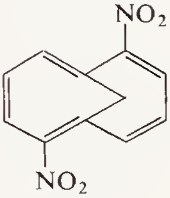

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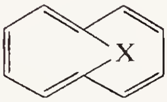


109

[60] H.-R. Blattmann, W. A. Böll, E. Heilbronner, G. Hohlneicher, E. Vogel, and J.-P. Weber, *Helv. Chim. Acta* **49**, 2017 (1966).

[61] H. Günther, *Angew. Chem. Intern. Ed. Engl.* **4**, 702 (1965); *Z. Naturforsch.* **20b**, 948 (1965).

[62] F. Gerson, E. Heilbronner, W. A. Böll, and E. Vogel, *Helv. Chim. Acta* **48**, 1494 (1965).

[63] W. Bremser, H. T. Grunder, E. Heilbronner, and E. Vogel, *Helv. Chim. Acta* **50**, 84 (1967).

[64] F. Sondheimer and A. Shani, *J. Am. Chem. Soc.* **86**, 3168 (1964); **89**, 6310 (1967).

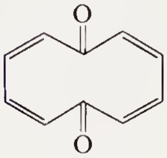
[65] E. Vogel and W. Grimme, *Angew. Chem. Intern. Ed. Engl.* **5**, 518 (1966).

[66] E. Vogel and W. Grimme, *Angew. Chem. Intern. Ed. Engl.* **5**, 1043 (1966).

[67] J. J. Bloomfield and W. T. Quinlin, *J. Am. Chem. Soc.* **86**, 2738 (1964).

[68] E. Vogel, W. Meckel, and W. Grimme, *Angew. Chem. Intern. Ed. Engl.* **3**, 643 (1964).

heating. Photolysis[69] was reported to give the two rearranged anhydrides, **114** and **115**. In another similar attempt Vogel *et al.*[70] prepared 9,10-ethano-9,10-



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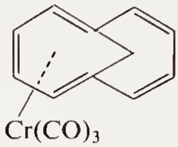

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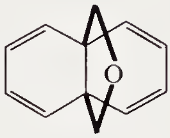

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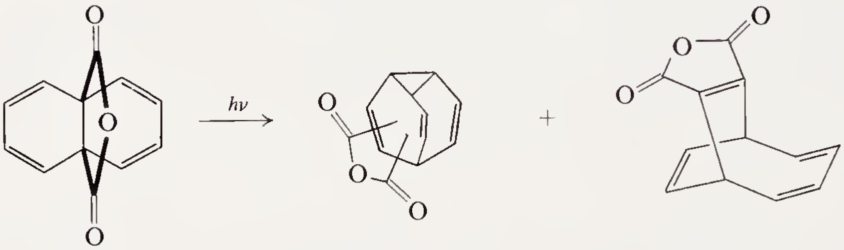
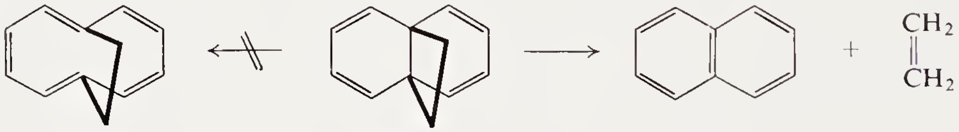
dihydronaphthalene **116** and found that, under thermolysis conditions expected to promote valence bond isomerization to **117**, this tetraene lost



113 **114** **115**



117 **116** **15**

ethylene to produce the stable, ubiquitous naphthalene. The latter authors have suggested that the effect of bridge size depends on two underlying factors. First, the energy of strain relief in going from the tricyclic tetraene **106** to the bicyclic pentaene **67** as a major driving force would be maximal in a species with a cyclopropane ring. Second, the geometry of the aromatic system is very dependent on bridge size and probably involves near coplanarity in a system with a single methylene bridge. Dobler and Dunitz[71] have verified this point of

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[69] E. Vogel, W. Grimme, W. Meckel, and H. J. Riebel, *Angew. Chem. Intern. Ed. Engl.* 5, 590 (1966).

[70] E. Vogel, W. Maier, and J. Eimer, *Tetrahedron Letters*, p. 655 (1966).

[71] M. Dobler and J. D. Dunitz, *Helv. Chim. Acta* **48**, 1429 (1965).

view through the use of X-ray crystallographic analysis of a suitable derivative which revealed the geometry depicted in Fig. 3 as representative of the 1,6 bridged cyclodecapentaenes.

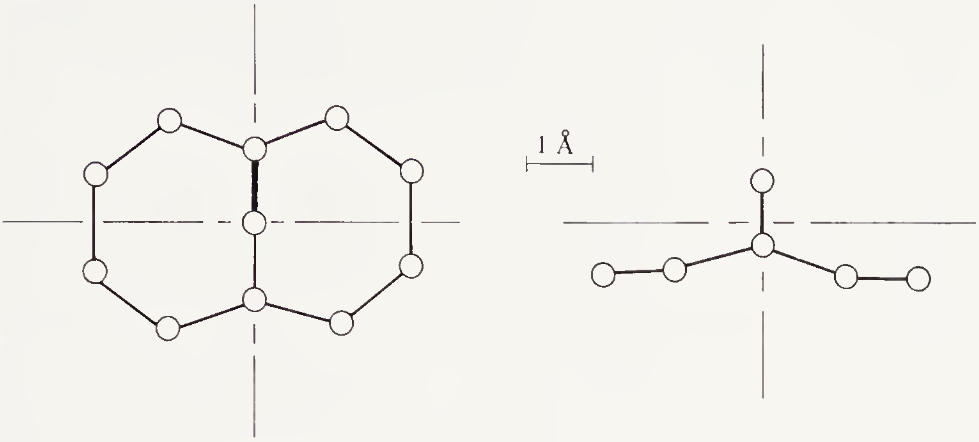
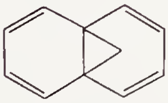


FIG. 3. Geometry representative of the 1,6 bridged cyclodecapentaenes as revealed by X-ray crystallographic analysis.

H. VALENCE BOND ISOMER APPROACH

The final scheme for synthesis of cyclodecapentaenes to be described here is the "valence bond isomer" or "valency tautomer" approach, a general synthetic plan deriving its name from the definition of Cope[31] (Section II,B). In this scheme,[72a] synthesis is aimed not at cyclodecapentaene itself but at a well-chosen valence tautomer. Synthesis of the polycyclic isomer, with the reasonable assumption that there exist means to overcome the energy barrier to interconversion, would be equivalent to direct construction of the 10-membered cycle. To illustrate, attention may be called to a special case of this general method, Vogel's synthesis of 16-methanocyclodecapentaene **67**, which resulted from a classic sequence superficially headed toward 9,10-methano-9,10-dihydronaphthalene **106**. In the 9,10-dihydronaphthalene case, there is a seeming flaw, in that the basis for this synthetic scheme is nothing more than



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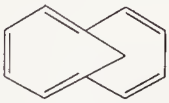


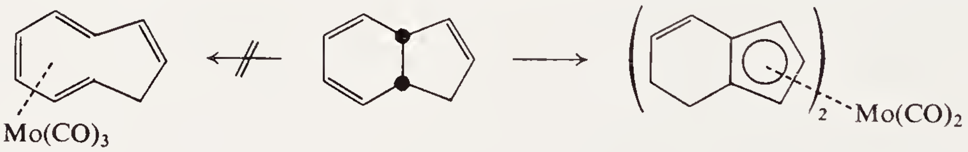
67

[72a] For a review see: E. E. van Tamelen, *Angew. Chem. Intern. Ed. Engl.* **4**, 738 (1965).

reversal of the reaction which Prelog suggested might frustrate any synthesis of cyclodecapentaene. Naturally, in regard to thermal processes, the outcome of the synthesis will be determined (assuming a negotiable energy barrier) by the equilibrium constant for interconversion of the two isomers. In the event of circumstances unfavorable for production of the cyclodecapentaene, rearrangement to the desired species might be promoted by means of photolysis or through the agency of suitable transition metal complexing agents applied under isomerization conditions.[72b]

Promotion of the interconversion of valence bond isomers by thermal or photochemical means is a technique with considerable precedent. Examples such as those cited in Section II,B, namely isomerizations of cyclooctatriene (**24**) and cyclononatriene (**22**) as well as transformations in the vitamin D field,[75] serve to bear this out. Recently, Woodward and Hoffmann[76] advanced a theory-based rationale for the known stereospecificity of such reactions based on consideration of the symmetry properties of the highest occupied molecular orbital, a principle first suggested in print by Oosterfeld.[75] The name "electrocyclic reaction" was proposed for the general type of transformation in which a σ-bond forms between the olefinic termini of a linear system containing conjugated π electrons (and the reverse process). For any electrocyclic reaction, comparison of the orbital symmetries of the ground or first excited state of a molecule permits a prediction for the stereochemical course of, respectively, the thermally or photolytically induced reaction. Thus in Fig. 4, allowed transformations of several valence bond isomers of cyclodecapentaene are predicted on the basis of the Woodward-Hoffmann selection rules. The isomers so treated are the two 9,10-dihydronaphthalenes **14** and **118** as well as the [6.2.0] isomer **119**. The photo-induced isomerization of *trans*-9,10-dihydronaphthalene (**118**) is predicted to be a conrotatory process, the two

[72b] A reported precedent[73] for this device, namely the isolation of a crystalline complex of cyclononatetraene (*i*) from the thermal reaction of 8,9-dihydroindene (*ii*) with molybdenum carbonyl has recently been proved false.[74] Instead, the crystalline substance has been shown to be a dimer complex of 4,5-dihydroindene moieties (*iii*).



i *ii* *iii*

[73] R. B. King and F. G. A. Stone, *J. Am. Chem. Soc.* **82**, 3296 (1963).

[74] R. B. King, *Chem. Commun.* p. 986 (1967).

[75] As quoted by: E. Havinga and J. L. M. A. Schlatmann, *Tetrahedron* **16**, 151 (1961).

[76] R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 395, 2511 (1965); R. Hoffmann and R. B. Woodward, *ibid.* **87**, 2046, 4388, 4389 (1965).

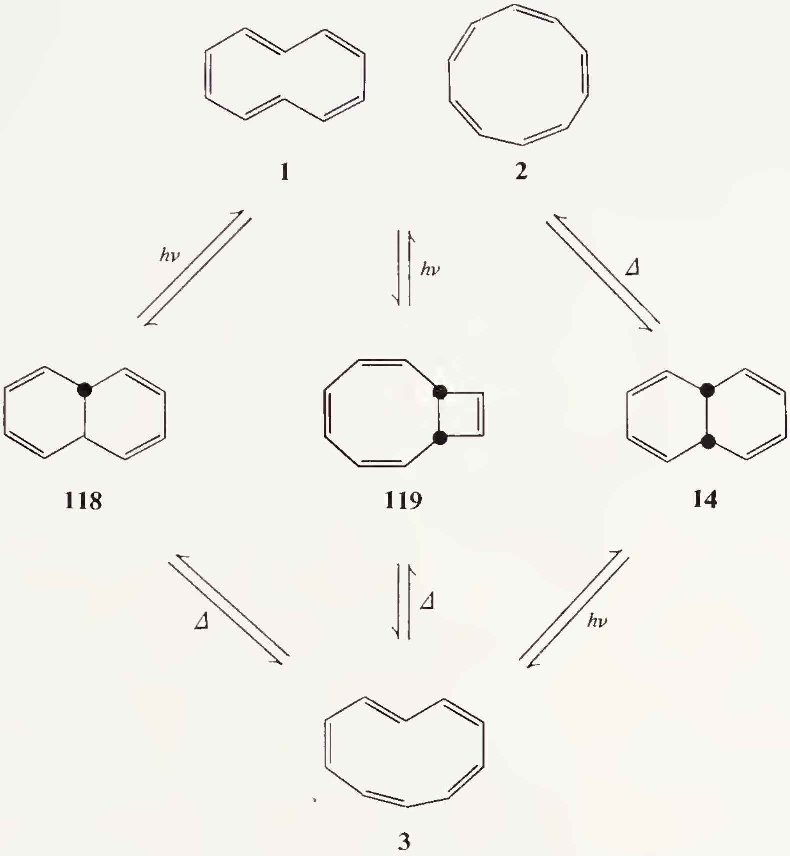


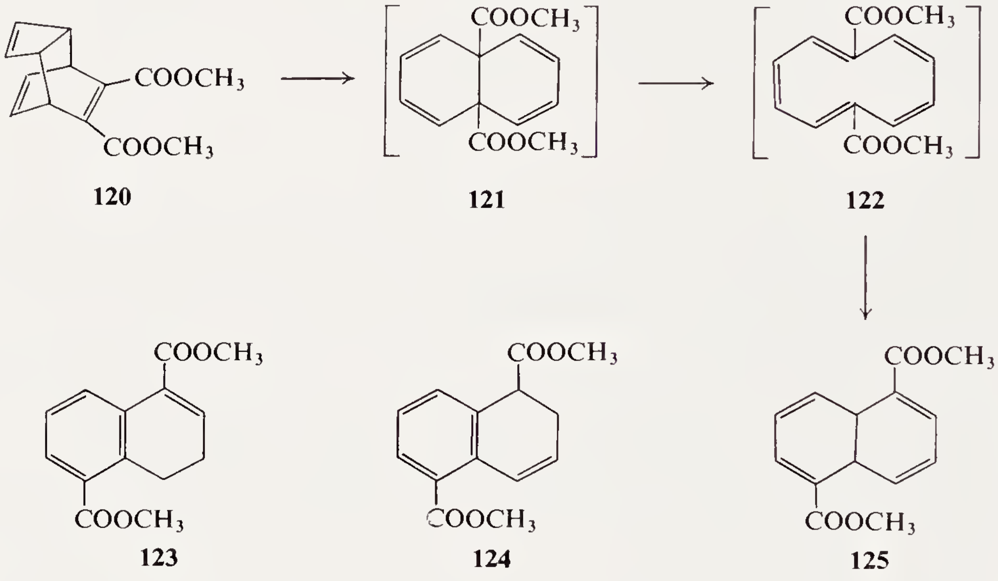
FIG. 4. Transformations of several valence bond isomers of cyclodecapentaene predicted on the basis of the Woodward–Hoffmann selection rules.

modes of conrotation affording either *cis,cis,trans,cis,trans*-cyclodecapentaene (**1**) or all-*cis*-cyclodecapentaene (**2**). The prediction for thermal opening is, on the other hand, a disrotatory process which would generate mono-*trans*,tetra-*cis*-cyclodecapentaene (**3**), an unlikely species on the basis of strain considerations. Similar treatment of the isomers **14** and **119** indicates two modes of disrotation, when promoted as specified in the figure, but one conrotatory mode. Because the Woodward-Hoffmann rules are based solely on consideration of orbital symmetry, they imply predictions for the stereochemical path of a given reaction, or suggest means to promote a given stereochemical reaction, by the choice of thermal or photochemical inducement. The rules are permissive, but not obligatory: if a given case is complicated by other energy factors, such as partner stability or bond–steric strain, which might significantly alter relative orbital energies or even prevent the reaction from occurring in a concerted fashion, the predictions are invalid. Cyclodecapentaene valence bond isomer chemistry is replete with examples which fit the selection rules, but also includes many examples where other pathways are apparently favored.

1. Substituted Valence Bond Isomers

Several research groups have taken up the chemistry of substituted valence bond isomers of cyclodecapentaene. It is interesting to note that although most classic methods of synthesis applied to cyclodecapentaene have clearly failed, attempts based on the valence bond isomer approach have often involved peculiar observations which suggest transient cyclodecapentaene intermediates. Observation of isomerization or other reaction of a polycyclic-valence bond isomer which leads to postulation of a transient cyclodecapentaene is worthwhile in itself; it adds to the circumstantial evidence concerning the stability and role of this 10 π-electron counter structure.

The valence bond isomer system 9,10-dihydronaphthalene–cyclodecapentaene (**1**–**26**) referred to by Prelog is the most obvious and certainly the most studied. Nenitzescu *et al.*[77] claimed the isolation of 2,6-dicarbomethoxy-9,10-dihydronaphthalene (**125**) from the pyrolysis of the Diels-Alder adduct from dimethyl acetylenedicarboxylate and cyclooctatetraene (**120**). Product **125** was proposed to have arisen by way of a 9,10-dicarbomethoxy-9,10-dihydronaphthalene (**121**) which opened to a dicarbomethoxycyclodecapentaene (**122**) then reclosed to **125**. This work was reinvestigated independently in two laboratories. Cookson *et al.*[78] and Pappas[79] found that the proposed 9,10-



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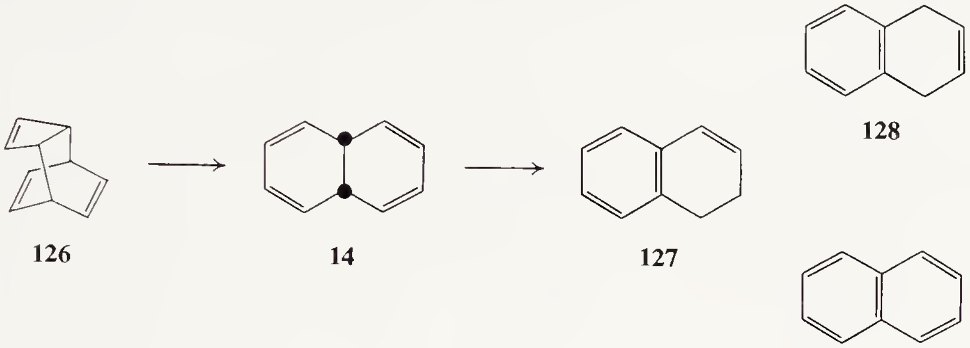
[77] M. Avram, C. D. Nenitzescu, and E. Marcia, *Ber.* **90**, 1857 (1957); M. Avram, G. Mateescu, and C. D. Nenitzescu, *Ann.* **636**, 174 (1960).

[78] R. C. Cookson, J. Hudec, and J. Marsden, *Chem. Ind. (London)* **21** (1961).

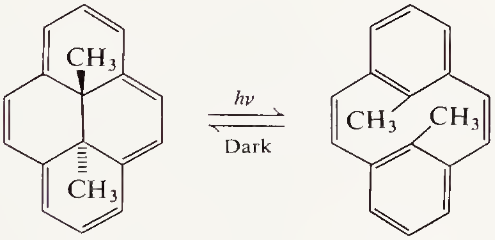
[79] B. C. T. Pappas, Ph. D. Thesis, Univ. of Wisconsin, 1963.

dihydro species **125** of Nenitzescu is, in fact, a mixture of the 1,2-dihydronaphthalenes **123** and **124**. Recently, Doering and Rosenthal[24] reported several experiments which shed light on this system. Working with the so-called Nenitzescu's hydrocarbon,[80] the tricyclic triene **126**, and changing the conditions from a static pyrolysis at atmospheric pressure to a flow pyrolysis under vacuum, they observed *cis*-9,10-dihydronaphthalene (**14**) as a primary product which itself was found to give rise to 1,2- and 1,4-dihydronaphthalene (**127** and **128**) as well as naphthalene. Mechanistic speculations still center around a transient cyclodecapentaene but are without any basis in experiment.



126 **14** **127** **128** **15**

Other investigators have treated valence bond isomers of annelated cyclodecapentaenes. One example is the synthesis by Boekelheide *et al.*[81] of *trans*-15,16-dimethyl-15,16-dihydropyrene (**129**), in its own right an interesting aromatic species having a fully conjugated 14 π-electron periphery. Aromaticity is attested to by the NMR chemical shifts: -4.2 δ (6 H, singlet), 8.0–8.5 δ (6 H, A_2B multiplet), and 8.55 δ (4 H, singlet). Photolysis of the dihydropyrene **129**



129 **130**

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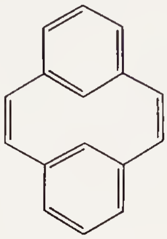
[80] M. Avram, E. Sliam, and C. D. Nenitzescu, *Ann.* **636**, 184 (1960).

[81] H.-R. Blattmann, D. Meuche, E. Heilbronner, R. J. Molyneux, and V. Boekelheide, *J. Am. Chem. Soc.* **87**, 130 (1965); V. Boekelheide and J. B. Phillips, *ibid.* **89**, 1695 (1967).

caused valency tautomerization to the "dibenzocyclodecapentaene," **130**. The half life of **130** in the dark was 2 hours at room temperature, the non-photolytic product being the dihydropyrene **129**. The NMR spectrum of the ring opened hydrocarbon **130** [1.52 δ (6 H, singlet), 6.56–6.95 δ (6 H, AB_2 multiplet), and 6.24 δ (4 H, singlet)] clearly indicated severe distortion and little or no conjugation with the 10-membered ring.

The parent dibenzocyclodecapentaene, **131**, should feature a less distorted carbon framework than does the dimethyl derivative **130**. Although the substance was reputedly isolated by Pellegrin[82] in 1899 from the reaction of *m*-xylylene dibromide with metallic sodium, other workers have not observed this interesting hydrocarbon among the reaction products. Recently, Boekelheide and Blaschke[83] prepared the dihydro analog **133** by the action of phenyllithium on the dibromide **132**. Light of either the visible or ultraviolet wavelength effected closure to the *trans*-tetrahydropyrene **134**. Attempts to dehydrogenate to 15,16-dihydropyrene led instead to the benzenoid aromatic **135**.



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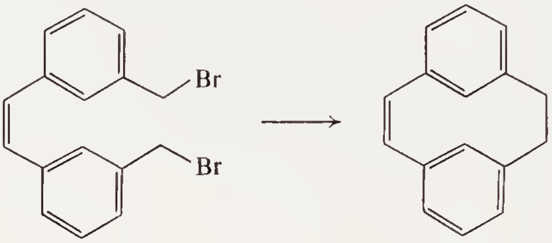
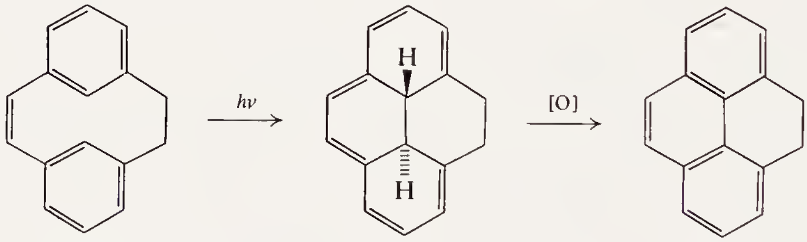


132 **133**



133 **134** **135**

Vogel *et al.*,[68] having available the anhydride **113**, prepared the corresponding diester, *cis*-9,10-dicarbomethoxy-9,10-dihydronaphthalene (**136**). With Riebel,[69] these investigators reported the photolysis of this diester to yield

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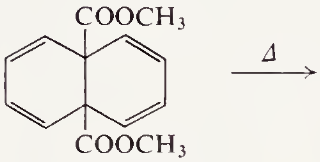
[82] M. Pellegrin, *Rec. Trav. Chim.* **18**, 457 (1899).

[83] V. Boekelheide and A. Blaschke, *J. Am. Chem. Soc.* **89**, 2747 (1967).

2,6-dicarbomethoxynaphthalene and dicarbomethoxybullvalene, among other products. While formation of the naphthalene ostensibly invites postulation of a cyclodecapentaene intermediate, the conversions do not conform easily to the Woodward-Hoffmann pattern. The diester **136** was found to undergo thermal rearrangement with facility[68] at 100°C to a complex mixture of dihydronaphthalenes. Analysis of this mixture was accomplished by heating it to over 150°C in order to dehydrogenate the dihydro species, followed by



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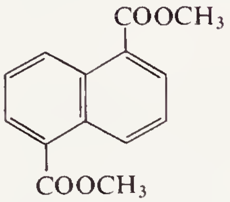

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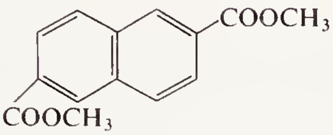

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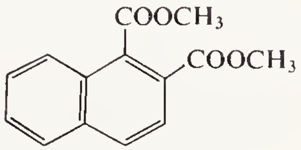

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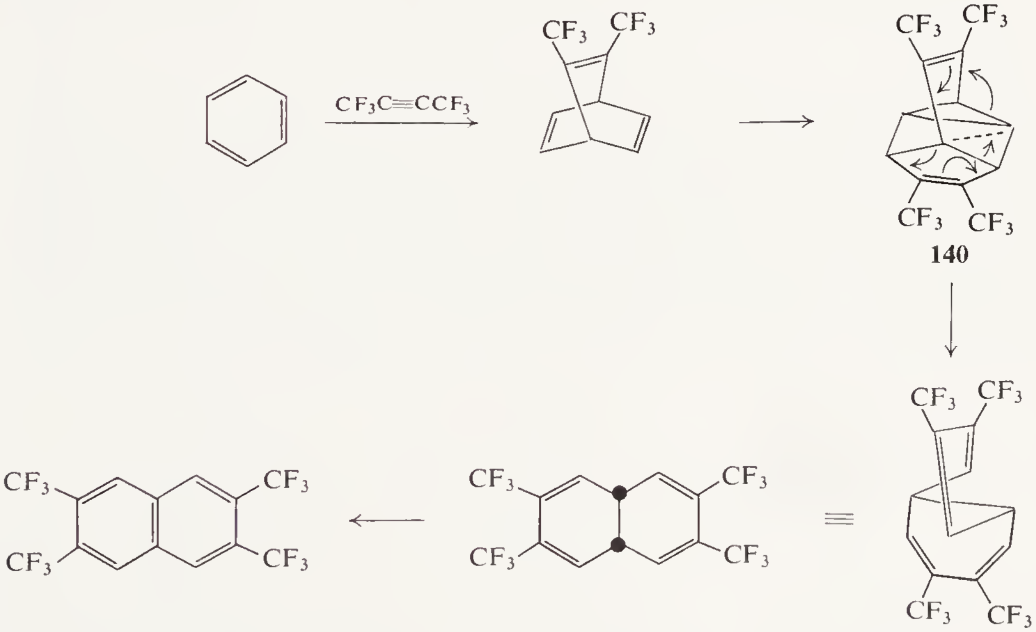

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FIG. 5. Postulation of a substituted intermediate **140** from the isolation of the substituted naphthalene derivative **142**.

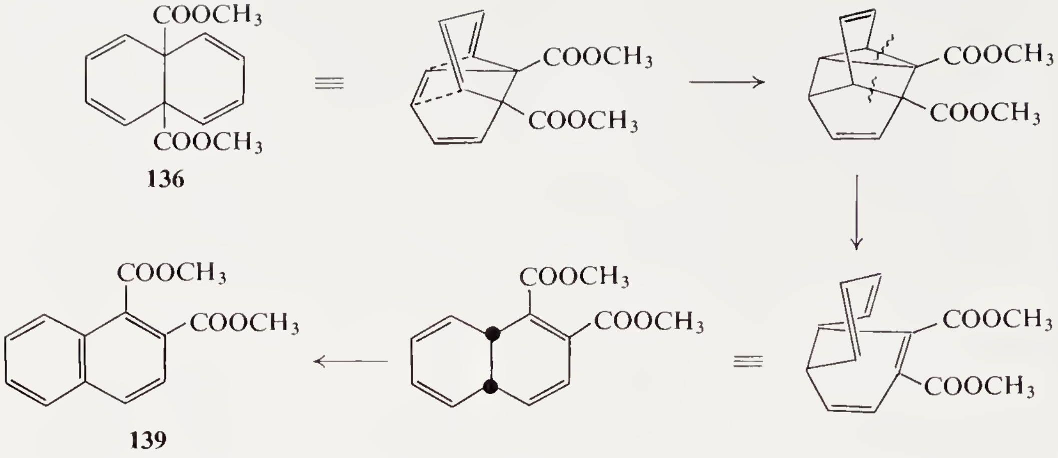
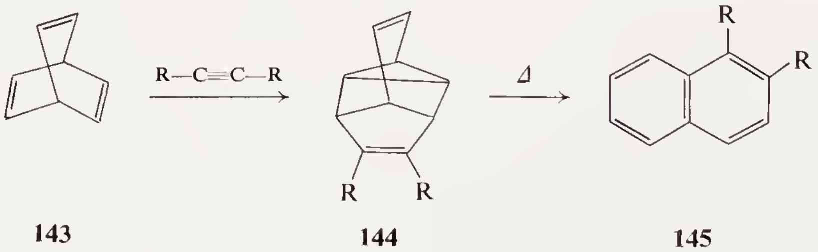


FIG. 6. Rearrangement of diester **136** to afford 1,2-dicarbomethoxynaphthalene could take place as depicted in this figure.

separation and identification of the resulting dicarbomethoxynaphthalenes. Isolation of 1,5- and 2,6-dicarbomethoxynaphthalene (**137** and **138**) was taken as evidence for the incursion of a 1,5-dicarbomethoxycyclodecapentaene (**121**), but isolation of 1,2-dicarbomethoxynaphthalene (**139**) indicated additional complexity. A clue to this more complicated process is provided by Krespan *et al.*[84] who studied the reaction of hexafluoro-2-butyne with benzene. Isolation of the substituted naphthalene derivative **142** led to postulation of a substituted tetracyclo[$2.2.2.0^{2,6}.2^{3,5}$]deca-3,7-diene intermediate **140**, as in Fig. 5. Rearrangement of this bridged system as shown (**140**) would give rise to the 9,10-dihydronaphthalene **141**, which oxidizes to **142**. Thus in the case of diester **136** rearrangement to afford 1,2-dicarbomethoxynaphthalene could take place as in Fig. 6. Some substantiation of this postulate is found in the work of Zimmermann and Grunewald,[85] who subsequently reported that barrelene (**143**) and either dimethyl acetylenedicarboxylate or dicyanoacetylene yield a well-defined adduct **144** (R = $COOCH_3$ or C≡N), which on further pyrolysis gives rise to large amounts of 1,2-dicyano- or 1,2-dicarbomethoxynaphthalene.



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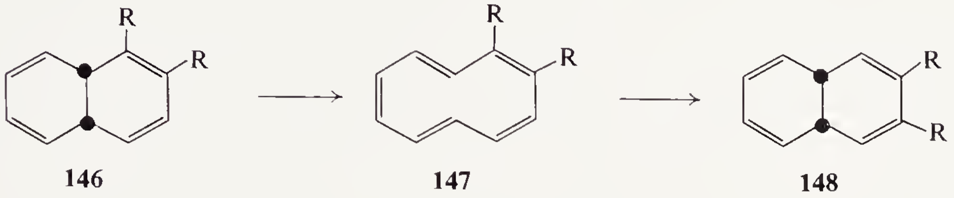
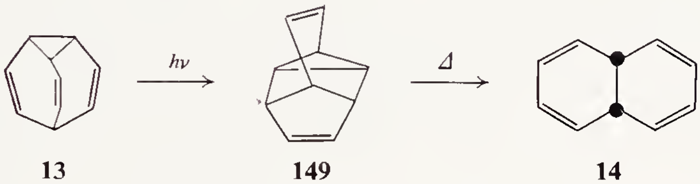
[84] C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.* **82**, 1515 (1960); **83**, 3428 (1961).

[85] H. E. Zimmermann and G. L. Gruenwald, *J. Am. Chem. Soc.* **86**, 1434 (1964).

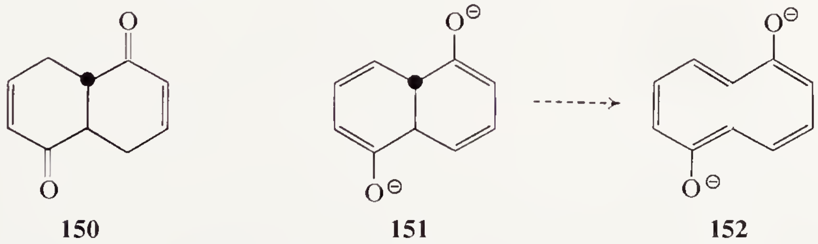
The isolation of only small amounts of 2,3-disubstituted naphthalenes lowers the likelihood of the specific cleavage indicated in Fig. 5, and once again isomerization of a cyclodecapentaene followed by reclosure (**146** → **147** → **148**) is suggested. Another piece of evidence for the transformations proposed was



provided by Jones,[86] who isolated the parent tetracyclic diene **149** as a photoproduct from bullvalene. Careful flow pyrolysis of this hydrocarbon resulted in facile, quantitative conversion to *cis*-9,10-dihydronaphthalene (**14**).



In connection with another proposed synthesis of a substituted cyclodecapentaene valence bond isomer, Johnson *et al.*[87] prepared the hexahydronaphthalenedione **150** by a straightforward sequence from 1,6-naphthalenediol. While attempting to detect rearrangement of derived enolate **151** to the dianion of a cyclodecapentaenediol, **152**, these investigators observed that dione **150** gave rise to a peculiar shifting of ultraviolet absorption maxima upon addition



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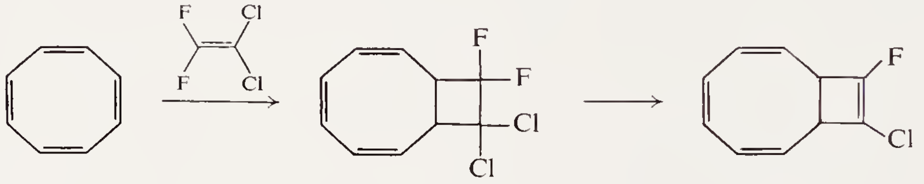
[86] M. Jones, Jr., *J. Am. Chem. Soc.* **89**, 4236 (1967).

[87] W. S. Johnson, J. D. Bass, and K. L. Williamson, *Tetrahedron* **19**, 861 (1963).

of base. The ultraviolet spectrum of **150** in 95% ethanol exhibits $\lambda_{max} = 217$ mμ (ε 18,000); however, upon addition of base, the maximum at 217 mμ disappeared and was replaced by a stronger one at 232 mμ (ε 32,000). A triplet also appeared at 325, 336, and 347 mμ, which diminished on standing, while a new absorption developed in the region 275–280 mμ. These observations are not incompatible with direct formation of the dihydroxycyclodecapentaene dianion followed by slow closure to the 9,10-dihydronaphthalene, which was kept at an undetectable concentration by rapid oxidation to a naphthalenediol dianion. Substantiation for this scheme was not provided; for example, attempts to secure a bisenol acetate derived from diketone **150** were unsuccessful.

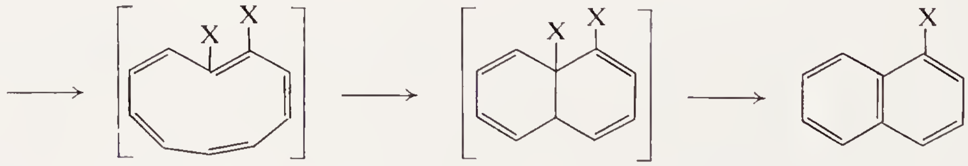
The most recently reported syntheses of substituted valence bond isomers of cyclodecapentaene are 10-chloro-9-fluorobicyclo[6.2.0]deca-2,4,6,9-tetraene (**154**), described by Schröder and Martini,[88] and the parent hydrocarbon



153 **154**

bicyclo[6.2.0]deca-2,4,6,9-tetraene (**119**) (see Section II,H,1), disclosed by Masamune *et al.*[89a] The chlorofluorotetraene **154** was prepared by 1,2 cycloaddition of 1,1-dichloro-2,2-difluoroethylene to cyclooctatetraene. The adduct **153**, obtained in modest yield but readily isolated by fractional distillation, reacted with methyllithium in ether at –20°C to afford the bicyclic tetraene in 70% yield. The product (**154**) was found to be a colorless liquid which re-

154



155 **156** **157**

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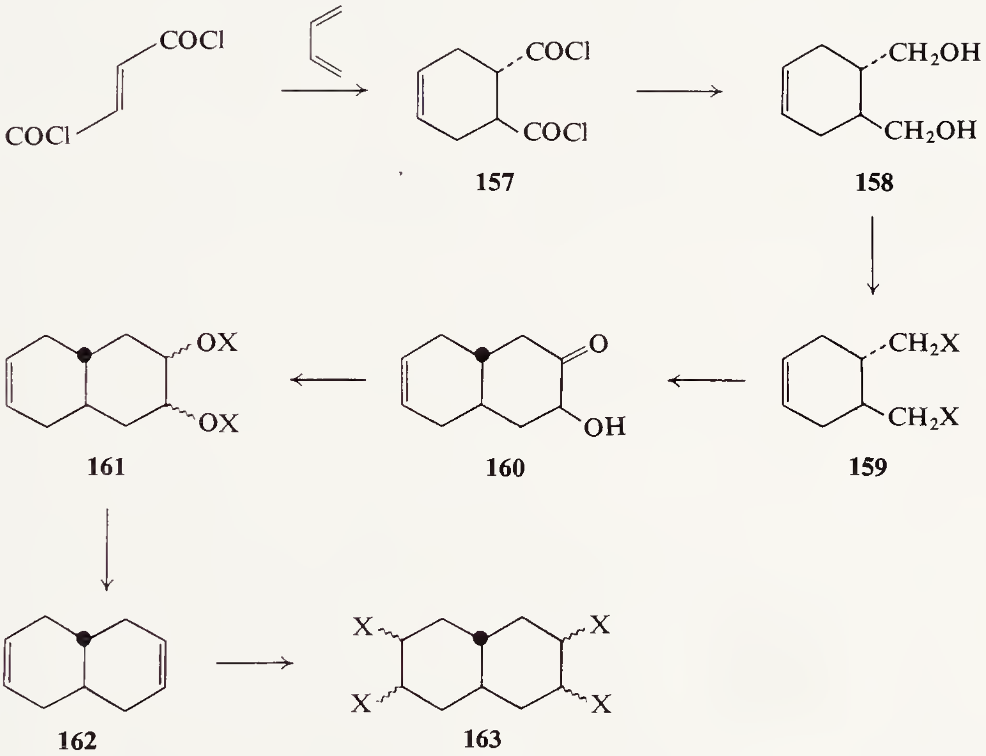
[88] G. Schröder and Th. Martini, *Angew. Chem. Intern. Ed. Engl.* **6**, 806 (1967).

[89a] S. Masamune, C. G. Chin, K. Hojo, and R. T. Seidner, *J. Am. Chem. Soc.* **89**, 4804 (1967).

arranged almost explosively at room temperature with loss of hydrogen halide to 1-chloro- and 1-fluoronaphthalene (8:1). Mechanistic speculation involves elimination from a 1,9-dihalogeno-9,10-dihydronaphthalene (**156**), itself generated by closure of a transient 1,2-dihalogenocyclodecapentaene (**155**).

2. *Unsubstituted Valence Bond Isomers*[89b]

In 1960, the unsubstituted *cis*- and *trans*-9,10-dihydronaphthalenes were set as synthetic goals, in the hope that these molecules would prove to be practical progenitors of cyclodecapentaene itself. In an early attempt by Winicov[90] at Wisconsin to synthesize the trans isomer **118** the Diels-Alder reaction was used to generate the first ring and establish trans stereochemisty at the potential ring juncture. Fumaryl chloride and buta-1,3-diene gave the bisacid chloride **157**, which was not purified but reduced to the diol **158** in 80 % yield overall by means of lithium aluminum hydride. This *trans*-diol was bis homologated in a classic sequence by preparation of the ditosylate **159** (X = Ts), displacement

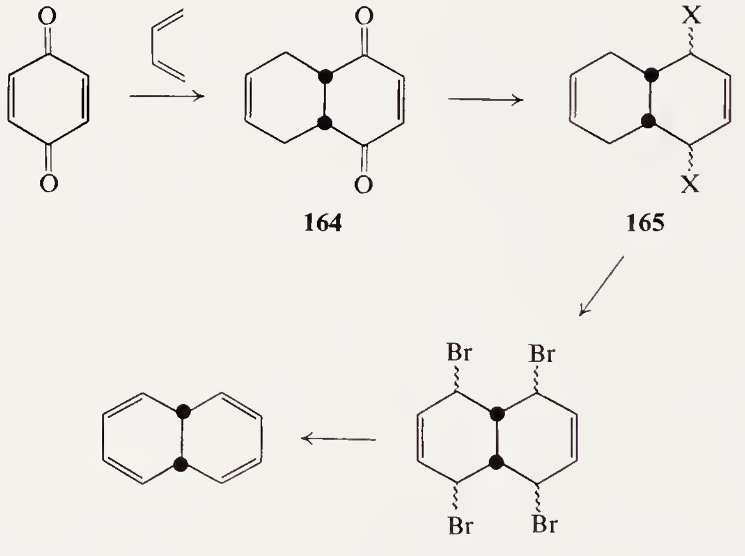


[89b] This section deals mainly with research efforts initiated at the University of Wisconsin and continued at Stanford University by E. E. van Tamelen and co-workers. Results in this area were first presented publicly in a June, 1963, ACS Organic Symposium as part of a general topic introduced as "Valence Bond Isomers of $(4n + 2)$ π-Electron Systems."

[90] H. Winicov, Ph. D. Thesis, Univ. of Wisconsin, 1960.

with cyanide to the dinitrile **159** (X = C≡N), and basic hydrolysis to the diacid **159** (X = COOH). Ring closure was effected in essentially quantitative yield by means of an acyloin reaction carried out in ether–liquid ammonia with sodium metal. The product, often a crystalline mixture of ketol **160** and the corresponding dione, was reduced to a mixture of epimeric diols **161** (X = H) by the action of lithium aluminum hydride. Conversion to the dimethanesulfonate **161** (X = Ms) followed by treatment of this material with sodium iodide in 2,5-hexanedione at reflux afforded 1,4,5,8,9,10-hexahydronaphthalene (**162**). From the diene **162**, a refractory tetrabromide **163** was prepared by direct bromination. Effective base treatment of **163** to promote *tetrakis* dehydrohalogenation to *trans*-9,10-dihydronaphthalene was precluded by its near insolubility. At the elevated temperatures and prolonged reaction times required because of the solubility of tetrabromide **163** (for example, potassium tertiary butoxide in tertiary butanol at reflux for 48 hours), only the unexceptional hydrocarbons naphthalene and 1,2-dihydronaphthalene were produced, and even then in low yield. Hydroxylation of diene **162** to **163** (X = OH) was accomplished with osmium tetroxide, and from the epimeric tetrols both the tetraacetate **163** (X = OAc) and the tetrastearate **163** (X = O stearoyl) were prepared. Pyrolysis of either of these tetraesters under distillative conditions afforded only low yields of a hydrocarbon tentatively identified as 1,2-dihydronaphthalene.

An approach to *cis*-9,10-dihydronaphthalene by Mrs. B. C. T. Pappas in 1963, proved successul as a synthetic venture.[91] Again, the Diels-Alder reaction



164 **165**

14 **166**

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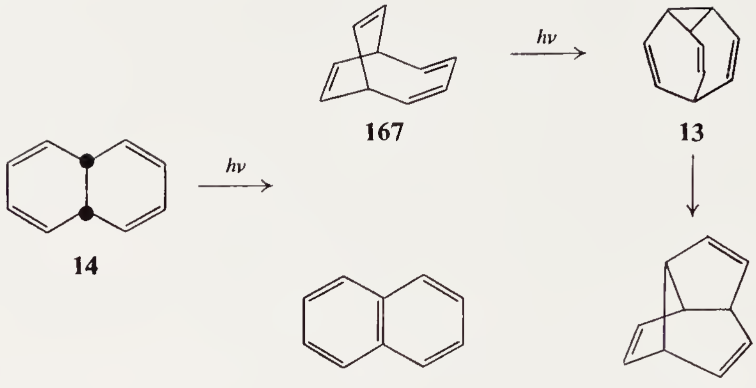
[91] E. E. van Tamelen and B. C. T. Pappas, *J. Am. Chem. Soc.* **85**, 3296 (1963).

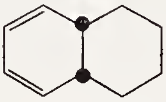
was employed to gain entry into the desired stereochemical system. The well-known butadiene–*p*-benzoquinone adduct, **164**, was reduced to the hexahydronaphthalenediol **165** (X = OH) with aluminum isopropoxide in isopropanol under distillative, Meerwein-Ponndorf-Verely reduction conditions. This diol was treated with 48% aqueous hydrobromic acid to give crystalline material, shown by NMR to have the gross structure of the unrearranged dibromide **165** (X = Br). Introduction of bromine at the allylic centers was accomplished with *N*-bromosuccinimide in a reaction initiated with benzoyl peroxide. The desired, oily diene tetrabromide **166** was separated from other halogenated materials by chromatography on Florisil and subjected to reductive elimination of bromine with lithium amalgam. This process led to a $C_{10}H_{10}$ hydrocarbon, isolated by gas–liquid partition chromatography, which was shown to be *cis*-9,10-dihydronaphthalene (**14**), the first valence bond isomer of cyclodecapentaene ever to be prepared. Evidence for the structure of this hydrocarbon, apart from its mode of synthesis, was found by hydrogenation to *cis*-decalin over prereduced Adams platinum catalyst in methanol at room temperature with an uptake of 4 equivalents of hydrogen. An ultraviolet maximum of 247 $m\mu$ ($\epsilon \sim 6000$) and a simple NMR spectrum [a vinyl A_2B_2 multiplet centered about 5.61 δ (4 H) and a broadened methine singlet at 3.25 δ (1 H)] were compatible with this structural assignment. Neither heat nor light detectably converted this bicyclic hydrocarbon to the monocyclic valence bond isomer 1 or 2. When heated in the temperature range 150–200°C as a solution in carbon tetrachloride, the hydrocarbon formed only naphthalene. Ultraviolet irradiation with use of a Vycor filter did not serve to convert *cis*-9,10-dihydronaphthalene to any product exhibiting peak absorption in the ultraviolet, an observation judged incompatible with the formation of a cyclodecapentaene. Attempts to detect cyclodecapentaene, assuming it existed in equilibrium with *cis*-9,10-dihydronaphthalene to an extent too small to be noticed spectrally, were made by heating the tetraene **14** with molybdenum hexacarbonyl, but without success.

Additional information concerning this system was provided some years later by Doering and Rosenthal,[24] who, during studies of the chemistry of bullvalene (**13**) discovered its thermal reorganization to *cis*-9,10-dihydronaphthalene. Having then a ready source of the latter, they reinvestigated its behavior upon thermolysis (Section II,A) and photolysis under somewhat different conditions. The photolysis of *cis*-9,10-dihydronaphthalene (**14**) in pentane at 0°C gave bullvalene (**13**) as a major product along with naphthalene and two unidentified hydrocarbons. This photolysis, subsequently studied in greater detail by Jones,[86] was shown to give rise also to bicyclo[4.2.2]deca-2,4,7,9-tetraene (**167**) as a primary product which undergoes further light-induced change to bullvalene (**13**), in turn photosensitive with respect to



167 **13** **14** **15** **168**

rearrangement to the tricyclic triene **168**. Moreover, Doering and Rosenthal[92] recorded the absence of any temperature dependence in the NMR spectrum of *cis*-9,10-dihydronaphthalene, and confirmed the tendency of the hydrocarbon to decompose to naphthalene on being heated in solution, by a disproportionation process. As proof of this latter reaction, they described the isolation and characterization of the two hexahydronaphthalenes **169** and **170** as well as the



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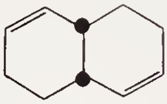

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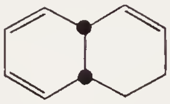
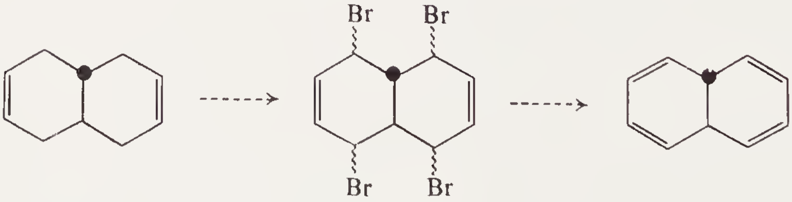


171

tetralin isomer **171**. These authors called attention to the analogy of this reduction to the diimide reduction and proved the stereospecific cis hydrogen transfer involved by reduction of 1,2-dimethylcyclohexene with *cis*-9,10-dihydronaphthalene.

Synthesis of *trans*-9,10-dihydronaphthalene (**118**), by a route modeled after the successful preparation of the cis isomer, seemed in order and was pursued by Burkoth. Preliminary studies took the form of extension of the work of Winicov,[90] specifically an attempt to put the diene **162** to more practical use.[41]



162 **172** **118**

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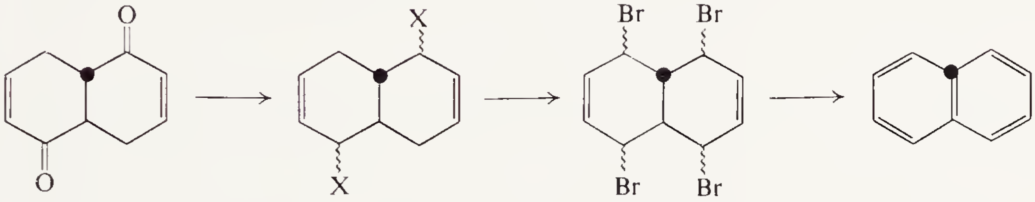
[92] W. von E. Doering and J. W. Rosenthal, *J. Am. Chem. Soc.* **89**, 4534 (1967).

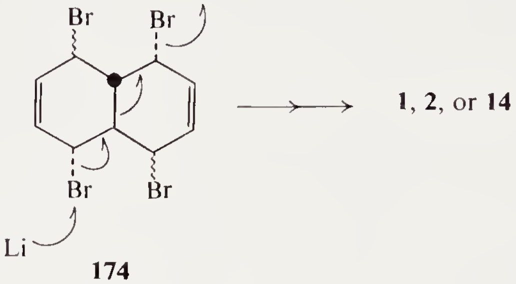
In the hope of generating the allylic tetrabromo species **172**, the hexalin **162** was treated with *N*-bromosuccinimide and a trace of benzoyl peroxide as initiator. An unresolvable mixture was obtained which decomposed readily upon subjection to normal laboratory manipulation, thus obstructing even partial purification. Postponement of purification to the next stage of synthesis provided no reprieve from the problem of product multiplicity, for treatment of crude bromine-containing material with lithium amalgam afforded a plethora of, presumably, hydrocarbon products with only naphthalene in major amount.

The attractiveness of fashioning a synthesis of *trans*-9,10-dihydronaphthalene (**118**) after the method proven useful for the cis isomer led the search for a suitably functionalized trans fused starting material to the interesting dienedione **150**, first prepared by Johnson *et al.*[87] (Section II,H,1). This readily available species is at the same oxidation level as the starting material in the cis series (**164**)[91] and as such might be elaborated according to an exactly analogous scheme. Essentially quantitative reduction of dienedione **150** was accomplished by soxhlet extraction of this substance into a suspension of a great excess of lithium aluminum hydride in ethyl ether at reflux. Direct conversion of the resulting diol **173** (X = OH) to a mixture of epimeric dienedibromides was managed using 48% aqueous hydrobromic acid. Critical evidence indicating **173** (X = Br) as the gross structure of the dibromides was found in the NMR spectrum: only one type of proton bonded to carbon bearing bromine was indicated, and that was necessarily allylic on the basis of chemical shift. Treatment of dienedibromide **173** (X = Br) with *N*-bromosuccinimide afforded a mixture of higher bromides from which a crude fraction, enriched in the tetrabromo species **172** could be obtained by rapid column chromatography on Florisil. Dehalogenation of this material through the agency of lithium amalgam in ethyl ether led to a novel hydrocarbon in major amount, accompanied by naphthalene. Both chemical and spectral evidence indicated this new substance, isolated by gas–liquid partition chromatography, to be *trans*-9,10-dihydronaphthalene **118**.[25]



150 **173** **172** **118**

The characterization of this hydrocarbon and a study of its chemical behavior proved to be the most fruitful, and yet the most mystifying, of all the work directed toward the synthesis of cyclodecapentaene. Certain considerations should be kept in mind during assessment of the physical and chemical properties of the hydrocarbon. The above synthetic route to *trans*-9,10-dihydronaphthalene is not an unambiguous one, and could (1) by a rational albeit unexpected dehalogenation process (**174**), produce cyclodecapentaene directly, or (2) by thermal closure of the resulting cyclodecapentaene, finally yield *cis*-9,10-dihydronaphthalene.



174

The new $C_{10}H_{10}$ hydrocarbon exhibited maximal ultraviolet absorption at 231 mμ in methanol and revealed surprisingly simple NMR behavior in that two virtually unsplit signals appeared at 5.9 δ (4 H) and 2.8 δ (1 H). The only observable product of air oxidation was naphthalene, as detected by NMR and gas–liquid partition chromatography. This process, observed to occur with great facility during handling of small quantities with normal precautions to exclude atmospheric oxygen, precluded the obtention of elemental analysis or quantitative reduction studies.

Qualitative reduction studies proved enigmatic. Reduction of the hydrocarbon over either prereduced Adams platinum catalyst or with diimide gave *cis*-decalin as the sole product. Reduction of authentic *cis*-9,10-dihydronaphthalene, proved nonidentical to the new hydrocarbon, also gave *cis*-decalin in each reduction as the sole product under identical conditions. The new hydrocarbon was observed to be stable under conditions approximating those involved in generation of diimide and no change was observed in the nature of the product if the diimide reduction was carried out at the lowest possible temperature (that is, upon warming from −78°C).

Flow pyrolysis of the hydrocarbon at 250°C in a system free of oxygen gave *cis*-1-phenylbuta-1,3-diene, identified by comparison with authentic material. Photolysis of hydrocarbon **118** gave a complex mixture to be discussed below.

These data (Fig. 7) could lead one to seriously consider a nonplanar cyclodecapentaene structure for the hydrocarbon. It could be imagined, for example, that all of the observed chemical behavior of the hydrocarbon could be explained by a valency tautomerism ring closure at an appropriate stage of the reaction to give decalin or naphthalene precursors. Moreover, the anomalous production of *cis*-decalin upon reduction, an observation not reconcilable with classic mechanisms of reduction, casts a deep shadow of doubt on the actual

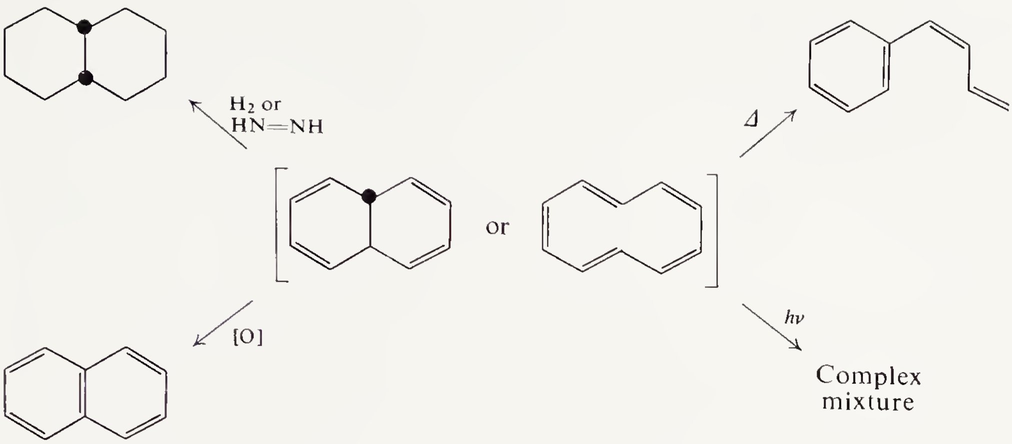


FIG. 7. Chemical behavior of *trans*-9,10-dihydronaphthalene.

presence of a 9,10 carbon–carbon bond since the possibility of cis ring fusion has been rigorously excluded. The ultraviolet maximum of 231 mμ might be easily explained on the basis of geometrical distortion of a polyene chromophore in a medium ring. Some pertinent examples in the 10-membered carbocyclic series are shown in Fig. 8.[93,94] The NMR spectrum indicating two protons upfield and eight downfield could also be readily rationalized on the basis of a cyclodecapentaene structure. Arguments for the upfield shift of two protons, owing to their position interior to a carbocycle ring with a ring current, can be refuted by calling attention to the lack of a corresponding downfield shift of the protons exterior to the ring. On the other hand, in a cyclic polyene sufficiently distorted from planarity to disrupt ring current, as indicated by the ultraviolet spectrum, one might imagine interior protons being thrust into the diamagnetic anistropy of a double bond across the ring in such a fashion that

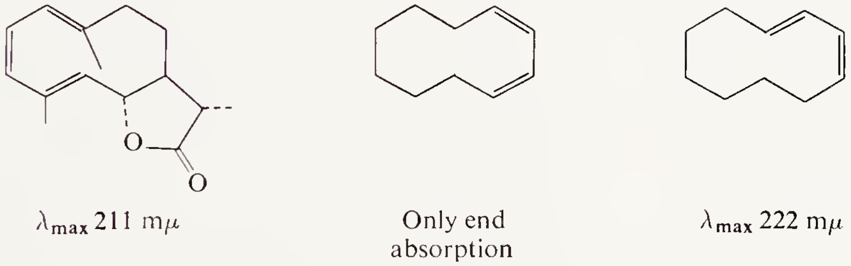


FIG. 8. Some pertinent examples in the 10-membered carbocyclic series.

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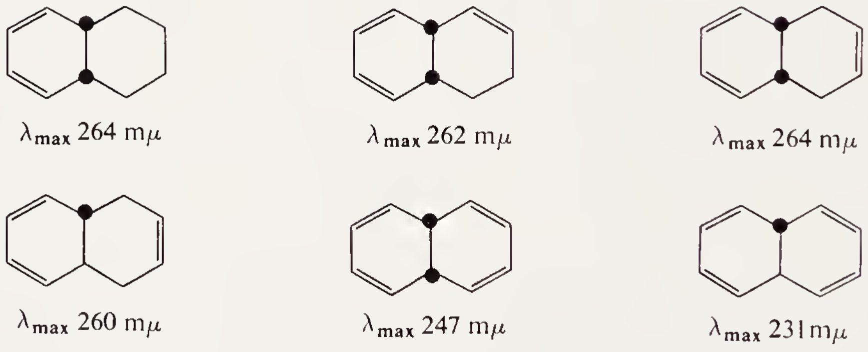
[93] E. J. Corey and A. G. Hortmann, *J. Am. Chem. Soc.* **87**, 5736 (1965).

[94] A. T. Blomquist and A. Goldstein, *J. Am. Chem. Soc.* **77**, 998 (1955).

an upfield shift might result. At the same time, a conformational mobility in which the interior and exterior protons lose their identity could account for the apparent presence of only one type of vinyl proton as well as the apparent lack of spin splitting.

Looking at the data from a different point of view leads to a more consistent and satisfying interpretation; the assignment of the structure *trans*-9,10-dihydronaphthalene (**118**) to the new hydrocarbon. The gross structure of a hydronaphthalene is quite consistent with (1) oxidation to naphthalene on exposure to air, (2) its method of synthesis, and (3) its reduction by means of either catalytic hydrogenation or diimide to *cis*-decalin. The latter piece of evidence, however, is inexplicable on the basis of the proposed stereochemistry of the ring juncture. The facility of oxidation to naphthalene would lend credence to the proposed vicinal dihydro aromatic species, while the symmetry and 4:1 integrated ratio of protons in the NMR spectrum establish the oxidation level as that of a dihydro species with the extra hydrogen-bearing carbons, necessarily those at the ring fusion. The ultraviolet maximum is at a wavelength shorter than usual for a homoannular disubstituted diene, but this observation can be rationalized on the basis of the known[87,95] hypsochromic shift of absorption maxima with increased ring strain. Such an effect could be anticipated for this system and is partially substantiated by the series of compounds shown in Fig. 9.[25,32,91,92] The proposed *trans*-9,10-dihydronaphthalene fits into this series as expected. The stereochemistry of the ring juncture is best regarded as trans, in spite of the anomalous reduction results, on the basis of (1) the proved nonidentity with *cis*-9,10-dihydronaphthalene and (2) a very satisfying NMR parallel. The cis and trans isomeric pair **175**[96] and **176**[97] (obtained by ultraviolet irradiation of **175**) provide a perfect precedent for the



λ_{max} 264 mμ

λ_{max} 262 mμ

λ_{max} 264 mμ

λ_{max} 260 mμ

λ_{max} 247 mμ

λ_{max} 231 mμ

FIG. 9. Pertinent ultraviolet maxima in the hydronaphthalene series.

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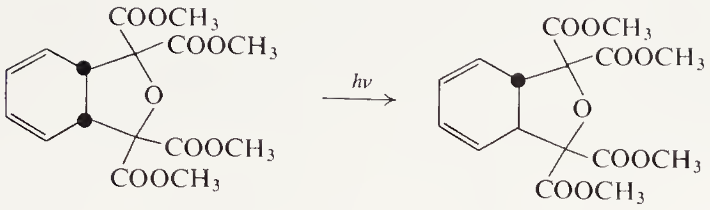
[95] E. E. van Tamelen, J. McNary, and F. A. Lornitzo, *J. Am. Chem. Soc.* 79, 1231 (1957).

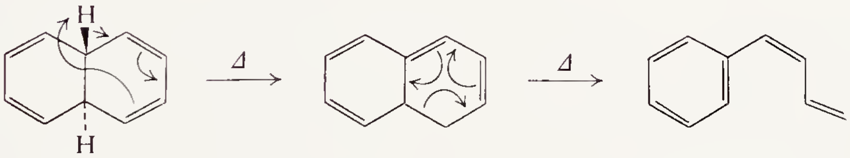
[96] R. E. Benson, W. J. Linn, and O. W. Webster, *J. Am. Chem. Soc.* **85**, 2032 (1963).

[97] G. V. Parry, Research Report, Stanford Univ., 1966.



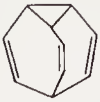
175 **176**

extremely simple NMR spectrum of the hydrocarbon **118**. Whereas the tetraester **175**, like *cis*-9,10-dihydronaphthalene, exhibits extensive splitting in the vinyl and methine regions 6.1–5.9, 5.8–5.5, and 4.02–3.98 δ (all multiplets in the integrated ratio of 2:2:2), isomer **176** revealed singlets in the vinyl (6.1 δ, 4 H) and methine (3.5 δ, 2 H) regions. Thus, the presence of a sharp singlet vinyl absorption in *trans*-9,10-dihydronaphthalene would seem to be a precedented case of fortuitous coincidence of chemical shift as well as dihedral angles to preclude spin splitting. The thermal reorganization of the hydrocarbon is readily rationalized on the basis of a *trans*-9,10-dihydronaphthalene structure also. Such a rearrangement might occur by a 1,5 suprafacial hydrogen transfer (sigmatropic change of order [1,5]) to **177**, this process being a thermally permitted one.[76] Subsequent valence bond isomerization would give *cis*-1-phenylbuta-1,3-diene (**178**), again by a thermal process. On the basis of the more self-consistent interpretation of the observations, we regard the hydrocarbon under scrutiny to be *trans*-9,10-dihydronaphthalene (**118**).



118 **177** **178**

Photolysis of **118**, the sole uninvestigated possible route to cyclodecapentaene, was complicated by product composition as well as by the instability and paucity of starting material, but ultimately led to the first physical detection and trapping of cyclodecapentaene.[25] On being photolyzed in pentane at room temperature for 2 minutes by means of unfiltered light of 2537 Å wavelength from a Rayonet photochemical reactor, the *trans*-tetraene **118** gave rise to a large number of products. The separation of some of these was accomplished by suitable combinations of gas–liquid partition chromatography and column chromatography on silica deactivated with aqueous silver nitrate solutions. The identification of the more readily separated of these species was accomplished by comparison of ultraviolet spectra and by gas–liquid partition chromatography comparison, involving coinjection with authentic materials under several sets of conditions, wherever possible. All-*trans*-deca-1,3,5,7,9-pentaene (**179**) was isolated in trace amounts, although the intense ultraviolet



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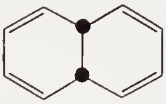

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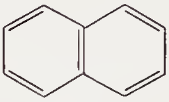

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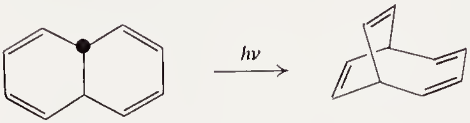
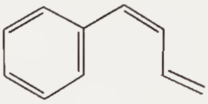


118 **167**



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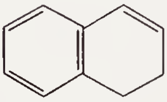


180

179

absorption of this species dominated the ultraviolet spectrum of the crude product mixture. The unexpected *cis*-1-phenylbuta-1,3-diene (**178**), 1,2-dihydronaphthalene (**180**), and naphthalene were detected as were the more interesting hydrocarbons bicyclo[4.2.2]deca-2,3,7,9-tetraene (**167**), bullvalene (**13**), and—perhaps most significantly—*cis*-9,10-dihydronaphthalene. Further elucidation of products was discouraged by the complexity of the mixture; at least five additional compounds separable only with difficulty, tentatively regarded as C_{10} hydrocarbons, were detectable by gas–liquid partition chromatography.

The presence of *cis*-9,10-dihydronaphthalene and its known photoproducts[24, 86] **167**, **13**, and **15** in comparatively major amount (50 %) was suggestive of a transient cyclodecapentaene. It was surmised that the monocyclic polyene, formed by a conrotatory process from excited state *trans*-9,10-dihydronaphthalene (**118**), was thermally unstable and underwent a disrotatory closure resulting in *cis*-9,10-dihydronaphthalene (**14**) (Fig. 10). In an effort to test this hypothesis, low temperature photolyses were carried out. When a solid solution of **118** was photolyzed as described above but at −190°C in ether–isopentane–ethanol (5:5:2), a complex mixture was apparently formed as evidenced by the ultraviolet spectrum recorded at that temperature. On warming the mixture momentarily to room temperature and then recooling it to −190°C in order to record again the ultraviolet spectrum, a new maximum at 247 mμ

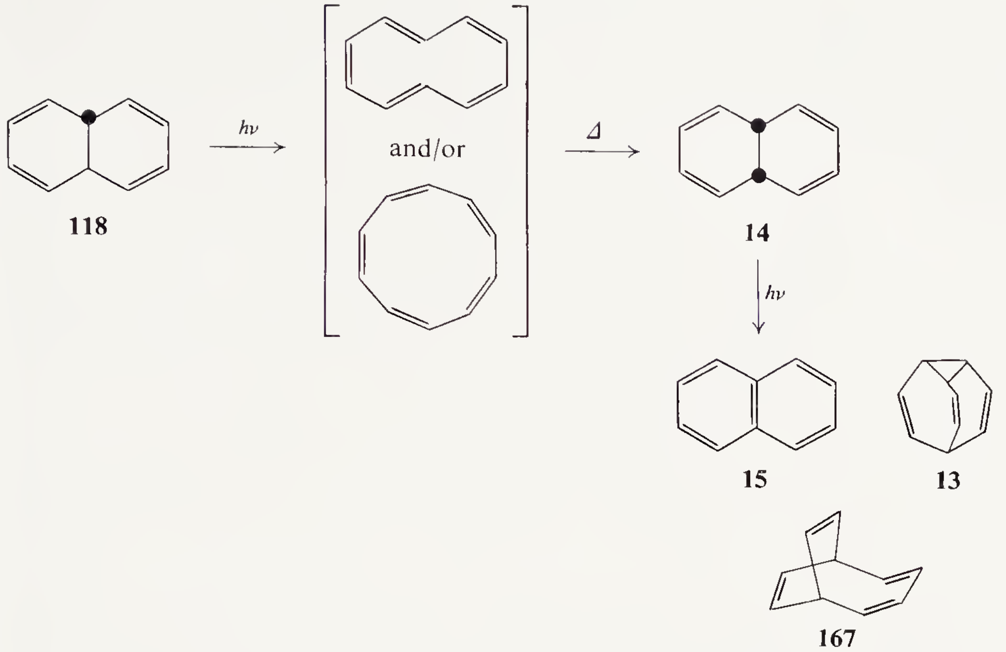
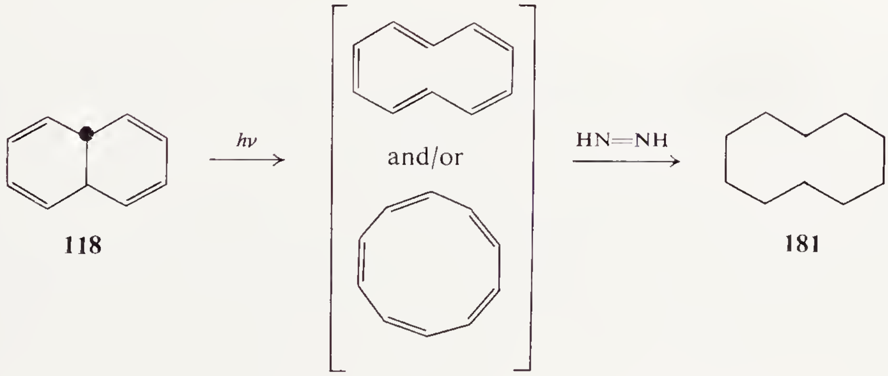


FIG. 10. Disrotatory closure of the thermally unstable monocyclic polyene, formed by a conrotatory process from excited state **118**, resulting in **14**.

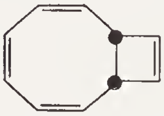
was revealed, corresponding to that of *cis*-9,10-dihydronaphthalene (**14**). A simple subtraction spectrum indicated that maxima at 267, 275, and 285 mμ had been destroyed.

The detection of a thermally labile progenitor of *cis*-9,10-dihydronaphthalene was certain, and although a cyclodecapentaene was clearly a candidate structure for this species, supporting evidence was demanded. A trapping experiment was performed by generating the unstable photoproduct at —190° C



and transferring it, with a minimum of warming, to a reaction mixture in which diimide was presumably already being generated at −78°C. The elusive cyclodecapentaene was converted to cyclodecane (**181**) in a yield of 40% (as estimated by gas–liquid partition chromatography). Reduction presumably took place at −78°C or during warming to room temperature. The cyclodecane was isolated by gas–liquid partition chromatography and compared with authentic material by mass spectral means. In a control experiment, room temperature photolysis of **118** followed by diimide reduction produced, at most, a trace of cyclodecane. The similarity in yields of the cyclodecane and the combination of *cis*-9,10-dihydronaphthalene and its photoproducts suggests that the two experiments are logically coupled and that the same species which is trapped as cyclodecane gives rise to *cis*-9,10-dihydronaphthalene and products derived therefrom. On the basis of these two experiments, the detection and trapping of a cyclodecapentaene seem certain. Elucidation of the detailed nature of the cyclodecapentaene with regard to configuration, conformation, and electronic character awaits more sophisticated experimental probes. It appears, however, that a basic question, viz., the position of the balance between the energy of stabilization due to delocalization in a potential aromatic system and the destabilizing effect of strain and/or nonbonded internal hydrogen repulsion, has been essentially answered.

Two other sources of *trans*-9,10-dihydronaphthalene were found subsequent to the Stanford work. Two other research groups isolated this hydrocarbon during synthetic approaches to another potential valence bond isomer of cyclodecapentaene, the bicyclo[6.2.0]tetraene **119**. Jones and Scott[98] first reported the preparation of the tosylhydrazone **182** (X = CH=N—NHTs), starting with the addition of carboethoxycarbene to cyclooctatetraene. The



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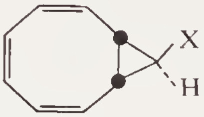

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ester **182** (X = COOEt), in a sequence involving the acid **182** (X = COOH) and the acid chloride **182** (X = COCl), was converted to the requisite aldehyde **182** (X = CHO). Pyrolysis of the dry sodium salt of the aforementioned tosylhydrazone derivative **183** of this aldehyde at 90°–120°C under vacuum gave none of the desired tetraene **119**. Instead, the bicyclic tetraene **167** was produced in major amount, along with *cis*- and *trans*-9,10-dihydronaphthalene, 1,2-dihydronaphthalene, naphthalene *cis*-1-phenylbuta-1,3-diene, and cyclo-

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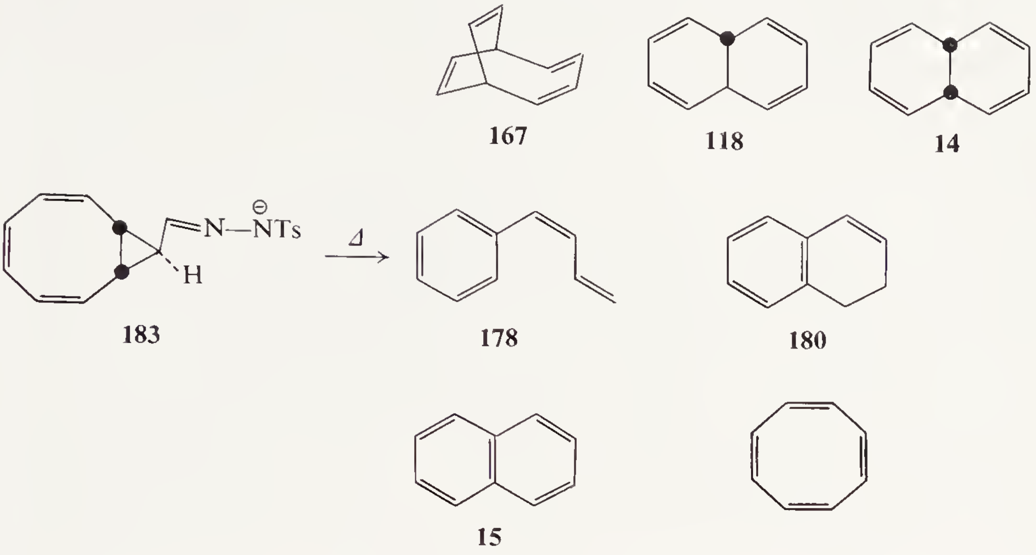
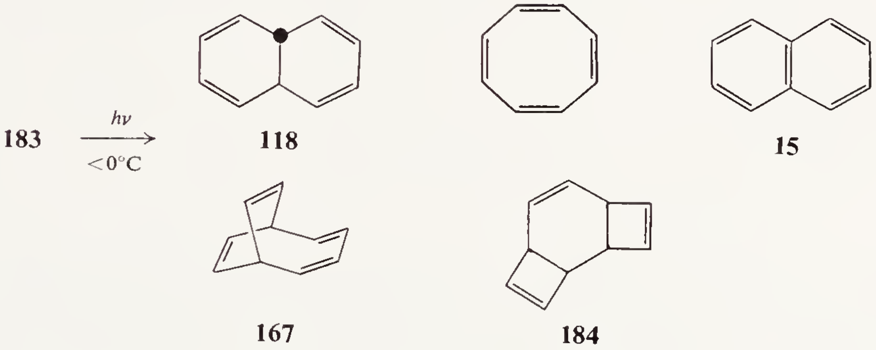
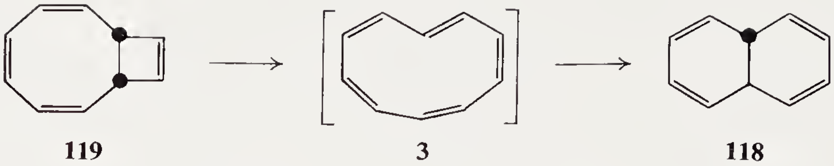
[98] M. Jones, Jr. and L. T. Scott, *J. Am. Chem. Soc.* **89**, 150 (1967).



octatetraene. Masamune *et al.*[89a] report that the low temperature photolytic decomposition of the tosylhydrazone salt **183** as a solution in dry tetrahydrofuran gives somewhat different results. Under these altered conditions, and with product analysis accomplished by gas–liquid partition chromatography,

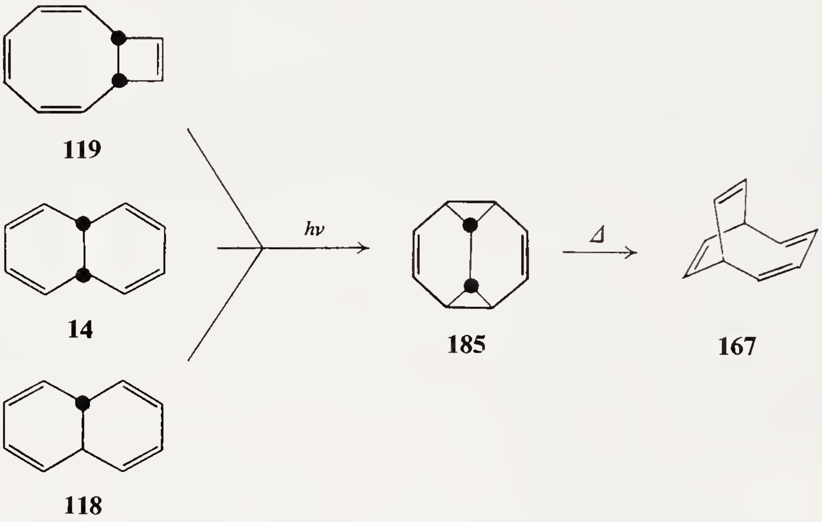


trans-9,10-dihydronaphthalene, cyclooctatetraene, and naphthalene were detected in major amounts along with trace amounts of the bicyclic tetraene **167** and the novel tricyclic triene **184** (unspecified stereochemistry). When manipulation during isolation of the hydrocarbons was performed below 0°C, a new $C_{10}H_{10}$ product was isolated at the expense of **118** and **15**. This substance, shown to be bicyclo[6.2.0]deca-2,4,6,9-tetraene (**119**), was readily and quantitatively isomerized to *trans*-9,10-dihydronaphthalene at 40°C in deuteriochloroform solution. The mechanistic proposal for this rearrangement features the thermally induced conrotatory opening of **119** to a mono-*trans*,



tetra-*cis*-cyclodecapentaene (**3**), an unstable intermediate presumed by the authors to be situated on the reaction coordinate at a position close to the transition state for reclosure in a disrotatory sense to **118**. A preliminary report of the photolysis of **119** names the bicyclic tetraene isomer **167** as one product in a complex reaction mixture presently under investigation.

Finally, Masamune *et al.*[100] have described the low temperature photochemical conversion of bicyclo[6.2.0]deca-2,4,6,9-tetraene (**119**) as well as both *cis*- and *trans*-9,10-dihydronaphthalene to the oft cited–never seen tetracyclic species **185**. Thermal reorganization of this tetracyclic diene gave



the known bicyclic tetraene **167**. Investigation of the excited-state chemistry of **185** and also the surprising formation of **185** from *both* 9,10-dihydronaphthalenes should provide additional important data concerning the complex $(CH)_{10}$ system.

III. Conclusion—Complexity of the $(CH)_{10}$ Valence Bond Isomer System

Valence bond isomers, other than those considered a priori to be likely precursors to cyclodecapentaene, have now also been shown to be interrelated by

[99] S. Masamune, H. Cuts, and M. Hogben, *Tetrahedron Letters*, p. 1017 (1966).

[100] S. Masamune, R. T. Seidner, H. Zenda, M. Wiesel, N. Nakatsuka, and G. Bigam, *J. Am. Chem. Soc.* **90**, 5286 (1968).

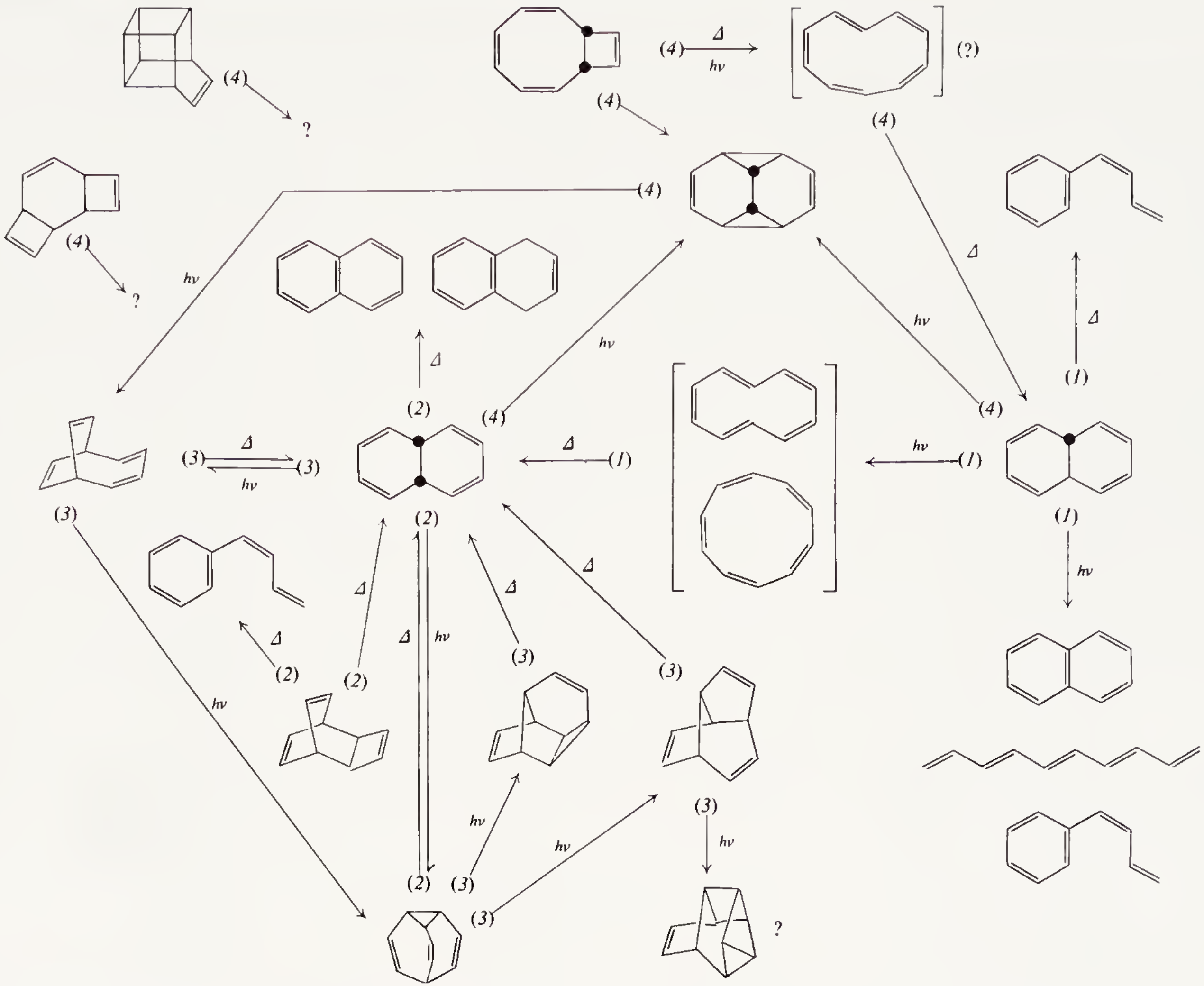


FIG. 11. The isomers known to date and their recorded pathways of isomerization are summarized in this figure. (1) van Tamelen *et al.*[25,49,91]; (2) Doering and Rosenthal[24,92]; (3) Jones *et al.*[86,98]; (4) Masamune *et al.*[89a,99,100]

facile and intriguing molecular rearrangements. The work of Doering and Rosenthal,[24,92] Jones,[86] Masamune *et al.*,[89a,100] as well as our own research[25,41,91] has revealed a complex intertwining of rearrangement processes open to $(CH)_{10}$ isomers, still a fountainhead for organic chemical research. The isomers known to date and their recorded pathways of isomerization are summarized in Fig. 11. The field continues to offer may opportunities for originating and testing of mechanistic proposals as well as synthesis of new $(CH)_{10}$ isomers and observance of their points of entrance into the labyrinth. As the system becomes more fully understood, it may serve as an ultimate proving ground for the Woodward–Hoffmann selection rules by helping set the limit of strain and helping gauge the influence of restrictive geometries on electrocyclic reactions.

4

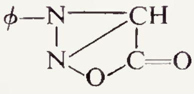
Sydnones and Other Mesoionic Compounds

Masaki Ohta and Hiroshi Kato[1]

I. Introduction

A. History

In 1935, Earl and Mackney[2] found that treating *N*-nitroso-*N*-phenylglycine with acetic anhydride gave an anhydro compound on intramolecular dehydration. A fused ring structure **1** was originally proposed and the generic name "sydnone" was suggested in honor of University of Sydney where the study was performed.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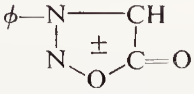
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[1] Present address: Department of Chemistry, Faculty of Science, Shinshu University, Matsumoto, Japan.

[2] J. C. Earl and A. W. Mackney, *J. Chem. Soc.* p. 899 (1935).

Later, in 1949, Baker *et al.*[3] found structure **1** to be untenable in the light of the properties of sydnone, and considered the substance to be a resonance hybrid of a number of dipolar and tetrapolar ionic structures. They further indicated that it would be misleading to arbitrarily select one contributing structure among a number of canonical forms with varying degrees of importance. A general adjcctive "mesoionic" (mesomerie + ionic) was therefore introduced and a ± symbol first suggested by Simpson[4] was adopted to represent electron distributions for compounds of this type. In this usage, 3-phenylsydnone is represented as **2**. A closely analogous concept had already been put forward with regard to nitron and Busch's "endothiadiazoles." Discussion of the structure of sydnone gave a strong impetus to generalized discussion of compounds of this type.

An inspection of the electronic arrangement of sydnone reveals that it may be regarded as an aromatic compound, similar to tropone, stabilized by delocalization of the six π-electrons within the ring. Thus, it may be classified as a new member of a vast family of nonbenzenoid aromatic compounds.

In the earlier stages of research on mesoionic compounds, attention was focused mainly on the structure and the π-electronic representation of sydnone. Much data, including dipole moment, spectroscopic measurements, and molecular orbital calculations, supported the concept that sydnone was indeed an aromatic compound. At the same time, the need to classify these compounds by the use of a special symbol or a special term like "mesoionic," in order to distinguish them from "normal organic compounds," has been criticized. In particular, strong objection to the use of such terminology has been raised by Katritzky.[5]

Concomitant to the discussion on the structure of sydnone, investigation of its chemical properties, with strong emphasis on its aromaticity, was launched. It has been shown that sydnones unsubstituted at the 4-position undergo electrophilic substitution reactions, such as nitration, halogenation, sulfonation, and metallation, characteristic of aromatic rings. Huisgen and Grashey[6] and Vasil'eva *et al.*[7] have found that sydnones react with a number of olefins and acetylenes by 1,3-dipolar addition and subsequent decarboxylation to give five-membered heterocyclic compounds. This interesting reaction is presumably a result of the polar nature of sydnones. This reaction has recently been applied to mesoionic compounds other than sydnones.

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[3] W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.* p. 307 (1949).

[4] J. C. E. Simpson, *J. Chem. Soc.* p. 94 (1946).

[5] A. R. Katritzky, *Chem. Ind.* (*London*) p. 521 (1955).

[6] R. Huisgen and R. Grashey, *Angew. Chem.* **74**, 29 (1962).

[7] V. F. Vasil'eva, V. G. Yashunskii, and M. N. Shchukina, *Zh. Obshch. Khim.* **30**, 698 (1960); *Chem. Abstr.* **54**, 24674 (1960).

The ring system in which the exocyclic oxygen atom of sydnone is replaced by an imino group has been named sydnone imine. Compounds of this class are stable only as salts or as *exo-N*-substituted derivatives. In many ways, sydnone imines differ considerably from sydnones, and a number of studies, both physical and chemical, have been made.

Although more than 200 combinations are theoretically possible for building up five-membered heterocyclic ring systems, which, a priori, may be regarded as having electronic arrangements similar to sydnone, many of them are expected to be difficult to synthesize.

Prior to the introduction of the term mesoionic, several ring systems were known which should now be considered as mesoionic compounds. Some thiadiazole and triazole derivatives, prepared by Busch and originally assigned bridged structures, were reformulated with hybrid structures by Schönberg. This concept is essentially the same as "mesoionic."

Although sydnones and sydnone imines have been extensively investigated physically and chemically, with strong emphasis on the question of their aromaticity, little is known concerning the aromaticity of other ring systems expected to have similar electronic structures. This problem certainly merits further study. An increasing number of reports on the preparation and properties of these latter ring systems has recently appeared.

The chemistry of mesoionic compounds was reviewed by Baker and Ollis[8] early in the exploration of this field. More recently, the chemistry of sydnones was reviewed in detail by Stewart[9] and briefly by Noël,[10] and a review on mesoionic compounds in general was prepared by Ohta and Kato.[11] The medicinal chemistry of the mesoionic species was reviewed by Kier and Roche.[12]

B. General Discussion

1. *Definition of the Term "Mesoionic"*

In 1949, Baker *et al.*[3] proposed the use of the adjective "mesoionic" for a group of compounds, which they represented only as hybrids of polar structures, and classified sydnones as "cyclic mesoionic compounds." Later,[13,14] it was suggested that this term should be reserved for a novel class of *heterocyclic* compounds, such as sydnone, which conform to the conditions

[8] W. Baker and W. D. Ollis, *Quart. Rev.* **11**, 15 (1957).

[9] F. H. C. Stewart, *Chem. Rev.* **64**, 129 (1964).

[10] Y. Noël, *Bull. Soc. Chim. France* p. 173 (1964).

[11] M. Ohta and H. Kato, *Nippon Kagaku Zasshi* **86**, 661 (1965).

[12] L. B. Kier and E. B. Roche, *J. Pharm. Sci.* **56**, 149 (1967).

[13] W. Baker and W. D. Ollis, *Chem. Ind.* (*London*) p. 910 (1955).

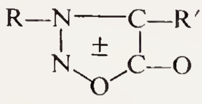
[14] W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.* p. 1542 (1950).

described above. The term in this sense is presently in general use in spite of the objection raised by Katritzky.[15] The detailed nature of a mesoionic compound is an important question in connection with the representation and nomenclature of these compounds. The pros and cons on the use of such a term will be discussed in more detail later. Let it suffice here to quote the definition of mesoionic compounds given by Baker[8]: "A compound may appropriately be called mesoionic if it is a five- or possibly a six-membered heterocyclic compound which cannot be represented *satisfactorily* by any one covalent or polar structure and possesses a sextet of electrons in association with all the atoms comprising the ring. The ring bears a fractional positive charge, balanced by a corresponding negative charge located on a covalently attached atom or group of atoms. As a corollary to the definition it follows that in any particular polar structure which may be written for a mesoionic compound the charges cannot wholly neutralize one another to give a covalent structure."

2. *Representation, Nomenclature, and Classification*

Whether or not sydnone and similar compounds with a "mesoionic" structure may be represented satisfactorily by a single covalent structural formula, and if not, how they may be represented and named has long been argued by a number of investigators. This problem has yet to be solved. Problems related to the mode of representation will be discussed in more detail in Section IV, in connection with the structure and aromaticity of mesoionic compounds.

Since Baker's[3] reformulation (**2**) of Earl's[2,16] original bicyclic formula (**1**), many alternate representations (**3**–**7**) have been proposed.



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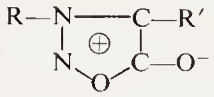
Baker[14]



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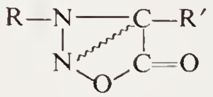
Baker[13]



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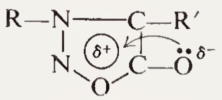
Earl[17]



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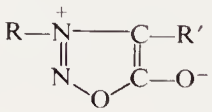
Bieber[18]



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Katritzky[5,15]

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[15] A. R. Katritzky, *Chem. Ind. (London)* p. 1391 (1955).

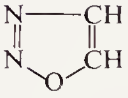
[16] R. A. Eade and J. C. Earl, *J. Chem. Soc.* p. 591 (1946).

[17] J. C. Earl, *Nature* **158**, 910 (1946).

[18] T. I. Bieber, *Chem. Ind. (London)* p. 1055 (1955).

Among these, formulas **2**, **3**, **4**, and **7** are most commonly used. In this review, structural formulas analogous to **3** will be utilized for mesoionic compounds in general.

Excluding the trivial names such as sydnone, two proposals have been made for naming these compounds. According to that made by Baker,[3] 3-phenylsydnone **3** (R = Ph, R′ = H) is named as ψ-5-keto-3-phenyl-3,5-dihydro-1-oxa-2,3-diazole. This nomenclature is based on the unknown 1,2,3-oxadiazole (**8**). Phenylsydnone **3** is designated as the 5-keto derivative **9** of the 3,5-dihydro derivative of **8**. The symbol ψ means that the compound belongs to a mesoionic ring system where the π-electrons are delocalized. Two other examples following this nomenclature are shown below:



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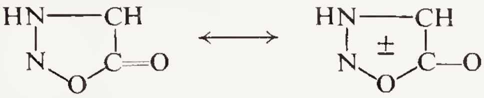

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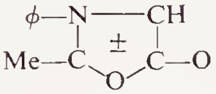
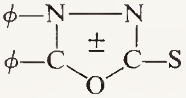
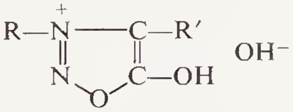


ψ-5-keto-2-methyl-3-phenyl-
3,5-dihydro-1,3-oxazole



ψ-5-thio-2,3-diphenyl-
3,5-dihydro-1-thia-3,4-diazole

An alternative nomenclature, proposed by Katritzky,[5] is based on the betaine structure **7**. It is one of the important contributors to the resonance hybrid and is named according to current nomenclature as the anhydro compound of quaternary base **10**. Thus, 3-phenylsydnone is called anhydro-5-hydroxy-3-phenyl-1-oxa-2,3-diazolium hydroxide. This nomenclature is currently used in Chemical Abstracts.



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Both of these designations are derived from conventional aromatic heterocycles (e.g., 1,2,3-oxadiazole). The former stresses the delocalization of electrons, while the latter deemphasizes the mesoionic concept. In this review, Baker's nomenclature will be used with a slight modification, namely omission of the symbol ψ representing the delocalization of electrons. Even if ψ is omitted, the delocalization of π-electrons is anticipated more or less reasonably from inspection of the structures given. In addition, only a single compound will correspond to this nomenclature regardless of the presence or absence of ψ.

The use of a conventional name is desirable in some cases to avoid complication and for ease of classification. Terms such as mesoionic oxazolone and mesoionic oxazole have actually been used. In this review, the names of five-membered heterocycles with the adjective mesoionic will be used when convenient.

Since the sydnone and sydnone imines have been most extensively investigated, they are discussed first in this review. The other mesoionic compounds are then discussed according to a classification by the number and arrangement of heteroatoms.

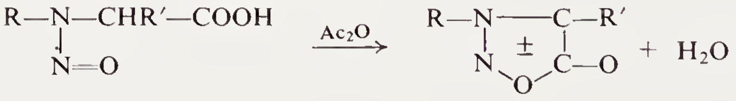
Although the concept of mesoionic compounds as defined by Baker may be applied to some six-membered heterocyclic ring systems, many such compounds may be adequately represented by betaine structures. Only five-membered compounds will be discussed in this article.

As the purpose of the present review is to discuss mesoionic substances as nonbenzenoid aromatic compounds, their uses are described only briefly. Considerable attention, however, has recently been paid to finding applications of these compounds in synthesis and pharmacology.

3. *Synthesis*

Before discussing individual mesoionic compounds, it may be worthwhile to consider how the heterocyclic rings that satisfy the criteria for a mesoionic ring are formed. The conditions of the formation of mesoionic rings do not differ in principle from those of other heterocyclic rings, with one exception. The starting material should be so selected that it will provide a ring with a positive and a negative charge at the nonadjacent positions of the resulting ring or a formal bond between them.

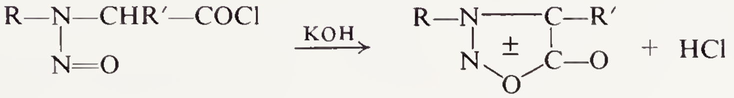
a. Ring Formation by an Intramolecular Elimination Reaction. Ring formation of this type may be exemplified by the formation of sydnone **3** from *N*-substituted *N*-nitrosoglycine **11**,[2] which can be represented in a general form by Eq. (1). Ring formation is accompanied by elimination of a given molecule (usually water) from the starting material. One can find ample examples of



(1)

11 **3**

mesoionic ring formation by this mode, and many of the oxo-type mesoionic rings so far known are prepared in this way. The formation of sydnone **3**,[14] a mesoionic oxatriazole **12**,[19] and dehydrodithizone **13**[20] by elimination of a molecule of hydrogen chloride, ammonia, and hydrogen, respectively, are shown in Eqs. (2)–(4) as examples of the elimination of molecules other than water.



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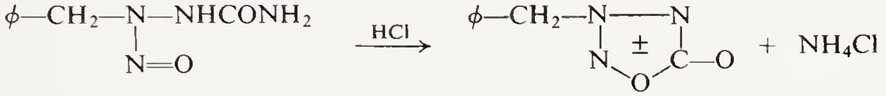
(2)



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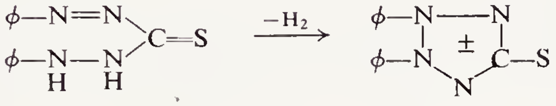
(3)



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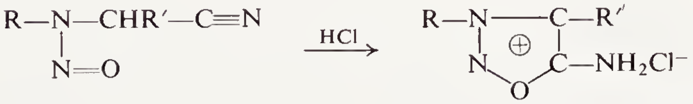
(4)

b. Ring Formation by Intramolecular Addition between Two Unsaturated Groups Accompanied by Formal Proton Migration. Ring formation of this type is exemplified by the preparation of sydnone imine hydrochloride **14** through the action of hydrogen chloride on *N*-nitrosoaminonitrile **15**[21,22] [Eq. (5)]. Many imino-type mesoionic compounds are prepared by this method. Needless to say, the reaction actually proceeds by an initial protonation of an unsaturated group, ring closure, and deprotonation.



15 **14**

(5)

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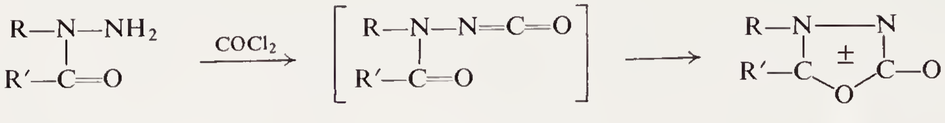
[19] W. G. Finnegan and R. A. Henry, *J. Org. Chem.* **30**, 567 (1965).

[20] E. Fischer and A. Besthorn, *Ann.* **212**, 316 (1882).

[21] H. Kato, M. Hashimoto, and M. Ohta, *Nippon Kagaku Zasshi* **78**, 707 (1957).

[22] P. Brookes and J. Walker, *J. Chem. Soc.* p. 4409 (1957).

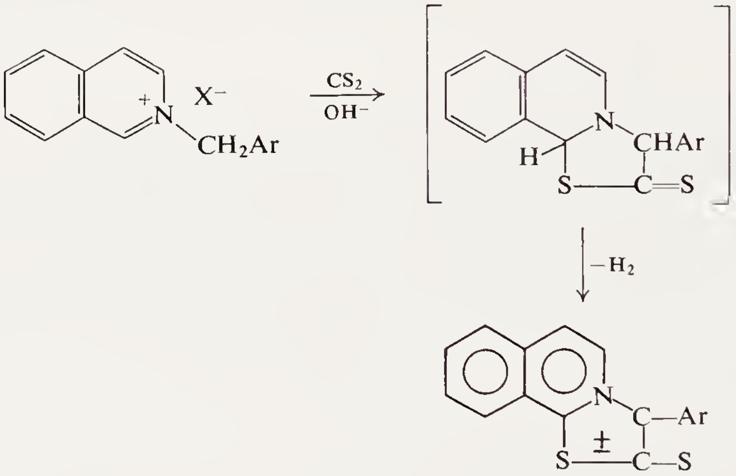
c. Ring Formation by Intramolecular Addition between Two Unsaturated Groups. Ring formation of this type is illustrated by the formation of "isosydnone" **16**[23] as shown in Eq. (6). In this case, one of the two unsaturated groups is usually part of a cumulative double bond, but such intermediates [e.g., (**17**)] are usually not isolable.



(6)

17 **16**

d. Dehydrogenation of a Heterocyclic Ring. Although many dihydro derivatives of aromatic heterocycles readily convert to the corresponding aromatized heterocyclic rings on dehydrogenation, few examples are known of mesoionic ring formation by removal of two hydrogen atoms from two non-adjacent positions of a heterocyclic ring. An example is given in Eq. (7) (also see Section III,A,3,*c*).[24]



(7)

e. Dehydration or Dehydrohalogenation from a Quaternary Base or Salt of a Heterocyclic Ring. The formation of mesoionic compounds by this mode is exemplified in Eq. (8) (also see Section III,B,2,*b*).[25] If the structures of sydnone

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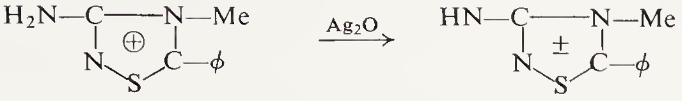
[23] M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Japan* **34**, 668 (1961).

[24] F. Kröhnke and H. H. Steuernagel, *Angew. Chem.* **73**, 26 (1961).

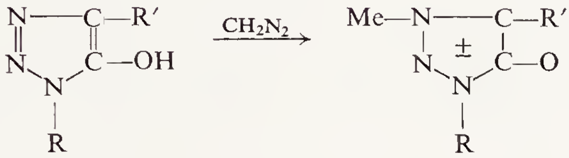
[25] J. Goerdeler and W. Roth, *Ber.* **96**, 534 (1963).



(8)

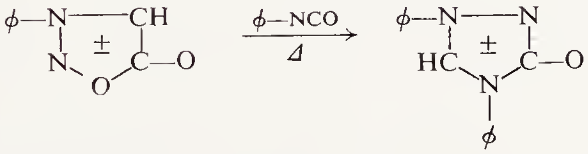
imine hydrochloride and similar compounds formed by type *b* reactions are more adequately represented by quaternary salts, then preparing the free bases from the salts should be regarded as an actual step of mesoionic ring formation. Accordingly, they should be classified in this group.

f. Alkylation of a Heterocyclic Ring. In some cases, a mesoionic ring is formed directly by alkylating a heterocyclic ring, as illustrated in Eq. (9) (also see Section III,B,*3*,*b*).[26]



(9)

g. Ring Formation by Cycloaddition. This is illustrated in Eq. (10).[27] In this case, the 1,3-dipolarophile probably should be a compound with a cumulative unsaturated bond.



(10)

II. Sydnones and Sydnone Imines

A. SYDNONES

1. Syntheses

The most common preparation of sydnones **3** is by treating *N*-substituted *N*-nitroso-α-aminocarboxylic acids **11** with acetic anhydride. This reaction requires a long period of time at room temperature but proceeds rapidly when heated.[28] Other reagents used to bring about the cyclization include acid chlorides, phosgene, sulfonyl chlorides, chloroformates, phosphorus oxy-

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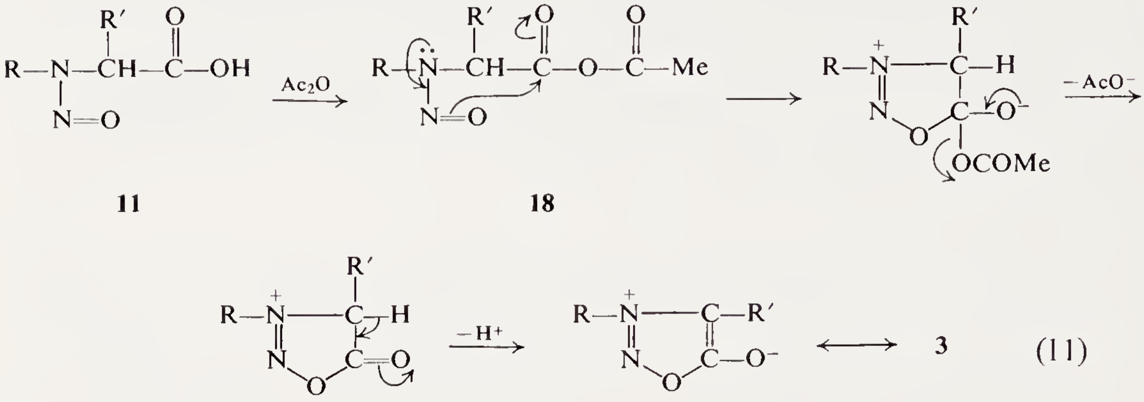
[26] M. Begtrup and C. Petersen, *Acta Chem. Scand.* **21**, 633 (1967).

[27] H. Kato, S. Sato, and M. Ohta, *Tetrahedron Letters* p. 4261 (1967).

[28] C. J. Thoman and D. J. Voaden, *Org. Syn.* **45**, 96 (1965).

chloride, and chloroacetyl chloride in the presence of a base.[29,30] Carbodiimides[31] or phenyl cyanate[32] are also effective for this purpose.

Ring closure of *N*-nitrosoglycine, **11**, by means of acetic anhydride is generally considered to proceed through a mixed anhydride (**18**).[14] The mechanism proposed by Baker is shown in the scheme [Eq. (**11**)] below:



(11)

If this mechanism of sydnone ring formation is operable, the driving force of the reaction may be the nucleophilicity of the oxygen atom of the nitroso group for the carbon atom of the carboxylic group and the reactivity of the acetate anion as an eliminated group. Accordingly, it is expected that the formation of the sydnone ring will be facilitated as the cationoid properties of the carboxyl carbon atom and the anionoid character of the nitroso oxygen atom increase. This expectation is realized. The following experimental results support the mechanism described above.

(*1*) The mixed anhydride **18** (R = Ph, R′ = H), isolated by reacting sodium salt of *N*-nitroso-*N*-phenylglycine and acetyl chloride, readily forms 3-phenylsydnone when allowed to stand at room temperature or heated in toluene.[14]

(*2*) Although ring formation mediated by acetic anhydride requires a long period of time at room temperature, trifluoroacetic anhydride rapidly promotes closure even at low temperature. The strongly electron-withdrawing trifluoro group facilitates elimination of the trifluoroacetoxy anion.[14]

(*3*) Treating *N*-nitrosophenylglycine with thionyl chloride in ether or dioxane, in the presence of pyridine, causes rapid sydnone formation.[14] This

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[29] R. Pütter and G. Wolfrum, British Patent 823,001 (1959); *Chem. Abstr.* **54**, 8854 (1960).

[30] R. Pütter and G. Wolfrum, German Patent 1,057,124 (1959); *Chem. Abstr.* **55**, 7436 (1961).

[31] R. Pütter and G. Wolfrum, German Patent 1,069,633 (1959); *Chem. Abstr.* **55**, 10472 (1961).

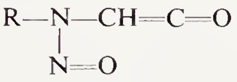
[32] D. Martin, *Ber.* **98**, 3286 (1965).

may be considered a consequence of increased cationoid character of the carbonyl group by the electron-withdrawing effect of chlorine in the resulting acid chloride.

(*4*) Treating *N*-nitrosophenylglycine ester or glycinamide with a number of reagents failed to give sydnone.[14] This is because the cationoid character of the carbonyl carbon is reduced in these compounds.

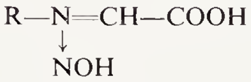
(*5*) Ring closure does not take place when *N*-nitroso-*N*-toluenesulfonylglycine is treated with acetic anhydride.[33] This is presumably because of the reduced nucleophilic character of the nitroso oxygen atom due to the presence of a strongly electron-withdrawing sulfonyl group.

Ring closure via a ketene (**19**)[17] or via prototropy to an intermediate (**20**)[34] was once proposed.



$$\mathrm{R{-}\underset{\underset{\displaystyle N{=}O}{|}}{N}{-}CH{=}C{=}O}$$

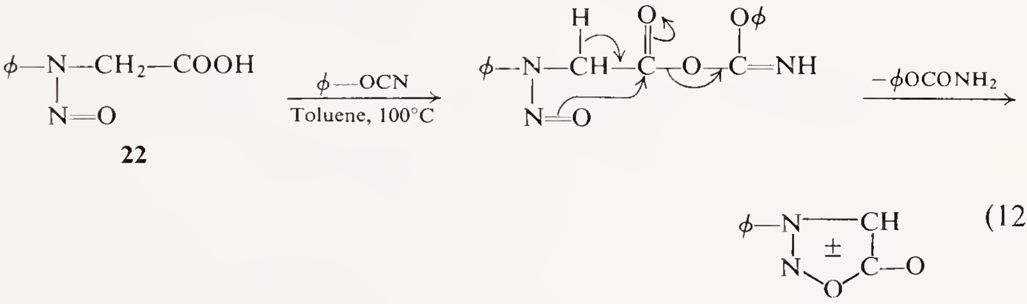
19



$$\mathrm{R{-}\underset{\underset{\displaystyle NOH}{\downarrow}}{N}{=}CH{-}COOH}$$

20

3-Phenylsydnone **21** is formed in 73% yield from *N*-nitroso-*N*-phenylglycine **22** using phenyl cyanate as the condensation reagent. The mechanism shown in Eq. (12) is proposed to account for the ring formation:



(12)

21

An interesting method of preparation of sydnones **3**, which consists of heating *N*-nitrososydnone imines **23** in organic solvents [Eq. (23)], has recently been reported.[35] This is the only known method permitting the preparation of sydnones from starting materials other than *N*-nitrosoglycines **11**.

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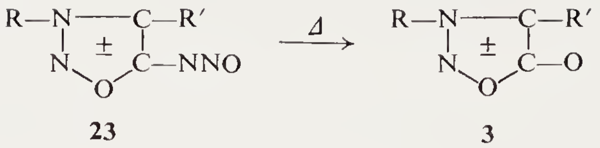
[33] M. Hashimoto, Ph.D. Dissertation, Tokyo Institute of Technology, Tokyo, Japan (1961).

[34] J. C. Earl, *Chem. Ind.* (*London*) p. 746 (1953).

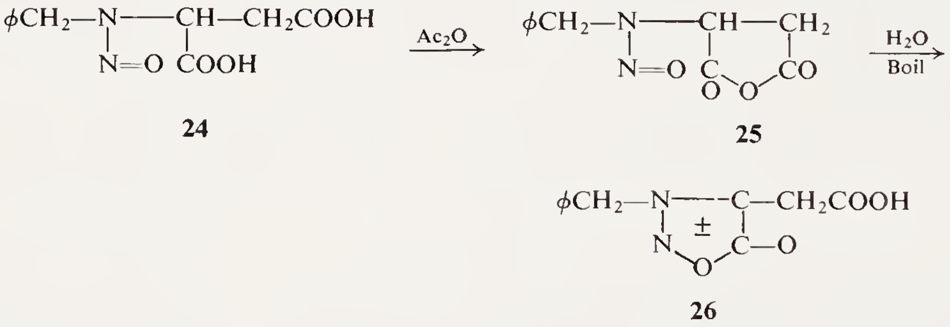
[35] L. E. Kholodov and V. G. Yashunskii, *Byul. Izobret Tovarnykh Znakov No.* **16**, 37 (1965); *Chem. Abstr.* **64**, 3557 (1966).



23 → **3** (13)

For the formation of sydnones **3** by ring closure of *N*-substituted *N*-nitrosoglycines **11**, it is evident that at least one hydrogen atom is required on the α-carbon atom and that the amino nitrogen atom should have a substituent other than hydrogen. It may be safely anticipated that sydnones are formed from **11** where both R and R′ are alkyl, allyl, aryl, or cycloalkyl; R′ may be a hydrogen atom. Further, either R or R′ may contain a functional group such as carboxyl, ether, nitrile, or hydroxyl.[36]

However, when an *N*-alkyl-*N*-nitroso-α-aminodicarboxylic acid is treated with acetic anhydride, sydnone ring formation competes with the cyclic acid anhydride formation by dehydration between the two carboxyl groups and the result is rather complicated. For example, reacting *N*-benzoyl-*N*-nitroso-DL-aspartic acid **24** and acetic anhydride gives the acid anhydride **25**, which is converted to sydnone **26** when allowed to stand in aqueous solution at room temperature or boiled briefly with water [Eq. (14)].[37] Further, treating



24 → **25** → **26** (14)

N-β-cyanoethyl-*N*-nitrosoglutamic acid **27** with acetic anhydride at room temperature gives a six-membered cyclic anhydride **28** as the principal product. This intermediate is likewise converted to sydnone **29** by the action of water [Eq. (15)].[37]

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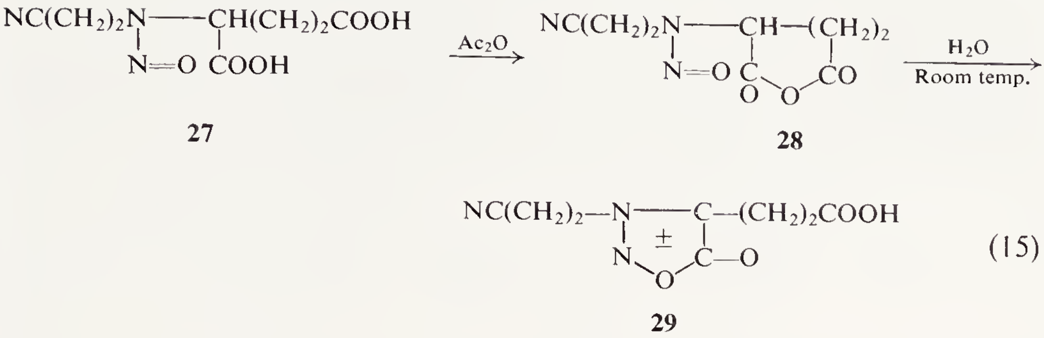
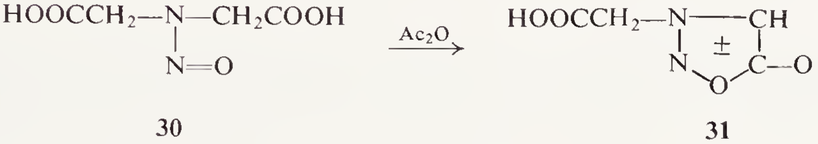
[36] F. H. C. Stewart, *J. Org. Chem.* 27, 687 (1962).

[37] F. H. C. Stewart, *J. Chem. Soc.* p. 3158 (1963).



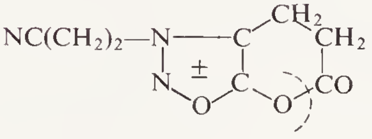
(15)

In the case of nitrosoiminodiacetic acid **30**, 3-carboxymethylsydnone **31** is obtained instead of the corresponding cyclic anhydride [Eq. (16)].[38, 39]



(16)

That **25** is less readily hydrolyzed to sydnone than **28** has been explained by the increased strain imposed by fusion of the smaller ring to the planar mesomeric nucleus of an intermediate such as **32**.[37]



32

The competitive reaction described above may also be explained by a conformational factor in the nitroso compound.[38] Namely, the preferred conformations of **24** and **30** may be shown as **33** and **34**, respectively, in the Newman projection.

Here, R represents the remainder of the molecule and the largest group is in a *trans* position. In conformation **33**, the nitroso and the carboxyl groups are not suitably situated for the formation of sydnone ring, but in **34**, both groups are.

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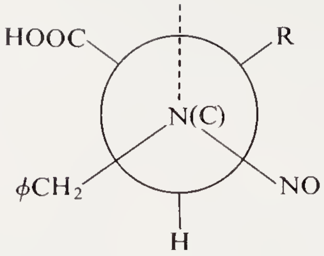
[38] F. H. C. Stewart, *J. Chem. Soc.* p. 701 (1963).

[39] F. H. C. Stewart, *Chem. Ind.* (*London*) p. 1411 (1961).



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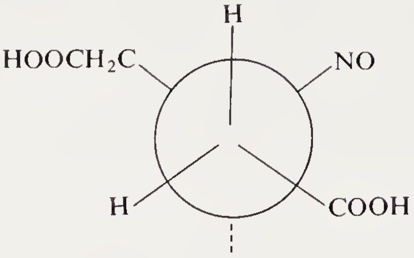
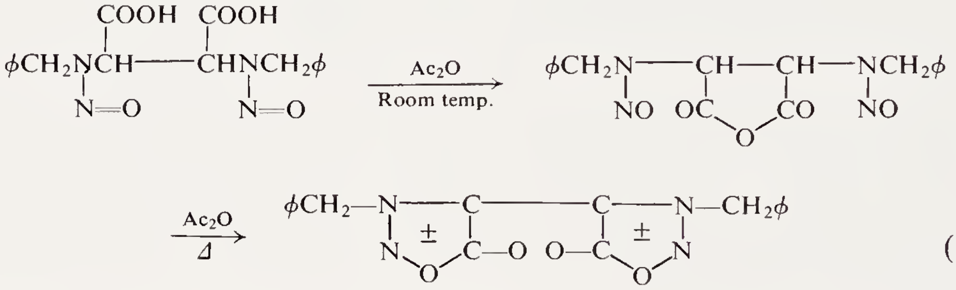
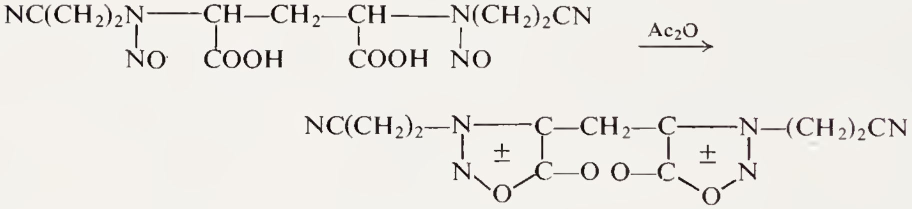


34

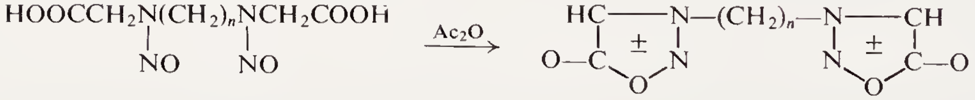
Bissydnones in which two sydnone rings are linked directly, by a polymethylene chain, or by phenyl have been prepared by cyclodehydration of the appropriate *N,N'*-dinitrosobisglycines. A few examples are shown in Eqs. (17)[40], (18),[38] (19),[41] and (20).[42]



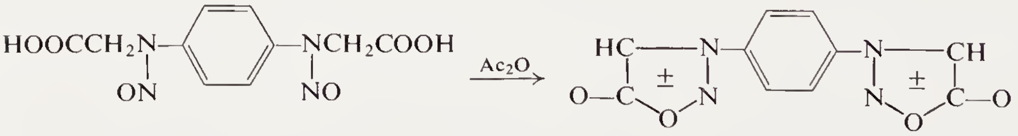
(17)



(18)



(19)



(20)

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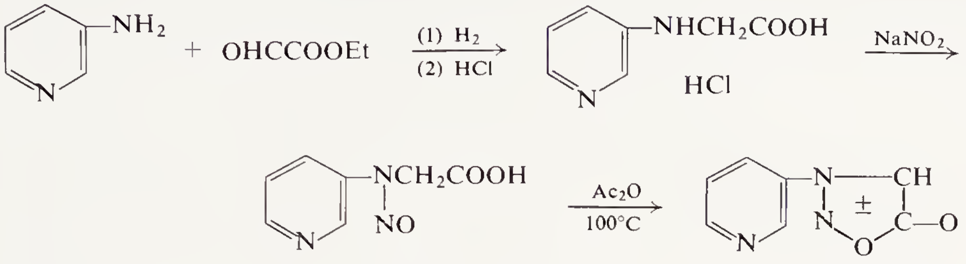
[40] F. H. C. Stewart, *J. Chem. Soc.* p. 2009 (1963).

[41] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **40**, 918 (1957).

[42] V. G. Yashunskii and L. E. Kholodov, *Zh. Obshch. Khim.* **32**, 3661 (1962); *Chem. Abstr.* **58**, 13939 (1963).

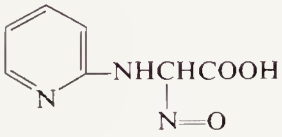
Only a few sydnones having a heterocyclic substituent have been reported.[43–45] *N*-(3-Pyridyl)sydnone, **35**, a unique compound exhibiting photochromism, was synthesized by Tien and Hunsberger[44] by cyclodehydration of *N*-nitroso-*N*-(3-pyridyl)glycine **36** with acetic anhydride [Eq. (21)].



(21)

36 **35**

4-Methyl and 4-phenyl analogs of **35** were also prepared[45] but were not photochromic. Attempts to synthesize *N*-(2-pyridyl)sydnone were unsuccessful due to formation of the C_α-nitrosoglycine derivative **37** on nitrosation of *N*-(2-pyridyl)glycine. *N*-(4-Pyridyl)glycine could be nitrosated to give *N*-nitroso-*N*-(4-pyridyl)glycine **38** which, however, did not produce the expected sydnone with acetic anhydride. Instead, a colorless substance $C_{10}H_{13}O_2N_3$ of unknown structure[46,47] was isolated.



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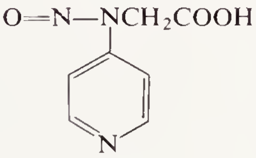

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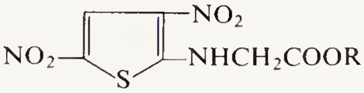

39

In an attempt to prepare 3-thienylsydnone, Tien and Hunsberger[48] found that neither *N*-(3,5-dinitro-2-thienyl)glycine nor its ester **39** could be nitrosated.

A few fused ring sydnones have been synthesized and, in principle, the procedure is similar to that used for synthesizing monocyclic sydnones.

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[43] G. S. Puranik and H. Suschitzky, *J. Chem. Soc.* (*C*) p. 1006 (1967).

[44] J. M. Tien and I. M. Hunsberger, *Chem. Ind.* (*London*) p. 119 (1955).

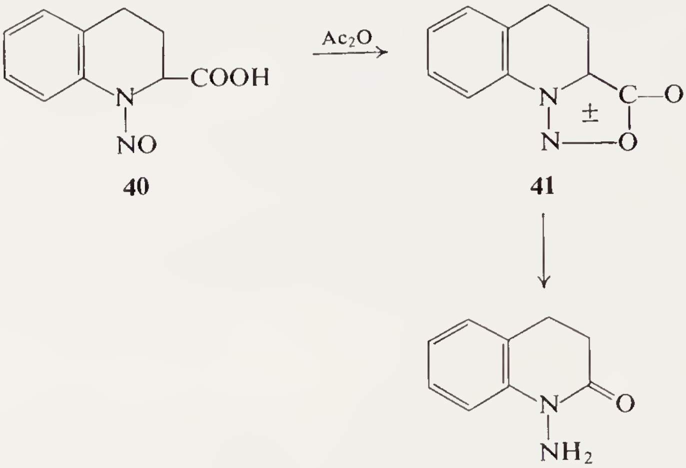
[45] M. Ohta and M. Masaki, *Bull. Chem. Soc. Japan* **33**, 649 (1960).

[46] M. Ohta and M. Masaki, *Bull. Chem. Soc. Japan* **33**, 1392 (1960).

[47] M. Ohta and M. Masaki, *Bull. Chem. Soc. Japan* **33**, 1150 (1960).

[48] J. M. Tien and I. M. Hunsberger, *J. Org. Chem.* **25**, 2056 (1960).

Hammick *et al.*[49,50] and Kruger[51] reported that treating 1,2,3,4-tetrahydro-1-nitrosoquinaldic acid **40** with acetic anhydride gave 3′,4′-dihydroquinolino[1′:2′–3:4]sydnone **41** [Eq. (22)].[52] Hydrolysis of **41** with dilute hydrochloric acid produced 1-amino-1,2,3,4-tetrahydro-2-oxoquinoline **42**.

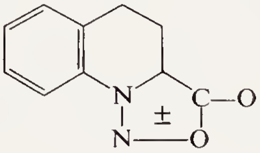


40 **41** **42**

(22)

Attempts to dehydrogenate **41** by a variety of procedures to yield a fully aromatic compound were unsuccessful.[50]

Tetrahydropyridosydnone **43**[50] and tetrahydroisoquinolinosydnone **44**[51] were prepared in a similar manner.



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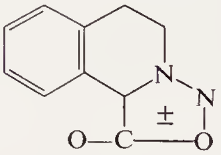

44

2. *Physical Properties*

a. Ultraviolet Spectrum. A survey of the ultraviolet absorption spectra of variously substituted sydnones reveals that alkylsydnones in general show an absorption maximum at around 290 mμ with an intensity ϵ of ca. 8000. The

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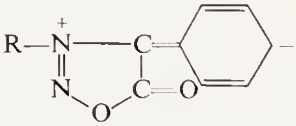
[49] D. L. Hammick, A. M. Roe, and D. J. Voaden, *Chem. Ind.* (*London*) p. 251 (1954).

[50] D. L. Hammick and D. J. Voaden, *J. Chem. Soc.* p. 3303 (1961).

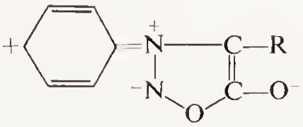
[51] S. Kruger, *Chem. Ind.* (*London*) p. 465 (1954).

[52] The nomenclature used by the original authors is adopted here.

maximum is shifted to longer wavelengths in aryl substituted sydnones because of conjugation. For example, 3-phenylsydnone has an absorption maximum at 310 mμ,[53] while 3-methyl-4-phenylsydnone has a maximum at 317 mμ.[54] Stewart pointed out that comparison of these two values suggests that an aryl substituent at the 4-position conjugates more effectively with the sydnone ring than one at the 3-position, i.e., the degree of the contribution from canonical form **45** is greater than that of **46** to the resonance hybrid of the corresponding sydnone.

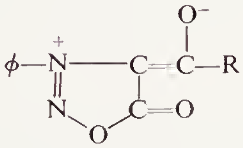


45

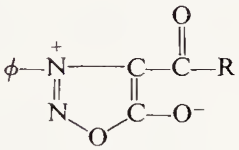


46

A still longer bathochromic shift is observed with 3,4-diphenylsydnone, which shows a maximum at 340 mμ.[55] An acyl substituent at the 4-position also has a considerable bathochromic effect, since 3-phenyl-4-acylsydnones show an absorption maximum at 324 mμ.[55] This fact suggests considerable contribution of structures such as **47** and **48** to the resonance hybrid. This view is supported by infrared data.



47



48

The absorption maximum of 3,3′-dibenzyl-4,4′-bissydnone is shifted to 350 mμ, suggesting the existence of an appreciable electronic interaction between the adjacent sydnone nuclei.[38]

The positions of absorption maxima of sydnones are fairly dependent on the solvent employed. Consequently, this absorption has been ascribed to an $n \rightarrow \pi^*$ transition since a blue shift of 10–20 mμ has been observed in changing the solvent from nonpolar cyclohexane to polar water.[56]

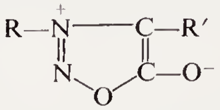
[53] J. C. Earl, R. J. W. LeFèvre, and I. R. Wilson, *J. Chem. Soc.* p. S103 (1949).

[54] F. H. C. Stewart, unpublished work. cf. *Chem. Rev.* 64, 129 (1964).

[55] C. V. Greco, J. Tobias, and L. B. Kier, *J. Heterocyclic Chem.* 4, 160 (1967).

[56] F. I. Metz, W. C. Servoss, and F. E. Welsh, *J. Phys. Chem.* 66, 2446 (1962).

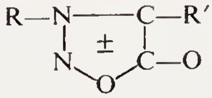
If the zwitterionic structure **7** contributes greatly to the whole resonance hybrid of sydnone, a hypsochromic shift caused by hydrogen bond formation with solvent would be anticipated. This prediction was substantiated by measurement of the absorptions of three sydnones in three different solvents, as shown in Table I. It was therefore concluded that contribution from structure **7** is important, at least in solution.[57]



7

TABLE I

DEPENDENCY OF ULTRAVIOLET ABSORPTION MAXIMA OF SYDNONES ON SOLVENTS[a]



R	R′	Pyridine (Å)	Ethanol (Å)	Water (Å)
$PhCH_2$	H	—	2920	2875
Ph	H	3200	3130	3015
Ph	Ph	3410	3340	3280

[a] W. A. Lees and A. Buraway, *Tetrahedron* **19**, 419 (1963).

The steric effect on the conjugation between the sydnone and phenyl rings has been studied.[50,58] The intensity of the absorption maximum decreases remarkably for 3-phenylsydnones substituted with methyl or ethyl at the *ortho* position of the phenyl ring. This is presumably a result of inhibition of coplanarity of the two rings. Such an effect was not observed with *o*-methoxy and *o*-ethoxy derivatives, suggesting that the alkoxy group is flexed, permitting a preferable coplanar configuration of the two rings. The steric effect due to the methyl group of 4-methyl-3-phenylsydnone appears to be less than that due to the methyl group of 3-*o*-tolylsydnone. It has almost no effect on the polarographic measurement. Steric hindrance of coplanarity is so increased with 3-(2,6-dimethylphenyl)-4-methylsydnone that the ultraviolet spectrum of this compound resembles that of alkylsydnones.

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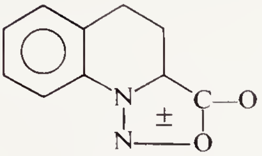
[57] W. A. Lees and A. Buraway, *Tetrahedron* **19**, 419 (1963).

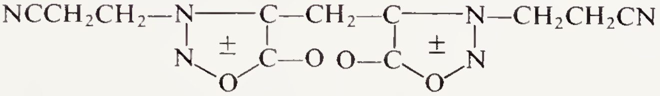
[58] P. Zuman and D. J. Voaden, *Tetrahedron* **16**, 130 (1961).

The ultraviolet spectrum of fused-ring sydnone **49** resembles much more that of 3-phenylsydnone than that of 3-(*o*-ethylphenyl)sydnone, indicating that the coplanarity of the two aromatic rings is restored by bridging.

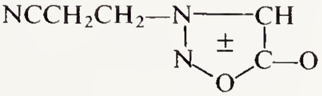


49

The absorption maxima of 3,3′-di(β-cyanoethyl)-4,4′-methylenebissydnone **50** and 3-β-cyanoethylsydnone **51** appear at 303 and 292 mμ, respectively, thus suggesting an electronic interaction between the two sydnone rings separated by a methylene group.[40]



50



51

b. Infrared Spectrum. A survey of the infrared spectra of a number of sydnones shows that the ring carbonyl band appears in the range 1730–1830 cm^{-1} (usually 1750–1770 cm^{-1}). Usually, the carbonyl absorption appears as a single peak, but in some cases it is split into a doublet with 20–40 cm^{-1} difference, presumably due to Fermi resonance.[59,60] The carbonyl absorption appears in a range which is generally expected for esters (1735–1750 cm^{-1}) or γ-lactones (around 1770 cm^{-1}) and is unusually high when compared with those of tropones (1638 cm^{-1}), 4-thiapyrones (1574–1609 cm^{-1}), or diazooxide (1562–1642 cm^{-1}). This might be taken as evidence favoring a normal carbonyl group, and may raise doubts as to the mesoionic structure, especially with respect to the importance of resonance contributors such as 7. However, compounds **52** and **53**, which have partial structures analogous to sydnone, have carbonyl absorptions at 1760 and at 1793–1808 cm^{-1}, respectively,[61] and some oxazolones and β,γ-unsaturated lactones show a relatively high-frequency carbonyl absorption band. These facts would suggest that, in the

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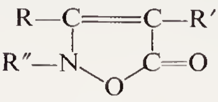
[59] B. E. Zaitsev and Yu. N. Sheinker, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 407 (1962); *Chem. Abstr.* **57**, 6763 (1962).

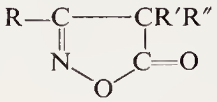
[60] Yu. G. Borod'ko and Ya. K. Syrkin, *Opt. Spektroskopiya* **11**, 482 (1961); *Chem. Abstr.* **56**, 4296 (1962).

[61] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961).

absence of a satisfactory model compound for comparison, it may be misleading to conclude, from the position of the carbonyl infrared band alone, that sydnone has a normal carbonyl group, i.e., that the contribution of structures such as **7** to the whole resonance hybrid of sydnone is negligible.



52



53

The integrated absorption intensity of the infrared carbonyl band of sydnone ($6\text{–}12 \times 10^4$ l/mole-cm^2) is greater than that of other common carbonyl compounds (ketones and aldehydes, 1.5–2.4; esters, 2.5–4.1; amides, 3.7–5.7; butyrolactones, 4.2×10^4). This value is lowered for sydnones with an electron-withdrawing group at the 4-position. This is due to neither the conjugation between the lone electron pair and the carbonyl group nor the strain of the ring. Instead, the electron shift toward the exocyclic oxygen atom in agreement with the calculated charge distribution of sydnone is postulated.[59,62,63]

The infrared spectrum of 4-acetyl-3-ethylsydnone shows the normal carbonyl absorption band observed in sydnones (1740 cm^{-1}) plus a second carbonyl band at 1635 cm^{-1}, obviously connected with the carbonyl group of the acetyl residue.[55,64] The marked displacement of this band in the direction of much lower frequencies compared to the bands of aliphatic and aliphatic–aromatic ketones is a strong indication of the powerful conjugative electron-donating properties of the sydnone system with respect to substituents at the 4-position.

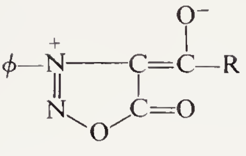
Kishimoto and Ohta[64] have suggested that there is a significant contribution from resonance form **47** (R = Me) to the total structure of 4-acetyl-3-phenylsydnone. A molecular orbital calculation[65] using the ω-Hückel technique for sydnones reveals, however, that the acetyl carbonyl is polarized, though less so than the sydnone exocyclic oxygen. Furthermore, the bond order of the acetyl carbonyl shows somewhat more double bond character than the ring carbonyl. These calculations imply some contribution from the contributing resonance structure **47** in a valence bond representation of the compound, but a relatively larger contribution from structure **48**.

[62] B. E. Zaitsev, Yu. N. Sheinker, Yu. D. Koreshkov, and M. E. Vol'pin, *Fiz. Probl. Spektroskopii, Akad. Nauk SSSR*, 1960 p. 442 (1962); *Chem. Abstr.* **59**, 12303 (1963).

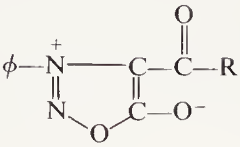
[63] B. E. Zaitsev, Yu. N. Sheinker, and Yu. D. Koreshkov, *Dokl Akad. Nauk SSSR* **136**, 1090 (1961); *Chem. Abstr.* **55**, 19480 (1961).

[64] K. Kishimoto and M. Ohta, *Nippon Kagaku Zasshi* **83**, 833 (1962).

[65] L. B. Kier and E. B. Roche, *J. Pharm. Sci.* **55**, 807 (1966).



47



48

Sydnones unsubstituted at the 4-position show a medium intensity absorption band at 3100–3200 cm^{-1}, arising from the ring C—H stretching frequency.[38,41,56,66–68]

Other assignments have been made for sydnones. These are reproduced in Table II.[69]

TABLE II

ASSIGNMENT OF SYDNONE[a] INFRARED ABSORPTIONS

Assignment	Absorption (cm^{-1})[b]
C=C and C=N skeletal in-plane	1504–1451 (s–m)
N=O stretching	1423–1405 (m–vw)
	1198–1172 (m–w)
C—O stretching	1290–1219 (m–w)
	878–822 (m–w)
N—N stretching	1084–1044 (m)
C—H out-of-plane	945–928 (s–m)
C—H out-of-plane and ring	752–719 (s–m)
C=C and C=N	1590–1532 (w)[c]
	1486–1439 (m)[c]
C—H	1038–1015 (m–vw)

[a] T. S. L. Mao, *Dissertation Abstr.* **25**, 1603 (1964).
[b] s, strong; m, medium; w, weak; vw, very weak.
[c] Tentative assignment.

c. Nuclear Magnetic Resonance Spectrum. The NMR spectra of some representative sydnone derivatives are shown in Table III.[70–72]

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[66] J. Fugger, J. M. Tien, and I. M. Hunsberger, *J. Am. Chem. Soc.* **77**, 1483 (1955).

[67] J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.* **83**, 178 (1961).

[68] V. G. Yashunskii, V. F. Vasil'eva, and Yu. N. Sheinker, *Zh. Obshch. Khim.* **29**, 2712 (1959); *Chem. Abstr.* **54**, 10999 (1960).

[69] T. S. L. Mao, *Dissertation Abstr.* **25**, 1602 (1964).

[70] F. H. C. Stewart, *Chem. Ind.* (*London*) p. 1926 (1963).

[71] K. D. Lawson, W. S. Brey, Jr., and L. B. Kier, *J. Am. Chem. Soc.* **86**, 463 (1964).

[72] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2426 (1962).

TABLE III

NMR of Sydnones

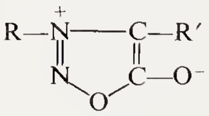
Sydnone	Solvent	$\tau_{syd\ H}$	$\tau_{3\text{-alk H}}$	$\tau_{4\text{-alk H}}$	$\tau_{\text{phenyl H}}$	Reference
3-Methyl	$CDCl_3$	—	5.90	—	—	*a*
3-*n*-Butyl	D_2O	3.66	—	—	—	*b*
3-Benzyl	$CDCl_3$	3.81	4.64	—	2.56	*c*
3-Phenyl	$CDCl_3$	3.22	—	—	2.30	*c*
3-Methyl-4-phenyl	$CDCl_3$	—	5.87	—	2.50	*c*
4-Methyl-3-phenyl	$CDCl_3$	—	—	7.83	2.32	*c*

[a] K. D. Lawson, W. S. Brey, Jr., and L. B. Kier, *J. Am. Chem. Soc.* **86**, 463 (1964).
[b] F. H. C. Stewart, *Chem. Ind.* (*London*) p. 1926 (1963).
[c] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2426 (1962).

The chemical shift of sydnone in chloroform is fairly concentration dependent. This has been interpreted as due to the formation of an aggregate of sydnone molecules which dissociates by hydrogen bond formation with the solvent.[71]

The NMR signals of the methyl groups at the 3- and 4-positions of sydnones appear at positions close to the values (τ 5.81 and 7.40, respectively) based on structure **7**, suggesting that the 3-nitrogen atom has a large share of positive charge. Probably because of this strong charge, no *ortho* deshielding effect is observed with 3-phenylsydnone.[70]

The NMR signal of the sydnone ring proton at the 4-position is reported to appear at a relatively high magnetic field. This was taken by Stewart[70] as evidence in favor of an azomethine imine-like structure **54** rather than the mesoionic structure. He concluded that most of the physical and chemical properties of sydnones can be explained satisfactory in terms of this structure. On the other hand, Daeniker[72] found a value of τ 3.66 for the 4-proton of 3-*n*-butylsydnone, in support of the mesoionic structure of sydnones.



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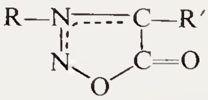

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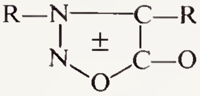
The signals of the α-protons on the substituents of the sydnone ring appear at a very low field. This was interpreted as a result of a deshielding effect by the aromatic ring current along with an electronegative effect of the nitrogen atom.[71]

d. Dipole Moment. The dipole moments of sydnones were studied extensively in an early phase of research on these compounds when their structural details were under heated discussion.[73–79] Values for some representative sydnone derivatives are listed in Table IV.

TABLE IV
DIPOLE MOMENTS OF SYDNONES[a]



R	R′	μ(D)
Ph	H	6.48
p-ClC_6H_4	H	5.01
p-MeC_6H_4	H	6.89
Ph	Br	6.42
Ph	Me	6.56
$PhCH_2$	H	6.27
Ph	Ph	6.61
p-ClC_6H_4	p-ClC_6H_4	5.17
Cyclohexyl	H	6.7

[a] R. W. Hill and L. E. Sutton, *J. Chim. Phys.* **46**, 244 (1949).

A value of 5–6 D was alloted as the dipole moment of the sydnone rings. This value excluded the bicyclic structure **55** originally proposed for sydnones, but at the same time ruled out a fully polarized structure **7** as a possibility. From the dipole moment values of many sydnone derivatives, it was concluded[77] that the R—N-3 bond lies almost in the plane of the five-membered ring and that the R—C-4 bond deviates no more than 10° from it. It was further stated that the magnitude of μ_π is about 4.8 D and its direction is roughly parallel to the N-2—O-1 bond. These results have been considered to agree with the postulate that sydnone has a monocyclic structure with delocalized π bonds.[77] In other words, the dipole moment data can most satisfactorily be explained only by

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[73] J. C. Earl, E. W. Leake, and R. J. W. LeFèvre, *Nature* **160**, 366 (1947).

[74] W. Baker, W. D. Ollis, V. D. Poole, J. A. Barltrop, R. A. W. Hill, and L. E. Sutton, *Nature* **160**, 366 (1947).

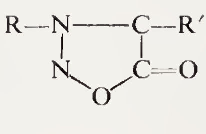
[75] R. A. W. Hill and L. E. Sutton, *J. Chim. Phys.* **46**, 244 (1949).

[76] R. A. W. Hill and L. E. Sutton, *J. Chem. Soc.* p. 746 (1949).

[77] R. A. W. Hill and L. E. Sutton, *J. Chem. Soc.* p. 1482 (1953).

[78] Yu. G. Borod'ko and Ya. K. Syrkin, *Dokl. Akad. Nauk SSSR* **134**, 1127 (1960); *Chem. Abstr.* **55**, 12039 (1961).

[79] J. C. Earl, E. M. W. Leake, and R. J. W. LeFèvre, *J. Chem. Soc.* p. 2269 (1948).



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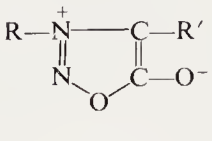

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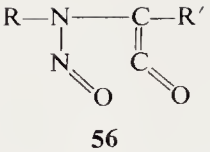

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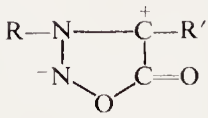

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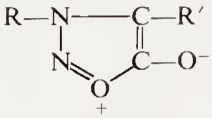

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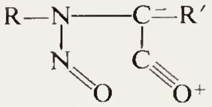
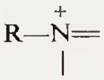


59

regarding sydnone as a resonance hybrid of many canonical forms such as **7** and **56**–**59**. Of these, contribution from structures with



$$\mathrm{R{-}}\underset{|}{\overset{+}{\mathrm{N}}}{=}$$

was considered most important. Where R is an aryl, it also appears to participate in the resonance.

e. X-Ray Analysis. X-Ray analysis of the crystal structure of sydnone was first performed by Schmidt.[80] It was found that the unit cell consists of four or eight molecules of sydnone. More detailed structural analyses of 3-*p*-bromosydnone[81,82] and 4,4′-dichloro-3,3′-ethylenebissydnone[83] were performed, and the structures are reproduced in Fig. 1.

(*a*) (*b*)

Fig. 1. (*a*) Bond distances and (*b*) bond angles in 4,4′-dichloro-3,3-′ethylenebissydnone. [W. E. Thiessen and H. Hope, *J. Am. Chem. Soc.* **89**, 5977 (1967).] Copyright (1967) by the American Chemical Society, and reproduced with their permission.

The sydnone ring including the exocyclic oxygen is planar, but the plane of the *p*-bromophenyl ring is twisted with an angle of 27.6° from the plane of the sydnone ring, in spite of the conclusion drawn from dipole moment studies.

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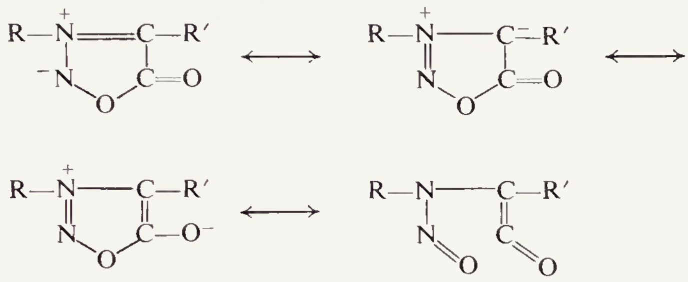
[80] G. M. J. Schmidt, *Bull. Res. Council Israel* **1**, 123 (1951); *Chem. Abstr.* **46**, 2871 (1952).

[81] H. Bärnighausen, F. Jellinek, and A. Vos, *Proc. Chem. Soc.* p. 120 (1961).

[82] H. Bärnighausen, F. Jellinek, J. Munnik, and A. Vos, *Acta Cryst.* **16**, 471 (1963); *Chem. Abstr.* **60**, 8215 (1964).

[83] W. E. Thiessen and H. Hope, *J. Am. Chem. Soc.* **89**, 5977 (1967).

Most remarkably, the bond length of the *exo* carbonyl bond is almost the same as those of normal carbonyl groups, and it casts doubt on the mesoionic structure, especially on the importance of structures such as 7. Furthermore, an unusually long bond length value is obtained for the C—O bond in the ring. This has led to the suggestion[83] that a ketene-like form **56** makes an important contribution to resonance [Eq. (23)]. The striking deformation of bond angles about the carbonyl group supports this view.



(23)

56

The C—Cl bond here is significantly shorter than the ordinary C—Cl bond (1.74 Å). This may represent delocalization of the chlorine lone-pair electrons onto the relatively positive ring nitrogen.

f. Photochromism. Of the many sydnone derivatives so far prepared, 3-(3-pyridyl)sydnone **35** is unique in that although it is colorless in the dark, it exhibits a deep blue color upon irradiation.[44, 84] The color fades slowly at room temperature and rapidly upon applying heat or electromotive force, regenerating the colorless species. This process may be repeated, although some fatigue has been observed. Photochromism is observed only in the solid state. Irradiation at low temperature produces a colorless species which is converted to the blue product on warming.[85]

An electron spin resonance (ESR) study with the colored substance revealed the presence of a radical. No radical, however, could be detected when the sample was irradiated under vacuum until air was admitted.[86] A similar ESR spectrum was observed by irradiation of 3-phenylsydnone.[85] From these results, it was concluded that irradiation of pyridylsydnone gives rise to two products, one colored and the other paramagnetic. The colored sample shows the same infrared spectrum as the colorless sample.[56]

Because the colored solid shows a photoconductivity absent in solution, it was concluded that a charge carrier is present in the colored species. It was

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[84] J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.* **77**, 6604 (1955).

[85] T. Mill, A. van Roggen, and C. F. Wahlig, *J. Chem. Phys.* **35**, 1139 (1961).

[86] H. S. Gutowsky, R. L. Rutledge, and I. M. Hunsberger, *J. Chem. Phys.* **29**, 1183 (1958).

further deduced that the coloration takes place at a crystal-deficient position while oxygen is converted to a lattice anion.[87]

Some sydnone derivatives closely related to 3-(3-pyridyl)sydnone have been prepared (Section II,A,1), but they are not photochromic.[45,67] It was suggested that photochromism is a general property of the mesoionic ring.[56]

g. Complex Formation. A 1:1 complex could be isolated by applying the solid–solid interaction technique to sydnones and metal halides. The complex could be formed with Friedel-Crafts type catalysts such as $TiCl_4$, $SbCl_5$, $SnCl_4$, $FeCl_3$, $ZnCl_2$, $TeCl_2$, and $AlCl_3$, but not from the halides of Cu, Co, and Ni. These complexes dissociate completely in both polar and nonpolar solvents. They are all charge-transfer complexes formed by sharing lone-pair electrons with the metal. It was therefore concluded that the most electronegative position in the sydnone ring is the exocyclic oxygen atom.[69,88,89]

3-Phenylsydnone forms a loose complex with iodine in acetonitrile.[90] Although the complex was not isolated, it was suggested that complex formation occurs at the exocyclic C—O group, since the infrared C—O and N—O bands of 3-phenylsydnone (1756; 843 cm^{-1}) were shifted to 1749 and 854 cm^{-1}, respectively. Based on a relatively large formation constant of the sydnone–iodine complex, a relatively small first ionization potential[90] of sydnone was anticipated.

h. Surface Properties. The monolayer film of 3-hexadecylsydnone is reported to be considerably expanded. Compression of this film begins at 46 $Å^2$/mole and collapses at 28 $Å^2$/mole. It is suggested that lateral cohesion is reduced by electrostatic repulsion between the sydnone nuclei, supporting the highly polar mesoionic structure of sydnones.[91]

i. Electric and Magnetic Properties. It might be expected that sydnones have special electric properties inherent in their special mesoionic structure, but the semiconductivity of sydnone is reported to lie above 50 kcal/mole.[92] Likewise, no anomaly was observed with the molar Kerr constant of sydnones.[93]

The diamagnetic susceptibility of some sydnone derivatives has been measured and an average value of 38.7 obtained. A value of 24.6×10^{-6} was evaluated from contributing ionic forms. Thus, the exaltation of the molar susceptibility of the sydnone ring (14.1) is similar to those of furan (13.4) and

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[87] M. D. Cohen and G. M. J. Schmidt, *J. Phys. Chem.* **66**, 2442 (1962).

[88] P. S. Gentile and T. S. L. Mao, *J. Inorg. Nucl. Chem.* **27**, 867 (1965); *Chem. Abstr.* **62**, 11400 (1965).

[89] T. L. Mao, *U.S. At. Energy Comm.* TID 20068 (1963); *Chem. Abstr.* **62**, 2488 (1965).

[90] H. Yamada and K. Kojima, *J. Am. Chem. Soc.* **82**, 1543 (1960).

[91] F. H. C. Stewart, *Australian J. Chem.* **14**, 654 (1961); *Chem. Abstr.* **57**, 2208 (1962).

[92] D. D. Eley, G. D. Parfitt, M. J. Perry, and G. H. Taysum, *Trans. Faraday Soc.* **49**, 79 (1953).

[93] M. R. Hearne and R. J. W. LeFèvre, *J. Chem. Soc.* p. 4753 (1962).

pyrrole (14.4). Accordingly, it has been stated that the sydnone ring is aromatized to the same extent as furan and pyrrole.[94]

j. Dissociation Constant. The pK_a's of some sydnone-4-carboxylic acids and sydnonylacetic acids are tabulated in Table V. From their correlation with the Taft-Hammett rule, it has been reported that the bulkiness of the 3-substituents engenders a large steric effect and that the 3-phenyl group shows a competitive nonpolar conjugation with the heterocycle and the carbonyl group.[95] 3-Carboxymethylsydnone shows a remarkably high acidity (pK_a 1.7)[96] resembling betaine (pK_a 1.7) and nitroacetic acid (pK_a 1.68). A high positive charge density on N-3 is indicated.

TABLE V

DISSOCIATION CONSTANTS OF CARBOXYL AND CARBOXYMETHYL DERIVATIVES OF SYDNONE[a]

R-3	R-4	pK_a (50% EtOH)
Ph	COOH	2.37
p-$\mathrm{MeC_6H_4}$	COOH	3.71
p-$\mathrm{MeOC_6H_4}$	COOH	3.75
p-$\mathrm{EtOC_6H_4}$	COOH	3.71
p-$\mathrm{ClC_6H_4}$	COOH	3.59
Cyclohexyl	$\mathrm{CH_2COOH}$	4.49
i-Pr	$\mathrm{CH_2COOH}$	4.46
$\mathrm{PhCH_2}$	$\mathrm{CH_2COOH}$	4.47
$\mathrm{PhCH_2CH(CH_3)}$	$\mathrm{CH_2COOH}$	4.32
$\mathrm{CH_2COOH}$	H	1.7[b]

[a] S. A. Zomova and V. G. Yashunskii, *Zh. Organ. Khim.* **2** (10), 1877 (1966).

[b] L. J. Fliedner, Ph.D. Dissertation, University of Massachusetts (1964).

k. Theoretical Treatment. A number of theoretical treatments based on MO theory have found application to sydnones.[97–100] However, only recent calculations by Kier *et al.* using ω-HMO[65] and EHT–MO[101] methods are reproduced in Fig. 2.

[94] Y. Matsunaga, *Bull. Chem. Soc. Japan* **30**, 227 (1957).

[95] S. A. Zotova and V. G. Yashunskii, *Zh. Organ. Khim.* **2** (10), 1877 (1966).

[96] L. J. Fliedner, Ph.D. Dissertation, Univ. of Massachusetts (1964).

[97] L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

[98] L. Paoloni, *Gazz. Chim. Ital.* **96**, 83 (1966); *Chem. Abstr.* **64**, 14981 (1966).

[99] D. A. Bochvar and A. A. Bagatur'yants, *Zh. Fiz. Khim.* **39**, 1631 (1965); *Chem. Abstr.* **64**, 3328 (1966).

[100] H. C. Longuet-Higgins, *J. Chim. Phys.* **46**, 244 (1949).

[101] L. B. Kier, *Tetrahedron Letters*, p. 1233 (1967).

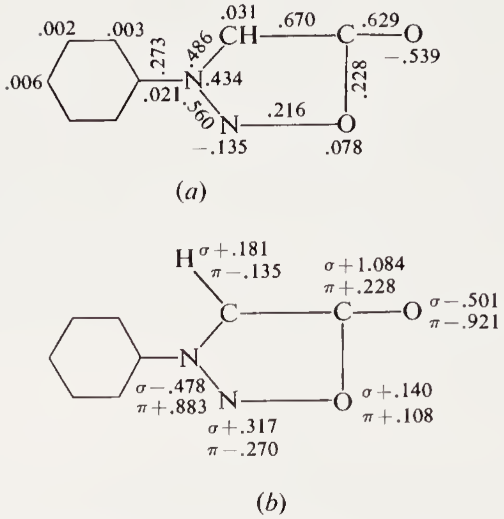

FIG. 2. Molecular orbital calculations on 3-phenylsydnone by (*a*) ω-HMO and (*b*) EHT–MO methods. [L. B. Kier, *J. Pharm. Sci.* **55**, 807 (1966); *Tetrahedron Letters* p. 1233 (1967).]

The dipole moments of 3-phenyl- and 3-methylsydnone calculated from the molecular diagram (6.47 and 7.06 D, respectively) agree nicely with the experimental values, and an excellent correlation was obtained between calculated energy levels and ultraviolet maxima.[65] The energy of 3-phenylsydnone calculated by EHT–MO method gave an energy minimum corresponding to a dihedral angle of 27°, in excellent agreement with the result obtained from the X-ray analysis of 3-(*p*-bromophenyl)sydnone.[101]

The molecular diagram shows a high charge density at the *exo* oxygen atom (0.15 V higher than butyrolactone). A high positive charge density at the N-3 atom and a high bond order for the C-4—C-5 bond lend support to an important contribution from structure **7** to resonance in the sydnone ring.[65]

l. Polarography. The polarography of sydnones has been studied in detail by Zuman. Sydnones are reduced by a four-electron process in alkaline solution ($\mathrm{pH} > 7.5$) to give hydrazinoacetic acid, and are reduced by a six-electron process in acid solution ($\mathrm{pH} < 6$) to give aminoacetic acid derivatives [Eq. (24)]. The transformations correspond to the reduction of unprotonated **3** and protonated (**60**) sydnone, respectively. A value of 0.17 has been obtained for ρ_π in the modified Hammett equation for this reduction process, and it was deduced that sydnone is an aromatic compound with mobile π electrons.

The half-wave reduction potentials of 3- and 4-mono-, and 3,4-disubstituted sydnones obey the modified Hammett equation $\Delta E_{1/2} = \rho_\pi R\sigma_X$. The fact that such a polar effect is observed for the N—O bond β to the phenyl group, may be taken as additional evidence supporting the aromatic nature of the sydnone ring.[102]

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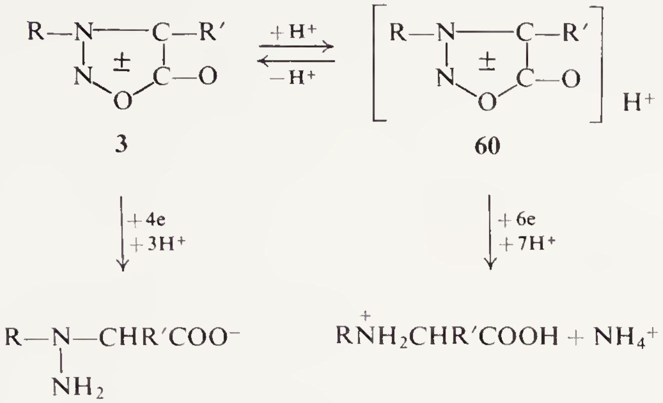
[102] P. Zuman, *Collection Czech. Chem. Commun.* **25**, 3265 (1960).



(24)

It has been suggested that the position most vulnerable to electron attack is the N—O bond. Support for a polar exocyclic carbonyl bond could not be obtained from polarographic studies, casting doubt on structure **4** as the best representation of sydnones.[103,104]

Polymethylenebissydnone is reduced in two successive stages by four-electron waves in alkaline solution, while the protonated form in acidic solution is reduced by a single 12-electron wave. This result suggests an interaction under acidic conditions between the two sydnone nuclei structurally isolated by methylene groups.[105]

The same reduction mechanism seems to be applicable to 4-chloro- and 4-methylsydnones, but with 4-bromo derivatives it was found that reduction of the 4-bromo group proceeds with reduction of the sydnone ring.[105]

A result almost parallel to those obtained from ultraviolet studies was derived by polarographic study of the steric effect of the *ortho*-substituted phenylsydnones. No steric hindrance, however, could be detected with 4-methyl-3-phenylsydnone by polarography.[58]

m. Sydnone Ring as a Substituent Group. A Hammett substituent constant σ^* of 0.710 has been calculated from the kinetic measurement of the displacement reaction of 3-(4-chloro-3-nitrophenyl)sydnone and methyl mercaptide.[106] This value is close to the σ^* for *p*-β-azoxyphenyl group, $Ph—N^+(—O^-)=N—R$, (0.769) which resembles the sydnone system. It was therefore concluded that the sydnone group is similar to, but slightly less activating than the β-azoxyphenyl group, while it does not resemble the *p*-α-azoxyphenyl (σ^* 0.595) and *p*-azido (σ^* 0.083) groups. This view may be supported by the low reactivity of the phenyl ring of 3-phenylsydnone toward S_E reactions.

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[103] P. Zuman, *Z. Phys. Chem.* p. 243 (1958).

[104] P. Zuman, *Collection Czech. Chem. Commun.* **25**, 3245 (1960).

[105] P. Zuman, *Collection Czech. Chem. Commun.* **25**, 3252 (1960).

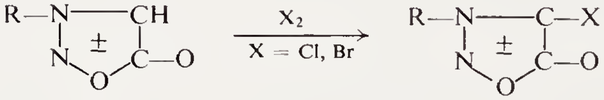
[106] C. Tin-Lok, J. Miller, and F. Stansfield, *J. Chem. Soc.* p. 1213 (1964).

It was further stated that a positive charge is substantially localized on the N-3 atom, and that sydnone may have a relatively small delocalization energy. Consequently, sydnone probably does not exist as indicated by the tropone-like structure **4**.[106]

3. Chemical Properties

That sydnone is aromatic in nature has been supported by a number of physical studies. Much work has been directed toward elucidating how this aromaticity is reflected by the chemical properties of sydnone. A characteristic property of an aromatic ring is its ability to undergo electrophilic substitution reactions with the retention of the ring. Indeed, sydnones unsubstituted at the 4-position display electrophilic substitution reactions such as halogenation, nitration, sulfonation, acylation, and metallation at this position. Although the sydnone ring exhibits aromaticity, it is relatively readily cleaved by acids or alkali and is subject to 1,3-dipolar addition reactions due, undoubtedly, to its polar nature. These facts suggest that the degree of aromaticity of the sydnone ring is about the same order as that of the furan ring.

a. Halogenation. Sydnones unsubstituted at the 4-position (**61**) are halogenated at this position to give 4-halogenosydnones, **62** [Eq. (25)]. Because



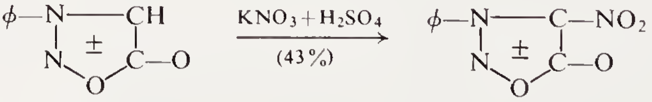
61 **62**

(25)

sydnones are fairly sensitive toward acids, it is advantageous to carry out the halogenation at low temperature or in the presence of a neutralizing agent, such as sodium hydrogen carbonate or calcium carbonate. The sydnone ring cannot be iodinated directly, but 4-iodo derivatives can be prepared indirectly via 4-chloromercuri or Grignard derivatives (Section II,A,3,*f*).

The halogenation reagents, reaction conditions, yields, and references for representative sydnones are shown in Table VI.

b. Nitration. Nitration of sydnones has been reported only for 3-phenylsydnone (**21**). 4-Nitro-3-phenylsydnones (**63**) is formed by reacting a mixture

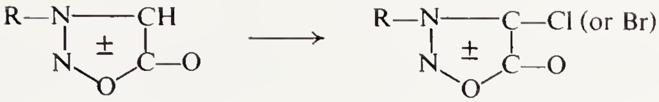


21 **63**

(26)

TABLE VI

HALOGENATION OF SYDNONES



Chlorination			
R	Reagent and conditions	Yield (%)	Reference
Ph	Cl_2, Ac_2O, 0°C	75	*a*
Ph	Cl_2, aq. HCl	50	*b*
Ph	$KClO_3$, aq. HCl	73	*b*
p-ClC_6H_4	Cl_2, Ac_2O, 0°C	51	*a*

Bromination			
R	Reagent and conditions	Yield (%)	Reference
Ph	Br_2, Ac_2O, 0°C	81	*c*, *d*, *e*
Ph	Br_2, Et_2O, H_2O, $NaHCO_3$	78	*d*
Ph	Br_2, EtOH, $NaHCO_3$	80	*f*
Ph	Br_2, KBr	78	*d*
Ph	$KBrO_3$, HBr	—	*b*
Ph	NBS, $CHCl_3$	78	*d*
Me_2CH	Br_2, AcOH, AcONa	70	*g*
p-$MeOC_6H_4$	Br_2, Ac_2O	95	*e*

[a] W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.* p. 1542 (1950).
[b] J. C. Earl, *Rec. Trav. Chim.* **75**, 1080 (1956).
[c] W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.* p. 307 (1949).
[d] H. Kato, K. Nakahara, and M. Ohta, *Nippon Kagaku Zasshi* **77**, 1304 (1956).
[e] G. S. Puranik and H. Suschitzky, *J. Chem. Soc.* (*C*) p. 1006 (1967).
[f] C. V. Greco, M. Pesce, and J. M. Franco, *J. Heterocylic Chem.* **3**, 391 (1966).
[g] L. B. Kier, D. Dhawan, and M. J. Fregly, *J. Pharm. Sci.* **53**, 677.

of nitric and sulfuric acid or potassium nitrate in concentrated sulfuric acid with 3-phenylsydnone [Eq. (26)].[14,107] Daeniker[41] reported that bissydnones **64** ($n = 2, 4, 6$) could not be nitrated.

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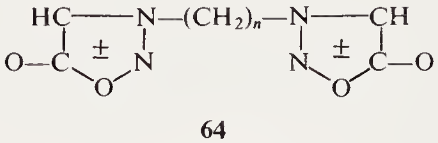
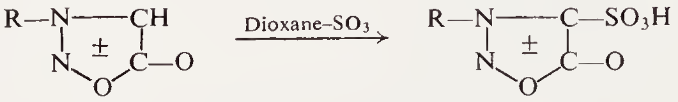
[107] M. Hashimoto and M. Ohta, *Nippon Kagaku Zasshi* **78**, 181 (1957).



64

c. Sulfonation. Direct sulfonation of several 3-substituted sydnones has been reported by Russian workers.[68,108] The sulfonation was carried out by treating sydnone **61** with the dioxane–sulfur trioxide complex in dichloroethane solution at 20–40°C [Eq. (27)]. The 3-substituted sydnone-4-sulfonic acids **65** thus formed were identified as barium salts or *S*-benzylthiuronium salts. Attempts to isolate the free acids **65** by neutralization of the barium salts were unsuccessful, since the sulfonic acid group splits off with the reformation of sydnone **61**.

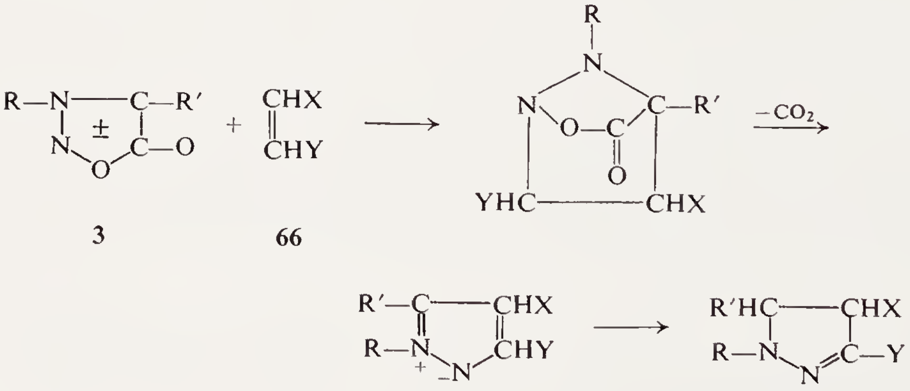


61 **65**

(27)

R = ϕ, p-MeOC$_6$H$_4$, p-EtOC$_6$H$_4$, m-ClC$_6$H$_4$, Et

d. Addition–Elimination Reaction. A novel reaction of sydnones, which was reported independently by Vasil'eva *et al.*[7] and Huisgen and Grashey,[6] is the 1,3-dipolar addition of a variety of unsaturated compounds to sydnones, accompanied by the loss of carbon dioxide. The reaction is usually carried out by heating the components in a suitable solvent and proceeds through addition to the 2- and 4-positions on the ring. This is followed by loss of carbon dioxide, yielding heterocyclic compounds. As an example, reacting olefinic compounds **66** with sydnones **3** affords pyrazoline derivatives **67**, which may be expressed by Eq. (28).



3 **66**

67

(28)

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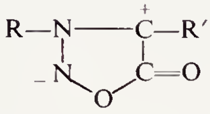
[108] V. F. Vasil'eva and V. G. Yashunskii, *Khim. Nauk Prom.* 3, 282 (1958); *Chem. Abstr.* 52, 20013 (1958).

Because sydnone may formally be regarded as an aromatic azomethine imine **57** (although the degree of contribution of canonical form **57** to the whole resonance of sydnone may be small), and because the addition–elimination reaction usually proceeds at a lower temperature than the decomposition temperature of sydnones, Huisgen regarded the first step of this reaction as analogous to 1,3-dipolar cycloaddition with linear azomethine imine system **68**.



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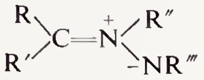
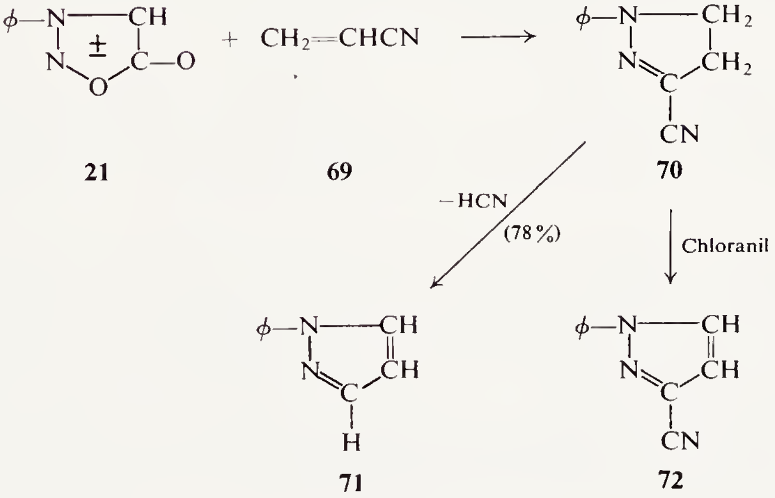


68

In the reactions with olefinic compounds, the initial reaction products are 2-pyrazolines **67** which, depending on the reaction conditions, may convert to fully aromatic stable pyrazoles by further elimination. For example, when 3-phenylsydnone **21** is heated for 6 hours with acrylonitrile **69** in dioxane,



(29)

cyanopyrazoline (**70**) is not isolated, but 1-phenylpyrazole **71** is formed, presumably, by eliminating HCN from (**70**) [Eq. (29)].[7,109,110] In the presence of chloranil, however, 1-phenyl-3-cyanopyrazole **72** is obtained in 84% yield.[111]

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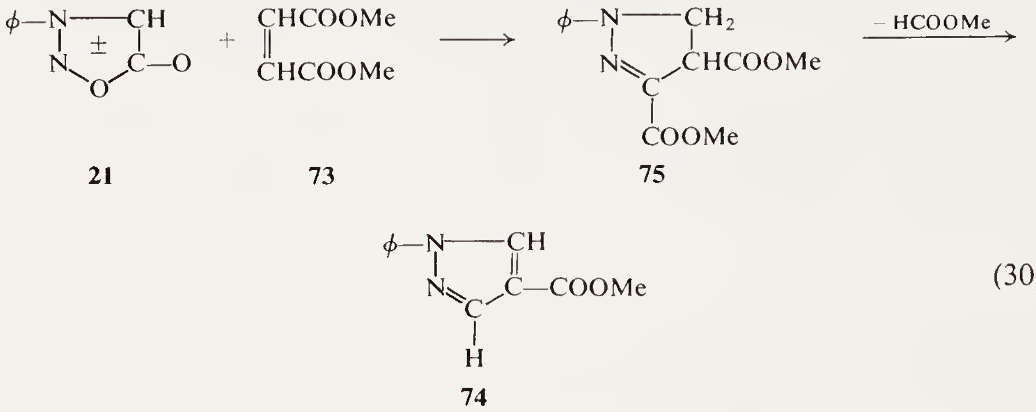
[109] V. F. Vasil'eva, V. G. Yashunskii, and M. N. Shchukina, *Zh. Obshch. Khim.* **31**, 1501 (1961); *Chem. Abstr.* **55**, 22291 (1961).

[110] V. F. Vasil'eva, V. G. Yashunskii, and M. N. Shchukina, *Zh. Obshch. Khim.* **33**, 3706 (1963); *Chem. Abstr.* **60**, 8017 (1964).

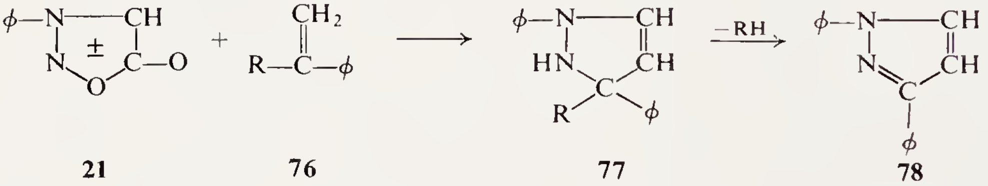
[111] R. Huisgen, H. Gotthardt, and R. Grashey, *Angew. Chem.* **74**, 30 (1962).

When 3-phenylsydnone **21** and dimethyl fumarate **73** are heated at 110°C for 50 hours, pyrazolecarboxylate **74** is isolated. Compound **74** is formed by eliminating methyl formate from the intermediate pyrazoline **75** [Eq. (30)].[111,112]



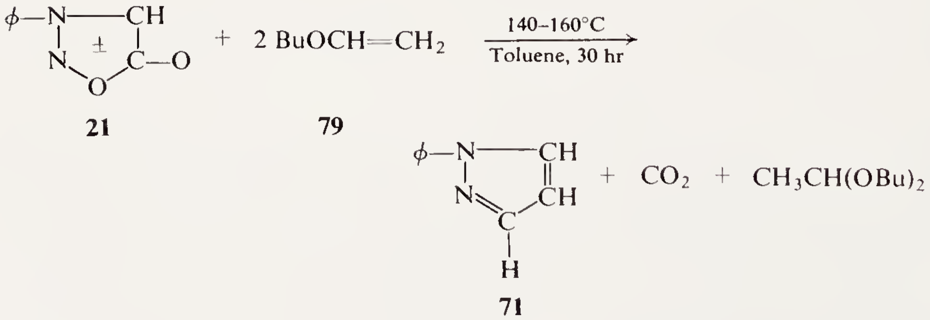
(30)

In the reaction of 3-phenylsydnone **21** and α-methylstyrene or 1,1-diphenylethylene **76**, the intermediate pyrazolines **77** aromatize by eliminating methane or benzene to give diphenylpyrazole **78** [Eq. (31)].[11]



(31)

Similarly, reacting **21** and butylvinyl ether **79** gives an aromatized pyrazole **71** by elimination of butanol as an acetal [Eq. (32)].[113]



(32)

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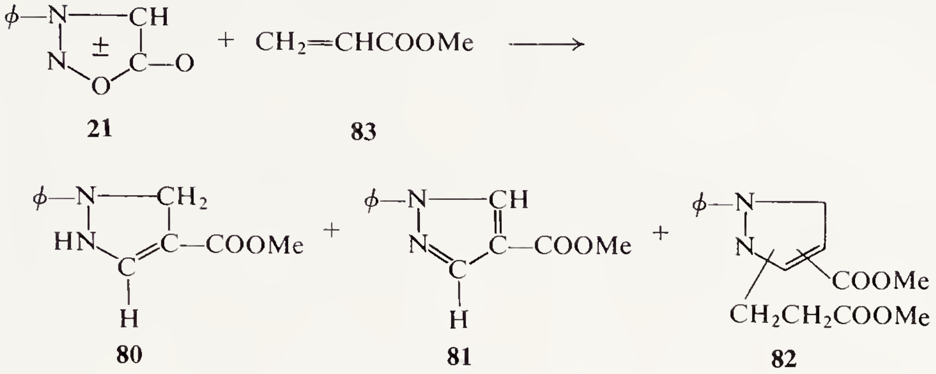
[112] A. Ya. Lazaris, *Zh. Organ. Khim.* **2**, 1719 (1966).

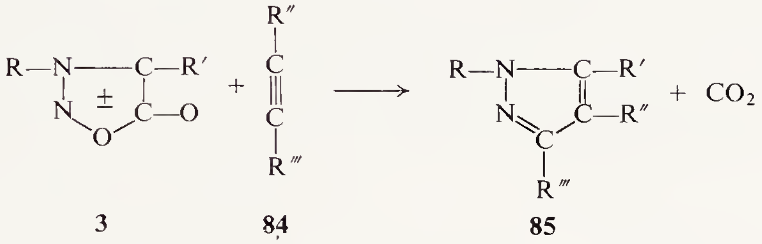
[113] V. F. Vasil'eva and V. G. Yashunskii, *Zh. Obshch. Khim.* **34**, 2059 (1964); *Chem. Abstr.* **61**, 8299 (1964).

A mixture of products **80**–**82** is formed by heating 3-phenylsydnone **21** with methylacrylate **83** in dioxane for 15 hours [Eq. (33)].[114,115]



(33)

The addition of acetylenic compounds **84** proceeds more readily than that of alkenes, giving pyrazole derivatives **85** in good yields [Eq. (34)].[6,116]



(34)

The degree of reactivity of acetylenic compounds **84** depends on the polarity of the substituents. The following order of increasing reactivity has been observed[6]:

$$HC\equiv CH < Alk{-}C\equiv CH < PhC\equiv CPh < PhC\equiv CH < HC\equiv CCH(OAc)_2 < HC\equiv CCH_2OH < PhC\equiv CCOOR < PhC\equiv CCOR < HC\equiv CCOOR < ROOCC\equiv CCOOR$$

In the reaction with monosubstituted acetylenes, sydnones form predominantly 3-substituted pyrazoles.

Such an addition–elimination reaction was originally observed with quinones.[117,118] For example, when 3-phenylsydnone **21** and *p*-benzoquinone are heated in tetrahydrofuran, a compound believed to be **86** is formed. Reaction of a variety of sydnones with toluquinone or 1,4-naphthoquinone has been reported.

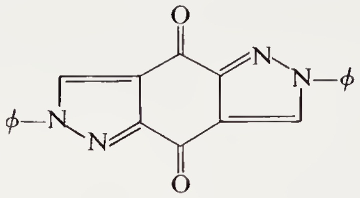
[114] V. F. Vasil'eva, V. G. Yashunskii, and M. N. Shchukina, *Zh. Obshch. Khim.* **32**, 1446 (1962); *Chem. Abstr.* **58**, 9052 (1963).

[115] V. F. Vasil'eva and V. G. Yashunskii, *Zh. Obshch. Khim.* **32**, 2888 (1962); *Chem. Abstr.* **58**, 9053 (1963).

[116] A. Alemagna and M. Barbetta, *Chim. Ind. (Milan)* **46**, 1189 (1964); *Chem. Abstr.* **62**, 13137 (1965).

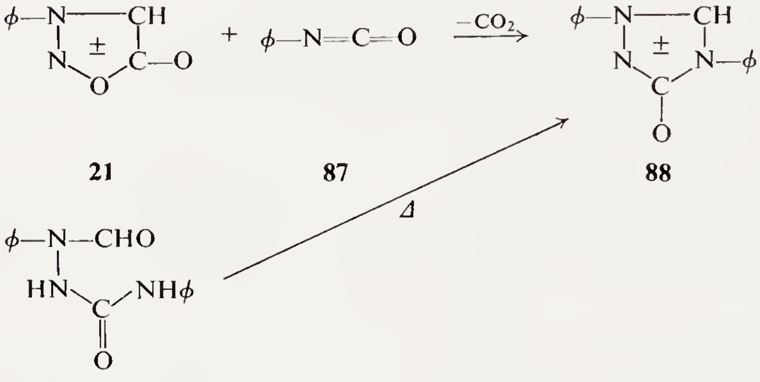
[117] D. L. Hammick and D. J. Voaden, *J. Chem. Soc.* p. 5871 (1965); *Chem. Ind. (London)* p. 739 (1956).

[118] H. Brockmann and T. Reschke, *Tetrahedron Letters* p. 4593 (1965).



86

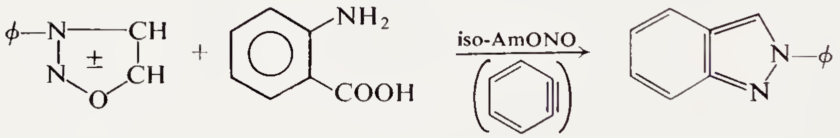
1,3-Dipolar addition of 3-phenylsydnone **21** and phenyl isocyanate **87** affords the mesoionic 1,2,4-triazole derivative **88** which is identical to the product obtained by heating *N*-formyl-1,4-diphenylsemicarbazide **89** [Eq. (35)].[27]



21 **87** **88** **89** (35)

Phenyl isothiocyanate and carbon disulfide, however, do not react with 3-phenylsydnone.

It has been reported that benzyne (dehydrobenzene) (**90**) also reacts with 3-phenylsydnone **21** in a 1,3-dipolar fashion to form 2-phenylindazole **91** [Eq. (36)].[119]



21 **90** **91** (36)

Benzaldehyde reacts with 3-phenyl-4-methylsydnone **92** to give benzal-(α-acetyl)phenylhydrazine (**93**).[120] This reaction is considered to proceed by an initial 1,3-dipolar addition of the carbonyl group, followed by decarboxylation and ring cleavage by an electron shift, as shown in Eq. (37).[120]

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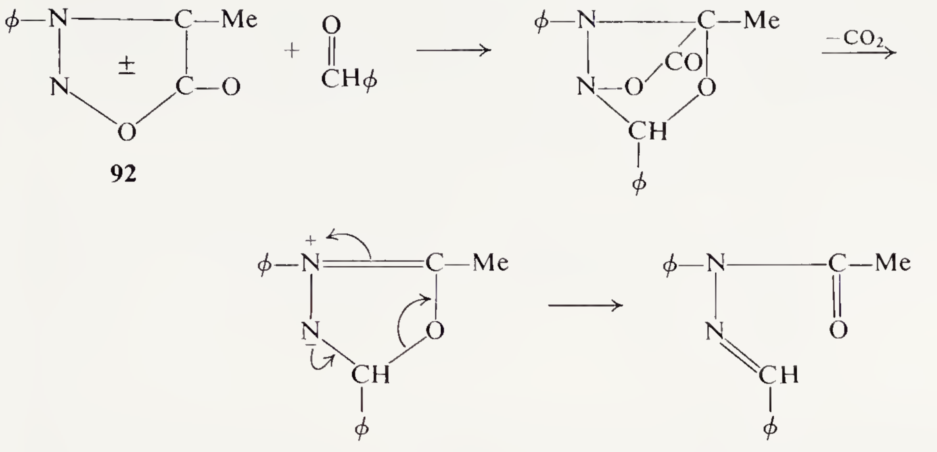
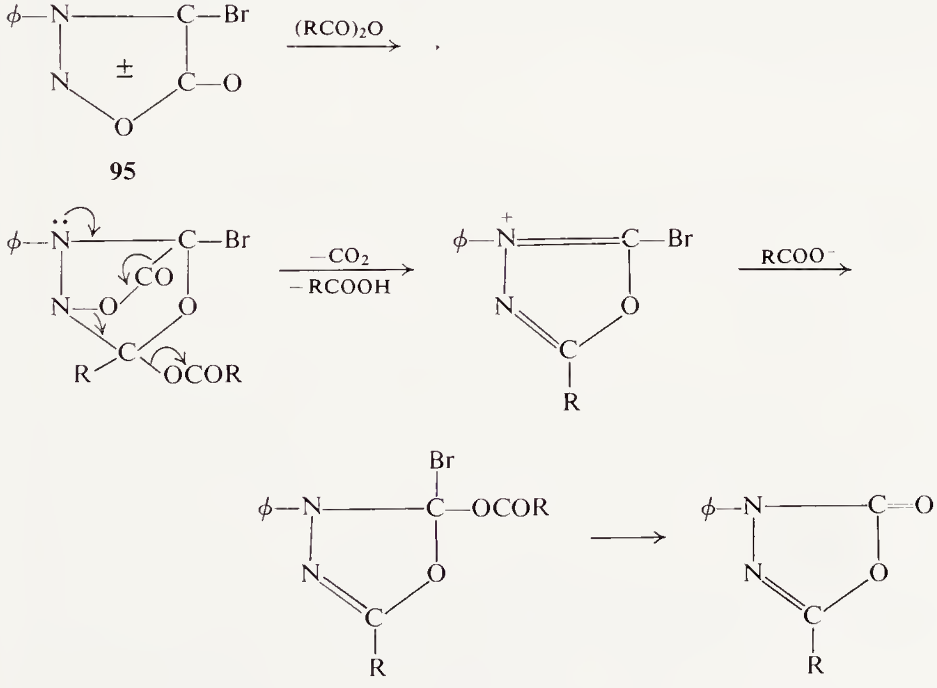
[119] A. Ya. Lazaris, *Zh. Organ. Khim.* **2**, 1322 (1966); *Chem. Abstr.* **66**, 65426 (1967).

[120] R. Huisgen, *Angew. Chem.* **75**, 604 (1963).



(37)

In the bromination of 3-phenylsydnone **21** in acetic anhydride, Baker *et al.*[3] observed a violet by-product, while Kato *et al.*[121] witnessed formation of a compound melting at 95°C, later identified by Stansfield[122] as 2-methyl-4-phenyl-1,3,4-oxadiazolin-5-one **94**. The mechanism of this reaction has been explained by Stewart[9] in terms of a 1,3-dipolar addition of an acid anhydride to the intermediate product, 3-phenyl-4-bromosydnone **95** as shown in Eq. (38).



(38)

94

R = Me, Et, *n*-Propyl

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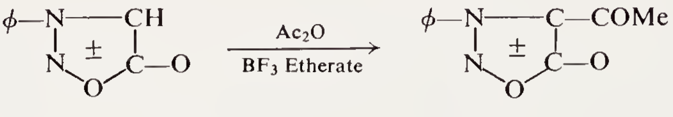
[121] H. Kato, K. Nakahara, and M. Ohta, *Nippon Kagaku Zasshi* 77, 1304 (1956).

[122] F. Stansfield, *J. Chem. Soc.* p. 4781 (1958).

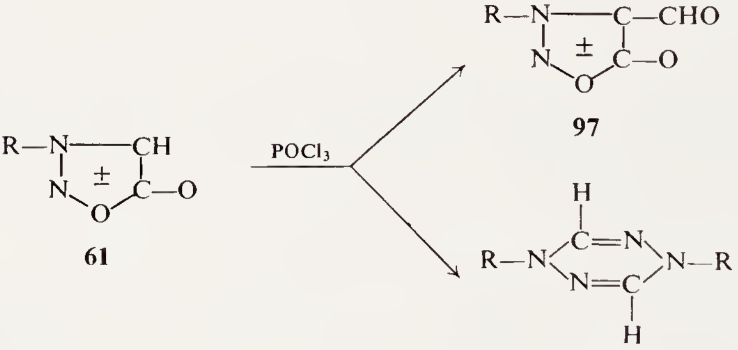
e. Acylation. 3-Phenylsydnone **21** is not acylated by the action of acetic anhydride or benzoyl chloride in the presence of $AlCl_3$, $ZnCl_2$, $SnCl_4$, or H_3PO_4, while 4-acetyl-3-phenylsydnone **96** is obtained [Eq. (39)],[123] with acetic anhydride and boron trifluoride etherate.



21 **96**

(39)

The acetylation of 3-ethylsydnone likewise proceeds with great ease under these conditions.[123] Acylation of 3-phenylsydnone is also effected by heating with a carboxylic acid and phosphorus pentoxide in benzene.[55] With a higher member aliphatic carboxylic acid, such as pivalic acid and decanoic acid, or with benzoic acid, however, this procedure is ineffective. Direct formylation of 3-phenylsydnone and 3-benzylsydnone by the Vilsmeier reaction gives the corresponding 4-formyl derivatives **97**.[124] When the reaction is carried out in *o*-dichlorobenzene, 3-arylsydnones with an electron-donating group in the benzene ring gives the corresponding 4-aldehydes **97**, but 3-(*p*-chlorophenyl)- and 3-(*p*-nitrophenyl)sydnone give tetrazine derivatives **98**, as shown in Eq. (40).[125a]



61 **97** **98**

(40)

A compound of the same type (**98**) (R = Ph) was formed by heating 3-phenylsydnone **21** with phosphorus pentasulfide in toluene.[125b]

f. Metallation. The hydrogen atom at the 4-position of 3-phenylsydnone **21** is acidic enough to be lithiated by *n*-butyllithium, affording 4-lithium-3-

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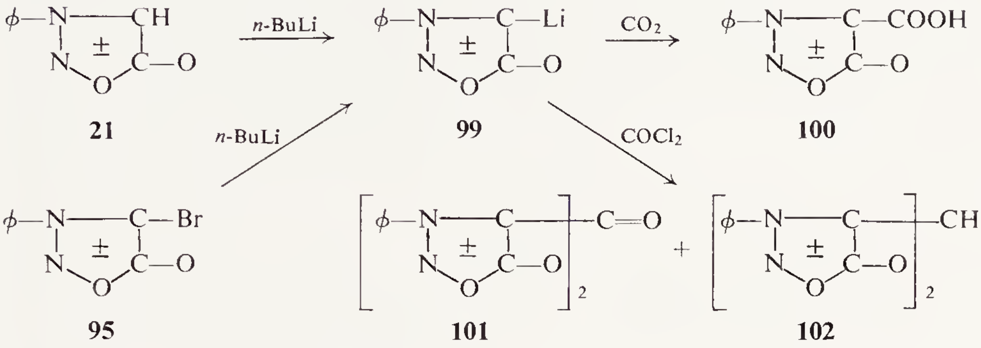
[123] V. G. Yashunskii and V. F. Vasil'eva, *Dokl. Akad. Nauk SSSR* **130**, 350 (1960).

[124] C. J. Thoman, D. J. Voaden, and I. M. Hunsberger, *J. Org. Chem.* **29**, 2044 (1964).

[125a] F. Dallacker and J. Kern, *Ber.* **99**, 3830 (1966).

[125b] W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.* p. 3389 (1950).

phenylsydnone (**99**). This substance was identified by converting it to 3-phenylsydnone-4-carboxylic acid (**100**) by carboxylation with carbon dioxide, as shown in Eq. (41).[126]



(41)

Alternatively, the lithium compound **99** can be prepared by halogen–metal interchange of 4-bromo-3-phenylsydnone, **95**, with *n*-butyllithium.[127] A variety of sydnone-4-carboxylic acids have been prepared from the 4-lithium derivatives by carboxylation.[128a] Reacting lithiumsydnone **99** and phosgene is reported to give bissydnonyl ketone **101** and bissydnonylcarbinol **102** [Eq. (41)].[128b-d]

Baker *et al.*[14] reported that 4-bromo-3-phenylsydnone (**95**) could not be converted to the corresponding Grignard with magnesium and that it was unaffected by refluxing with sodium or dioxane. In contrast, Ohta and Kato[129] found that 4-bromo- or 4-iodo-, but not 4-chloro-3-phenylsydnone, react with metallic magnesium in ether in the presence of methyl iodide to form the corresponding Grignard reagent **103**.

The Grignard **103** is also prepared by heating 4-bromo-3-phenylsydnone **95** with methylmagnesium iodide in ether.[130] The sydnone Grignard thus formed reacts normally with a variety of reagents to give the correspondingly substituted sydnones as exemplified in Eq. (42).[129,130] An exception was found with carbon dioxide, which failed to give sydnone-4-carboxylic acid **100**.

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[126] C. V. Greco, M. Pesce, and J. M. Franco, *J. Heterocyclic Chem.* **3**, 391 (1966).

[127] H. Kato and M. Ohta, *Bull. Chem. Soc. Japan* **32**, 282 (1959).

[128a] S. A. Zotova and V. G. Yashunskii, *Zh. Organ. Khim.* **1**, 2218 (1965).

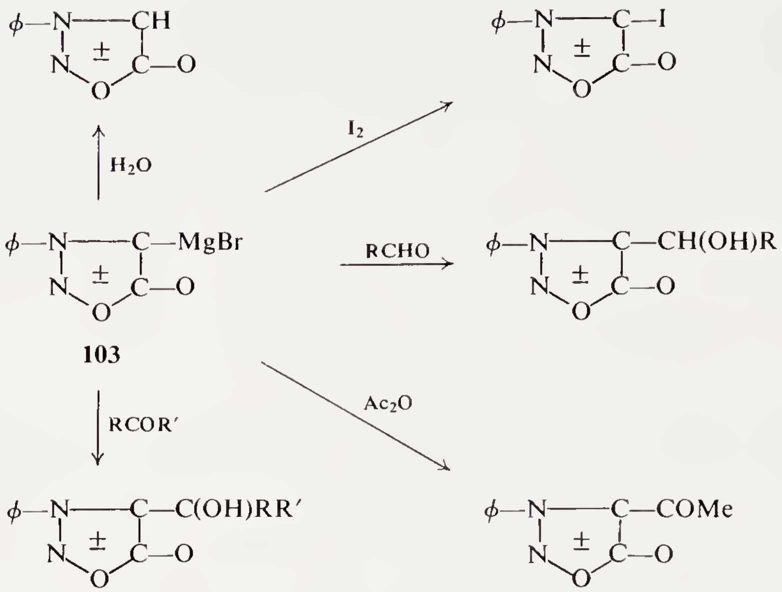
[128b] N. Suciu and Gh. Mihai, *Tetrahedron* **21**, 1369 (1965).

[128c] N. Suciu and Gh. Mihai, *Tetrahedron* **24**, 33 (1968).

[128d] N. Suciu and Gh. Mihai, *Tetrahedron* **24**, 37 (1968).

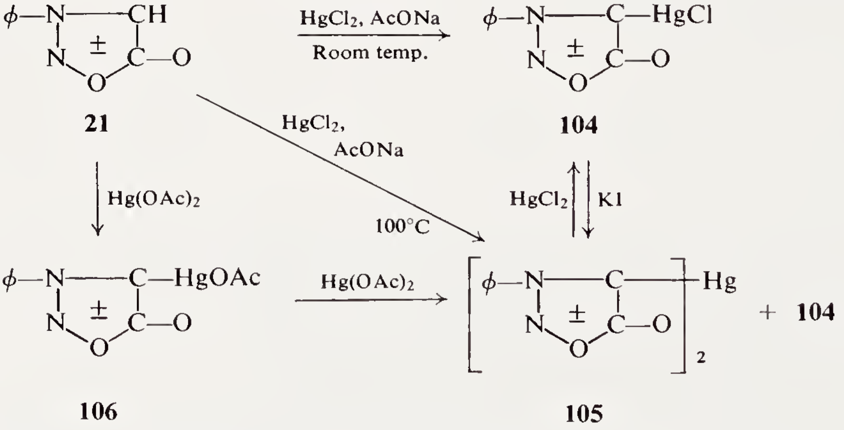
[129] M. Ohta and H. Kato, *Nippon Kagaku Zasshi* **78**, 1653 (1957).

[130] C. H. Wang, *Bull. Inst. Chem. Acad. Sinica* p. 46 (1966); *Chem. Abstr.* **66**, 94964 (1967).



(42)

One of the substitution reactions supporting the aromaticity of sydnone is mercuration. As pointed out by Hunsberger, sydnone shows a reactivity comparable to that of thiophene or furan. Thus, 4-chloromercuri-3-phenylsydnone **104** is formed by treating 3-phenylsydnone **21** with mercuric chloride and sodium acetate in aqueous methanol at room temperature.[131] When this reaction is carried out under reflux, bis(3-phenyl-4-sydnonyl)mercury, **105**, is formed along with **104**.[68] When **21** is mercurated with mercuric acetate in methanol[131] or acetone,[68] 4-acetoxymercuri-3-phenylsydnone **106** is obtained. Compound **104** is converted to bissydnonylmercury **105** by treatment with potassium iodide, which regenerates **104** with mercuric chloride, and is converted to **106** by treatment with mercuric acetate, as shown in Eq. (43).



(43)

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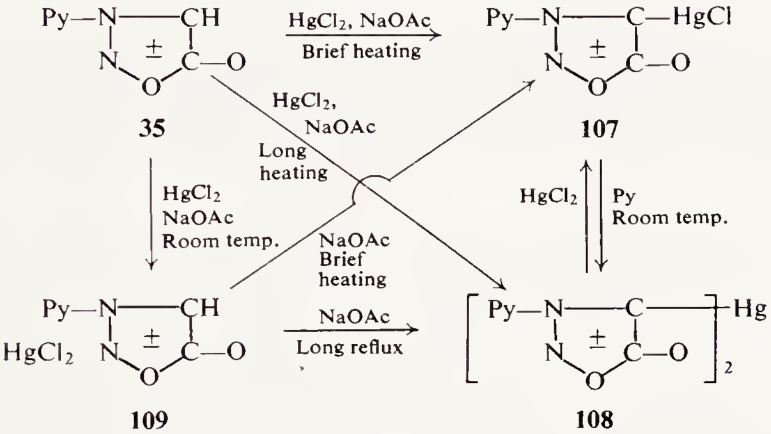
[131] K. Nakahara and M. Ohta, *Nippon Kagaku Zasshi* 77, 1306 (1956).

Treating **104** with potassium bromide and bromine or with iodine gives the corresponding 4-bromo- or 4-iodosydnone.[131]

Hunsberger and his co-workers[67] tried a similar mercuration with photochromic 3-(3-pyridyl)sydnone **35** and found that **35** is converted to the 4-chloromercuri derivative **107** by heating briefly with mercuric chloride and sodium acetate. It converts to the bissydnonyl derivative **108** on longer heating, while an adduct, presumably **109**, forms at room temperature. The latter, when heated with sodium acetate, converts to either **107** or **108** depending on the duration of heating [Eq. (44)].

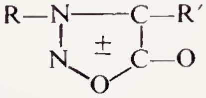


(44)

Py = 3-pyridyl

g. Deuteration. It has been found that 3-phenylsydnone **21** undergoes acid-catalyzed deuteration at the 4-position by deuterium oxide.[123]

h. Hydrolysis. Although 3-phenylsydnone **21** is recovered with only slight decomposition when heated with 0.1 *N* hydrochloric acid, it is hydrolyzed with more concentrated hydrochloric acid to give phenylhydrazine, formic acid, and carbon dioxide. Sydnones **3** in general are similarly hydrolyzed to give substituted hydrazines, carboxylic acids, and carbon dioxide as shown in Eq. (45) when heated with fairly concentrated hydrochloric acid.[2,16,132] This reaction has been recommended and used as a method of preparation of substituted hydrazines which are accessible only with difficulty by other means.



3

$$\xrightarrow{HCl} RNHNH_2HCl + RCOOH + CO_2 \qquad (45)$$

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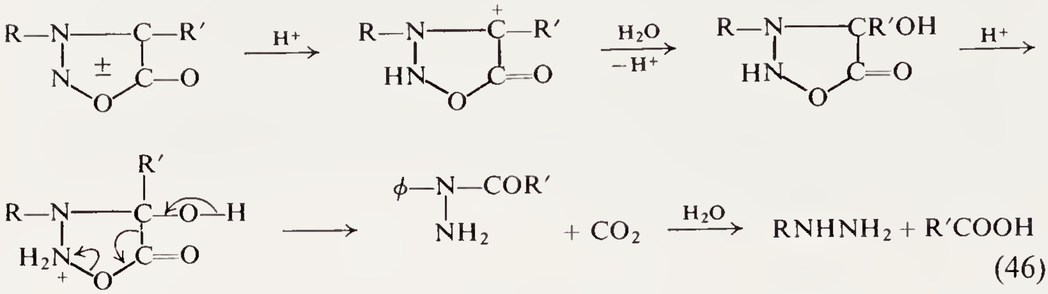
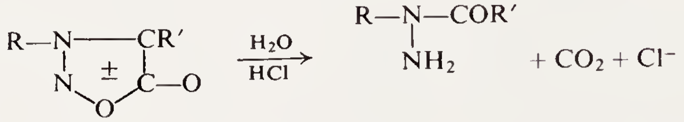
[132] J. C. Earl, *Rec. Trav. Chim.* 75, 1080 (1956).

A probable mechanism of the acid hydrolysis of **3** has been suggested by Baker and Ollis[8] as shown in Eq. (46).



(46)

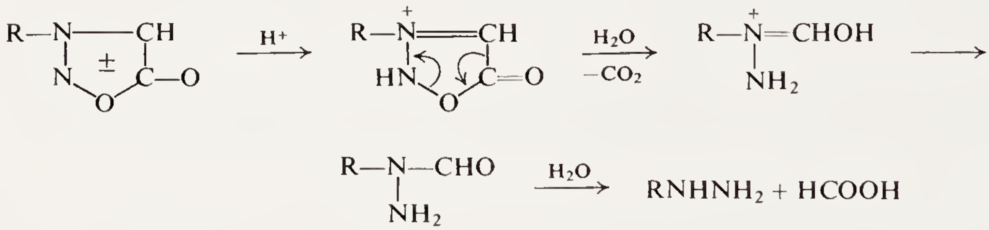
The evidence cited by Baker *et al.* in support of this mechanism is Kenner and Mackay's[133] claim that α-acylhydrazine **110** was obtained quantitatively when sydnone **3** was hydrolyzed in benzene with an equimolar quantity of water and ethereal hydrogen chloride [Eq. (47)]. However, the experimental details of this reaction have not been reported, and Hunsberger[134] and Hashimoto[135] failed to isolate acylhydrazines by this method.



3 **110**

(47)

In order to ascertain the possibility of N-3–N-2 aryl migration during the course of acid hydrolysis of sydnone as suggested by Sugerman,[136] Staley and Clarke[137] carried out the hydrolysis of 3-phenylsydnone-2-^{15}N. They observed that the aniline obtained by reducing the resulting phenylhydrazine contains only the natural abundance of ^{15}N, thus supporting the mechanism proposed by Baker and Ollis. Kier considered a similar mechanism, shown in Eq. (48).[12]



(48)

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[133] J. Kenner and K. Mackay, *Nature* **160**, 465 (1947).

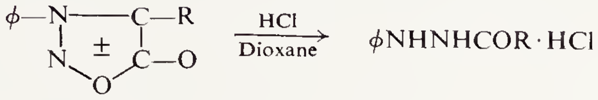
[134] I. M. Hunsberger, private communication (1962).

[135] Mutsuko Hashimoto, unpublished work (1960).

[136] G. Sugerman, Ph.D. Thesis, Chemistry Department, Fordham University, 1962.

[137] J. Staley and D. D. Clarke, *J. Org. Chem.* **29**, 2483 (1964).

β-Acylhydrazine salts **111** have been isolated by treating 3,4-disubstituted sydnones **112** with hydrogen chloride in dioxane, as shown in Eq. (49).[138]

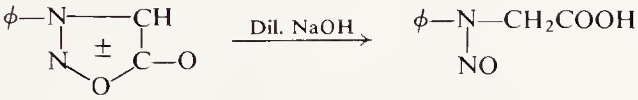


(49)

112 **111**

R = ϕ, Me

Hydrolysis of 3-phenylsydnone **21** by heating with dilute aqueous sodium hydroxide regenerates *N*-nitroso-*N*-phenylglycine, **22**, as shown in Eq. (50).[3]



(50)

21 **22**

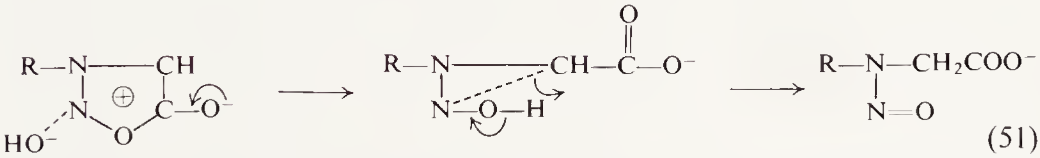
In contrast to this, when 3-phenylsydnone **21** is heated with water containing sodium carbonate, sodium acetate, or sodium oxalate, it decomposes to give carbon dioxide and a dark resin which dissolves in sulfuric acid with a greenish-brown color. No nitroso compound is formed.

This decomposition is inhibited by the presence of phenol, chloral hydrate, or *o*-phenylene diamine; the sydnone is recovered unchanged.[139, 140]

From kinetic studies of the alkali-catalyzed solvolysis of 3-substituted sydnones, Garrett[141] observed that reactivity decreases in the following order, correlating with the order of increasing I effect:

$$\text{furfuryl} > \text{methyl} > \text{propyl} > \text{phenethyl} > \text{isopropyl} > \textit{sec}\text{-butyl} > \textit{tert}\text{-butyl} > \text{1,1,3,3-tetramethylbutyl}$$

Consideration of the above results has led him to propose a mechanism shown in Eq. (51), which involves an incipient 2,4 bond or quasi-diazomethane (**113**) as an intermediate.



(51)

113

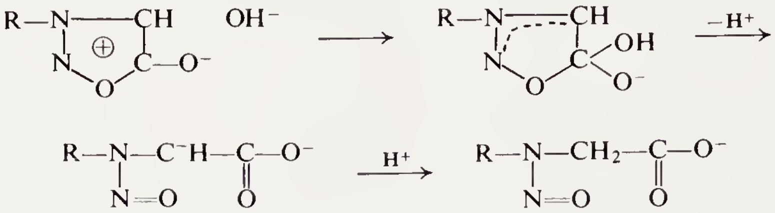
[138] S. A. Zotova and V. G. Yashunskii, *Zh. Organ. Khim.* **3**, 942 (1967); *Chem. Abstr.* **67**, 53276 (1967).

[139] R. A. Eade and J. C. Earl, *J. Chem. Soc.* p. 2307 (1948).

[140] J. C. Earl, *Tetrahedron* **1**, 338 (1957).

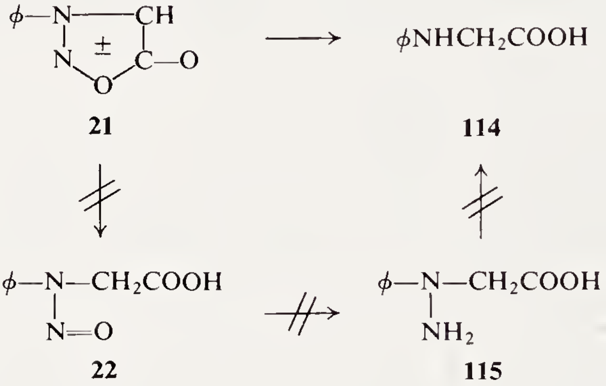
[141] E. R. Garrett, *J. Pharm. Sci.* **53**, 42 (1964).

Kier and Roche,[12] on the other hand, considered attack of the hydroxyl anion at the 5-position to be more likely, and proposed the mechanism shown in Eq. (52). According to the original authors, it explains the order of the rate of the hydrolysis of 3-alkylsydnones.



(52)

i. Reduction. The platinum oxide-catalyzed[3] or zinc and acetic acid[142] hydrogenation of 3-phenylsydnone **21** yields phenylglycine **114** and ammonia [Eq. (53)].



(53)

According to Earl,[142] the reduction is not preceded by ring opening to give *N*-nitroso-*N*-phenylglycine **115** since the latter gives much less ammonia when reduced under the same conditions as sydnone. He also suggested that the reduction of sydnone is similar to that of compounds containing an $=\overset{|}{N}\rightarrow O$ group (e.g., azoxybenzene → azobenzene) or an $=\overset{|}{N}\rightarrow N\!-$ group (e.g., azide → amine), where reductive fission with unsymmetrical addition of hydrogen occurs. Based mainly on this similarity, structure (**116**) was proposed for sydnones in an early stage of his work.

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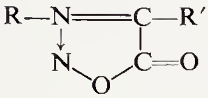
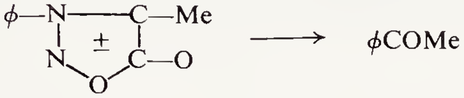
[142] J. C. Earl, *Rec. Trav. Chim.* 75, 346 (1956).



116

Cathodic reduction studies of sydnones are described earlier (Section II,A,2,*l*).

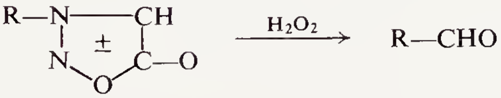
j. Oxidation. In an effort to obtain sydnone-4-carboxylic acids by oxidizing a methyl side chain on the aromatic sydnone ring, Hashimoto and Ohta[143] treated 3-phenyl-4-methylsydnone **92** with potassium permanganate in acetone or with hydrogen peroxide in acetic acid. They observed the formation of acetophenone instead of the expected carboxylic acid [Eq. (54)].



(54)

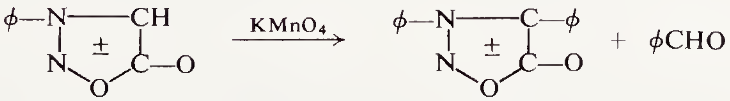
92

This result suggests that the phenyl group at the 3-position rearranged from N-3 to C-4 during the course of oxidation. Similarly, 3-phenylsydnone and 3-*p*-tolylsydnone **61** (R = Ph and *p*-MeC_6H_4) gave benzaldehyde and *p*-tolualdehyde, respectively, upon treatment with hydrogen peroxide [Eq. (55)]. The oxidation of 3-phenylsydnone **21** with permanganate gave 3,4-diphenylsydnone **117** and benzaldehyde [Eq. (56)], while 3,4-diphenylsydnone was not affected by either of these reagents. It was suggested that, by oxidizing the sydnone ring, aryl radicals which attack the 4-position of the sydnone molecule are generated. This mechanism may be supported by the high free-valence value of the 4-position of sydnone (calculated by Orgel *et al.* as 0.562) which corresponds to that of 9- or 10-position of anthracene where radical substitution occurs readily.



(55)

61



(56)

21 **117**

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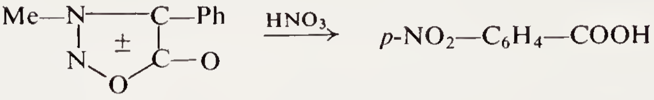
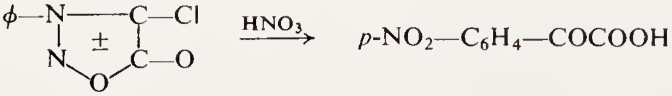
[143] M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Japan* **31**, 1048 (1958).

The sydnone ring is frequently cleaved by oxidation with fuming nitric acid. For example, as shown in Eq. (57), 3-methyl-4-phenylsydnone **118** is oxidized to *p*-nitrobenzoic acid when warmed with fuming nitric acid or when heated briefly at 100°C with a mixture of acetic acid and nitric acid.[144]

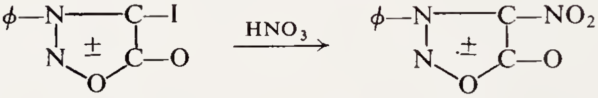


118 (57)

4-Chloro-3-phenylsydnone **119** is oxidized by fuming nitric acid in the cold to give *p*-nitrooxanilic acid **120** [Eq. (58)], while 4-iodo-3-phenylsydnone **121** gives 4-nitro-3-phenylsydnone **63** under the same reaction conditions [Eq. (59)]. The action of fuming nitric acid on 3-phenylsydnone **21** in the cold affords 2,4-dinitrophenol.[145]



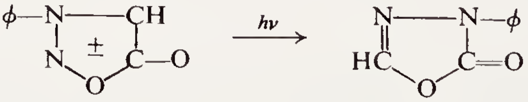
119 **120** (58)



121 **63** (59)

k. Pyrolysis and Photolysis. Although Earl[34] reported the detection of an odor of isocyanides during many decompositions of sydnones, no detailed study on sydnone pyrolysis has been performed.

The photolysis of sydnone is reported only with 3-phenylsydnone.[146] When a solution of 3-phenylsydnone **21** in benzene or dioxane is illuminated by a high pressure mercury lamp, 4-phenyl-Δ^2-1,3,4-oxadiazolin-5-one **122** is formed along with ten other products of unknown structures [Eq. (60)].



21 **122** (60)

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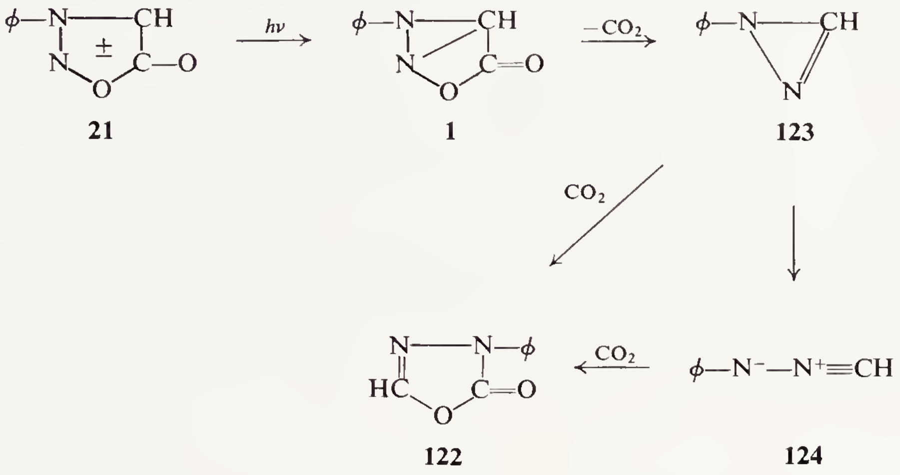
[144] F. H. C. Stewart, *Chem. Ind. (London)* p. 1718 (1962).

[145] H. Kato and M. Ohta, *Bull. Chem. Soc. Japan* **35**, 1418 (1962).

[146] C. H. Krauch, J. Kuhls, and H.-J. Piek, *Tetrahedron Letters* 4043 (1966).

When this experiment was carried out under a stream of $^{14}CO_2$, it was found that 80% of the activity in the reaction products was incorporated in **122**. Based mainly on this result, they suggested the mechanism shown in Eq. (61).



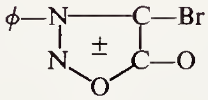
(61)

The reaction occurs by way of phenyldiazirine **123** probably formed via an excited intermediate **1** which is the structure Earl first suggested for sydnones. The direct action of carbon dioxide on **123** or on resonance-stabilized nitrile-imine **124** would give **122**. That the yield of **122** increased with an increasing partial pressure of carbon dioxide supports the above-described mechanism. The photolysis did not occur in solid dioxane at –20°C, and no 1,3-dipolar cycloaddition occurred by photolysis of 3-phenylsydnone **21** in the presence of acetylenedicarboxylate or acenaphthylene.

The photochromism of 3-(3-pyridyl)sydnone has been described (Section III,A,2,*f*).

l. 4-Halogeno Derivatives. The study of the chemical properties of functional derivatives of sydnones as well as of their substitution reactions may serve as a criterion concerning their aromaticity. A number of studies have been made on this subject. Among many functional derivatives of sydnones, 4-halogeno derivatives **62** are most readily obtained, and the reaction of 4-bromo-3-phenylsydnone **95** has been most extensively studied.

Bromosydnone **95** readily converts to the Grignard **103** and lithiates to **99** as



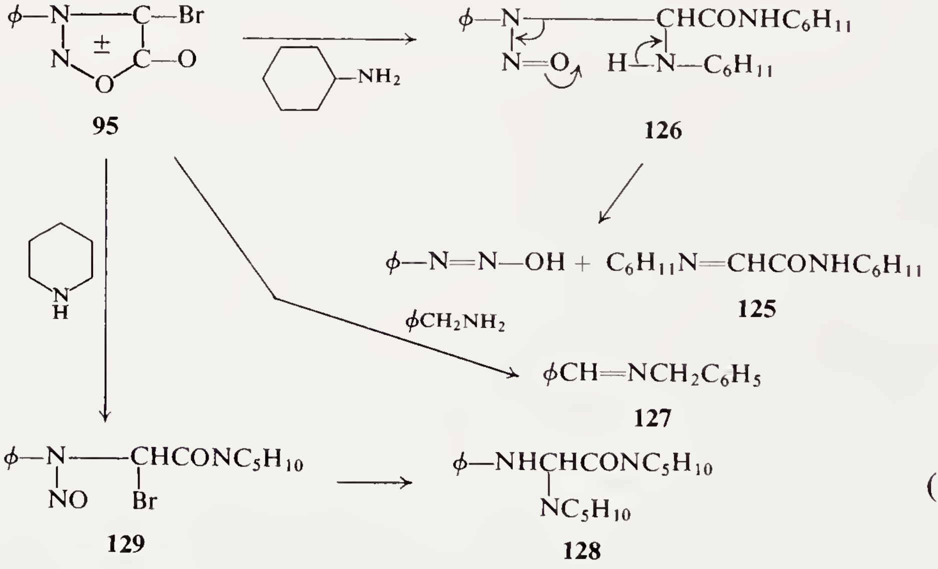
95

$$\xrightarrow{\text{NaOH}} \phi NH_2 + NaNO_2 + (COONa)_2 \qquad (62)$$

described previously, but displacing the bromine atom by other functional groups does not always proceed with ease. On heating **95** with aqueous sodium hydroxide, a strong odor of phenyl isocyanide was noted and the ring was cleaved to give aniline, sodium nitrite, and sodium oxalate [Eq. (62)].[139]

4-Chloro-3-phenylsydnone **119** is similarly hydrolyzed by 2 *N* sodium hydroxide.[132]

The reaction of 3-aryl-4-halogenosydnone and amines was investigated.[43, 147–149] It was found that although 4-bromosydnone **95** does not react with amines at room temperature, it undergoes ring cleavage on heating to give a variety of products, depending on the nature of amines employed. Thus, the reaction with cyclohexylamine gives an anil **125** with evolution of nitrogen, probably through an intermediate **126**. Benzylamine reacts similarly to give benzylidenebenzylamine **127**, while piperidine yields a diamino acid amide **128** presumably by way of an intermediate **129** [Eq. (63)]. The last reaction has been recommended as a new preparative method of diamino acid amides.



(63)

Kato and Ohta[150] reported that 4-bromo-3-phenylsydnone **95** is reduced to 3-phenylsydnone **21** on treatment with sodium hydrogen sulfide, sodium sulfide, or sodium *p*-thiocresylate, while treatment with thiourea gives rise to bissydnonyl sulfide **130** [Eq. (64)].

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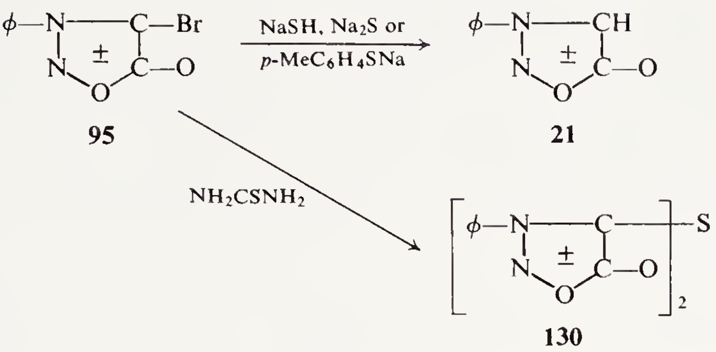
[147] H. Kato and M. Ohta, *Chem. Commun.* p. 525 (1966).

[148] M. Bellas and H. Suschitzky, *J. Chem. Soc.* (*C*) p. 189 (1966).

[149] H. Suschitzky, *Angew. Chem.* **79**, 636 (1967).

[150] H. Kato and M. Ohta, *Bull. Chem. Soc. Japan* **30**, 210 (1957).



(64)

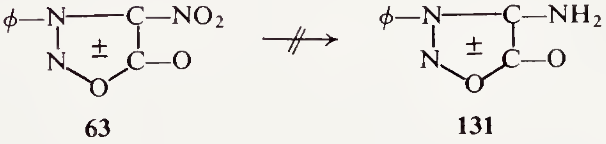
The action of excess hydrazine hydrate on **95** also yields 3-phenylsydnone **21**.[148,150] The reduction of **95** by zinc and acetic acid causes cleavage of the ring to give *N*-phenylglycine **114**.[150] Bromosydnone **95** was unaffected by silver nitrate, sodium nitrite, sodium phenolate, sodium acetate, guanidine, or sodium iodide.[150]

The facts that bromosydnone **95** liberates iodine from potassium iodide in the presence of hydrochloric acid and that **95** oxidizes sodium hydrogen sulfide and similar compounds suggest that **95** acts as an oxidation agent by liberating a bromine cation.

The behavior of 4-halogenosydnones towards fuming nitric acid has been previously described (Section II,A,3,*j*).

m. Nitro and Amino Derivatives. 4-Nitro-3-phenylsydnone **63**, obtained by nitrating 3-phenylsydnone **21**, is the only derivative in which a nitro group is attached directly to the sydnone ring. In spite of the presence of a strongly electron-withdrawing nitro group, the 4-nitro derivative is fairly unstable. It cannot successfully be recrystallized from ethanol and readily decomposes on heating with dilute acid. The structures of the decomposition products have not yet been elucidated.[14]

Reduction of 4-nitro-3-phenylsydnone **63** with a variety of reducing agents has been attempted in the hope of obtaining corresponding 4-amino derivative **131** [Eq. (65)]; all such attempts, however, were unsuccessful.[24,33,151]



(65)

Hashimoto *et al.*[33] reported that when **63** was reduced with iron and water at 70°C, ferrous sulfate and aqueous ammonia, or aluminum amalgam, a strong

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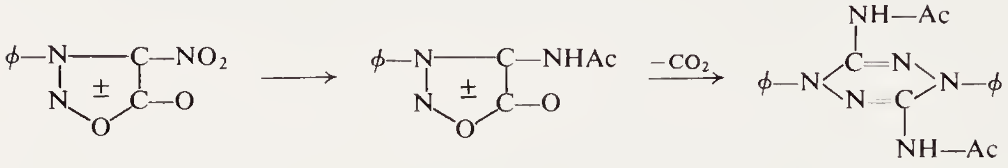
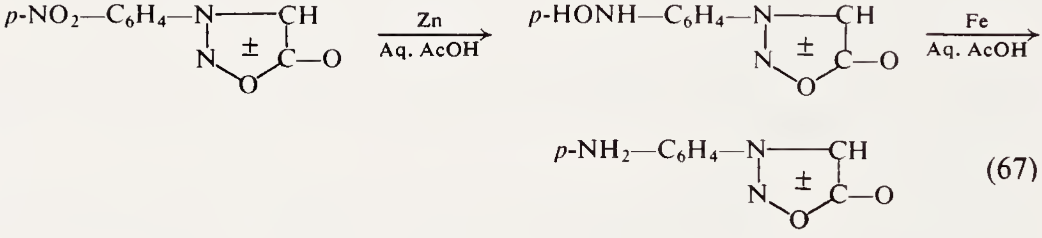
[151] T. T. Yee, W. E. McEwen, and A. P. Wolf, *Tetrahedron Letters* p. 3115 (1965).

odor characteristic of isocyanide was emitted. No products could be characterized by catalytic reduction over palladium charcoal or by hydrazine hydrate in dioxane. Oxamide was formed when **63** was treated with hydrogen sulfide in aqueous ammonia. A compound considered as a tetrazine derivative, **132**, was formed when **63** was reduced by zinc powder in an acetic acid–acetic anhydride mixture. The formation of **132** may be explained by the intermediate formation of 4-acetamidosydnone **133** followed by its decarboxylation and dimerization, as shown in Eq. (66).



63 **133** **132** (66)

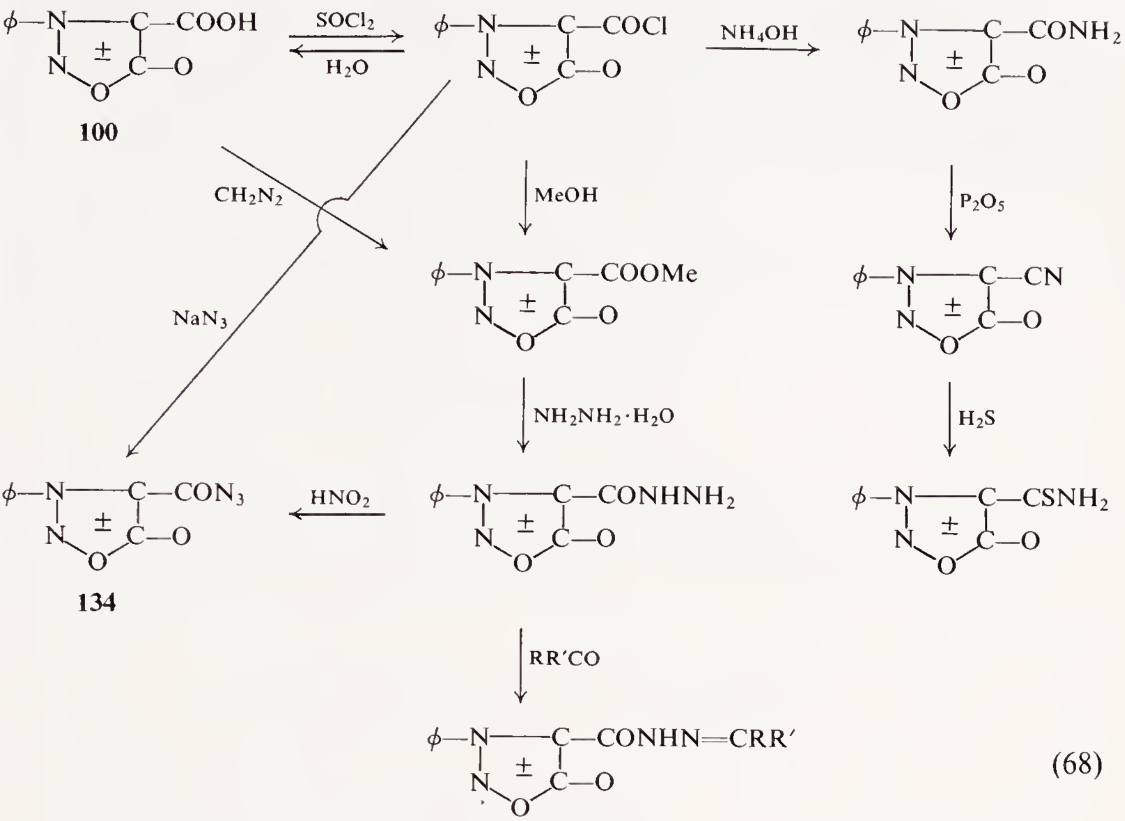
Although the reduction of the nitro group at the 4-position of the sydnone ring could not be realized, a nitro (or a hydroxylamino) group on an aryl substituent at position 3 may be successfully reduced to an amino group under carefully controlled conditions.[152] An example is shown in Eq. (67).



(67)

n. Carboxyl Derivatives. A considerable number of 3-substituted sydnone-4-carboxylic acids have been prepared via the corresponding 1-lithium derivatives.[64, 95, 126, 153] A variety of acid derivatives have been prepared from 3-phenylsydnone-4-carboxylic acid **100** as shown in Eq. (68).[64, 127, 128a, 154] An attempt to convert the acyl azide **134** to the corresponding amine by Curtius rearrangement was not successful.[64]

[152] I. C. Popoff and G. H. Singhal, *Abstr. Am. Chem. Soc. 153rd Meeting* (1967).
[153] L. B. Kier, D. Dhawan, and M. J. Fregly, *J. Pharm. Sci.* **53**, 677 (1964).
[154] M. Hashimoto, H. Kato, and M. Ohta, *Nippon Kagaku Zasshi* **79**, 172 (1958).



(68)

Some 3- and 4-carboxymethylsydnones have been prepared by direct ring closure.[38,95,96] The pK_a's of these carboxyl and carboxymethyl derivatives are listed in Table V.

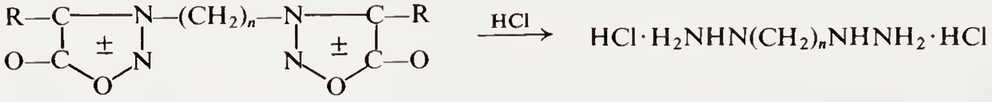
The strong acidity of 3-carboxymethylsydnone and its ready decarboxylation above its melting point suggest a high positive charge localization on the nitrogen atom at the 3-position.

4. *Application*

a. Synthetic Application. Eade and Earl[16] pointed out that sydnones which are easily hydrolyzed by acid to form monosubstituted hydrazines, can be useful reagents for the characterization of carbonyl compounds. The formation of monosubstituted hydrazines from sydnones was recommended by Fugger *et al.*[66] as a general and convenient method of coverting primary amines to the corresponding monosubstituted hydrazines, especially when the hydrazines are otherwise accessible with difficulty.

The utility of this synthesis was increased by the demonstration that it can be performed in satisfactory overall yields without purifying or isolating any of the intermediates. In this manner, hydrochlorides of benzylhydrazine, *n*-butylhydrazine, and *n*-hexylhydrazine were prepared in yields of 59, 79, and 90% based on sydnones, respectively.[66, 84]

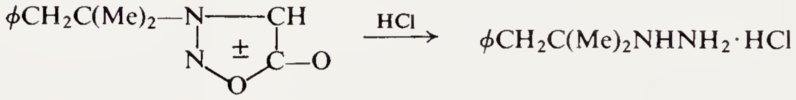
Daeniker and Druey[41, 155] made use of this synthesis for the preparation of aliphatic bishydrazine salts **135** [Eq. (69)].



135 (69)

$R = H, Me; n = 2, 4, 6$

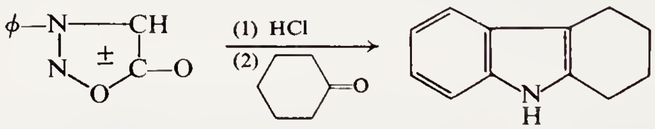
Shetty[156] applied the sydnone method to obtain 1-phenyl-2-methyl-2-hydrazinopropane hydrochloride **136** having intense vasopressor activity. The synthesis began with 2-phenyl-*t*-butylamine and proceeds via the corresponding sydnone **137** [Eq. (70)].



(70)

137 **136**

Ainsworth and Suschitzky[157] made use of the acid hydrolysis of arylsydnones in an approach to the synthesis of tetrahydrocarbazoles. Thus 3-phenylsydnone **21**, on treatment with hot ethanolic hydrochloric acid followed by addition of cyclohexanone, gave tetrahydrocarbazole **138** though in low yield [Eq. (71)]. Several other applications of sydnones for the preparation of hydrazines are reported.[158–161]



(71)

21 **138**

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[155] J. Druey and H. U. Daeniker, U.S. Patent 2,945,036; *Chem. Abstr.* **55**, 4550 (1961).

[156] V. Shetty, *J. Org. Chem.* **26**, 3002 (1961).

[157] D. P. Ainsworth and H. Suschitzky, *J. Chem. Soc.* (*C*) p. 315 (1967).

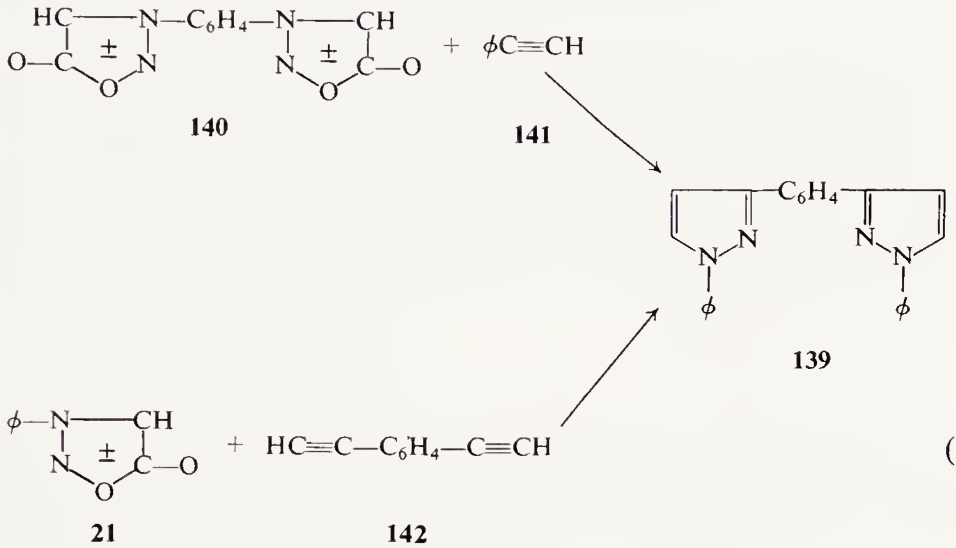
[158] J. Hadáček and J. Svehla, *Publ. Fac. Sci. Univ. Masaryk Cislo* **357**, 257 (1954).

[159] M. Wilhem and D. Y. Curtin, *Helv. Chim. Acta* **40**, 2129 (1957).

[160] W. H. Edgerton, U.S. Patent 2,916,495; *Chem. Abstr.* **52**, 5694 (1960).

[161] V. G. Yashunskii and V. F. Vasil'eva, *Zh. Obshch. Khim.* **30**, 2754 (1960); *Chem. Abstr.* **55**, 13415 (1961).

As described before (Section II,A,3,*d*), sydnones can play a role as 1,3-dipolarophiles in the 1,3-dipolar cycloaddition reaction developed by Huisgen, undergoing addition reactions with alkenes or alkynes with subsequent loss of carbon dioxide to form pyrazole derivatives. This type of reaction affords a convenient and versatile route for the preparation of five-membered heterocycles. For example, Stille *et al.*[162] reported that phenylenedipyrazoles **139** can be prepared by reacting *p*-phenylene-3,3-bissydnone **140** with phenylacetylene **141**, or of 3-phenylsydnone **21** with diethynylbenzene **142** [Eq. (72)].



(72)

Another example, reported by Lazaris,[119] is the preparation of 2-phenylindazole **91**, in which a mixture of anthranilic acid and 3-phenylsydnone **21** was treated with isoamyl nitrite. Obviously, benzyne (**93**) is formed as an intermediate which adds to sydnone [Eq. (36)].

b. Biological Activities. Of the many potential applications of sydnones, the one which has attracted the utmost attention is their biological activity. A considerable number of sydnones have been prepared and studied for their pharmacological activity. Some of these exhibit marked activity but none has proved active enough for practical use. Recently, Kier and Roche[12] presented a comprehensive review on the medicinal chemistry of mesoionic compounds which is worth referring to for detailed information on this subject. In this section, only a brief survey will be presented.

Studies on the biological activity of sydnones have been carried out from a variety of standpoints. From the results obtained, some suggestions have been made about the mechanisms of action. The fact that α-amino acids or their

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[162] J. K. Stille, F. W. Harris, and M. A. Bedford, *J. Heterocyclic Chem.* 3, 155 (1966).

N-nitroso derivatives are the precursors of sydnones is one of the bases for expecting biological activity. Dhawan and Kier[163] pursued a correlation between the partition coefficient and convulsive potency of sydnones without considerable success.

Structural features, such as mesoionic structure, aromaticity, molecular size, nature of substituents, etc., may be another important basis for expecting biological activities.

Sydnone derivatives which have been subjected to pharmacological tests are those having a variety of substituents including hydrocarbon residues located at nonring sites and those having functional groups attached directly on the ring.

These derivatives were tested against a variety of infections and diseases of plants and animals and were found to be more or less active in the following tests: activity against microorganisms,[22,164] fungal infections of plants[165–167] or ascaridal diseases,[31,168] antitumor[41,67,169,170] and antimalarial[152,169,171] activity, activity as central nervous stimulants,[163,172–174] anticonvulsant[175] or depressant,[172] analgesic[12,172] hypoglycemic,[172] diuretic,[153,176] or hypotensive[55,153,176,177] activity.

B. SYDNONE IMINES

The *exo*-imino analog of sydnone, called sydnone imine, has a structure similar essentially to sydnone and comprises a group of mesoionic compounds which have been extensively studied. Sydnone imines do not exist as free bases

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[163] D. Dhawan and L. B. Kier, *J. Pharm. Sci.* **53**, 83 (1964).

[164] D. P. Wright, Jr., J. J. Licari, and E. J. Frazza, German Patent 1,097,751 (1959); *Chem. Abstr.* **56**, 10639 (1962).

[165] D. Davis, H. J. Becker, and E. F. Rogers, *Phytopathology* **49**, 821 (1959); *Chem. Abstr.* **54**, 7043 (1960).

[166] A. E. Smith and J. A. Riddell, German Patent 1,120,800; *Chem. Abstr.* **56**, 15868 (1962).

[167] E. F. Rogers and D. Davis, U.S. Patent 3,189,520; *Chem. Abstr.* **63**, 7605 (1965).

[168] Farbenfabriken Bayer Akt.-Ges. British Patent 823,001; *Chem. Abstr.* **54**, 8854 (1960).

[169] C. V. Greco, W. H. Nyberg, and C. C. Cheng, *J. Med. Pharm. Chem.* **5**, 861 (1962).

[170] British Patent 1,002,890; *Chem. Abstr.* **63**, 18106 (1965).

[171] S. G. Boots and C. C. Cheng, *J. Heterocyclic Chem.* **4**, 272 (1967).

[172] T. Bruzzese, S. Casadio, E. Marazzi-Uberti, and C. Turba, *J. Pharm. Sci.* **54**, 1041 (1965).

[173] L. B. Kier and D. Dhawan, *J. Pharm. Sci.* **51**, 1058 (1962).

[174] L. B. Kier, L. E. Fox, D. Dhawan, and I. W. Waters, *Nature* **195**, 817 (1962).

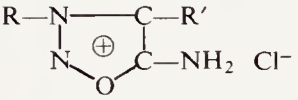
[175] P. Oehme, E. Goeres, K. Schwarz, G. Petsch, H. D. Faulhaber, and P. Lange, *Acta Biol. Med. German* **14**, 369 (1965); *Chem. Abstr.* **63**, 6191 (1965).

[176] M. J. Fregly, L. B. Kier, and D. Dhawan, *Toxicol. Appl. Pharmacol.* **6**, 529 (1964).

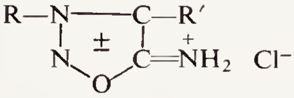
[177] L. B. Kier, A. Al-Shamma, D. Campbell, P. Patil, and A. Tye, *Nature* **210**, 742 (1966).

but their salts and the free bases and salts of *exo*-*N*-acyl derivatives are stable enough to be isolated.

Although the nonexistent free sydnone imine may formally be regarded as having essentially the same ring structure as sydnone, the actual structures of sydnone imine salts and isolable derivatives have not been fully elucidated in spite of considerable information available from physical and chemical studies. In some cases, sydnone imines show quite different properties from sydnones. The subject in question is similar to that concerning the structural representation of sydnones. We can write, for example, the following formulas (**14**, **143**–**146**) for sydnone imine hydrochloride.



14



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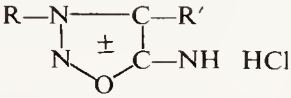

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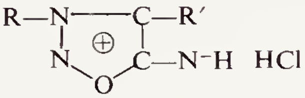

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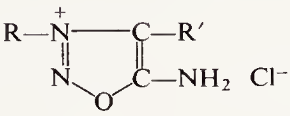


146

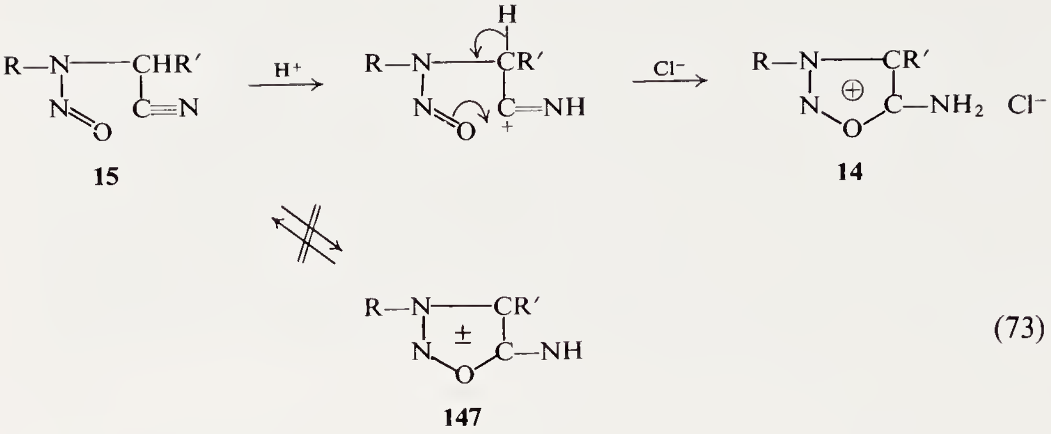
At the present time, for lack of a definite choice among these formulas, a representation such as **14** will be used throughout this text for the acid salts of imino-type mesoionic compounds.

1. Synthesis

To date, there is but one route leading to the formation of sydnone imine salts. The synthesis was first reported independently by Ohta *et al.*[21] and Brookes and Walker.[22] It consists of strong acid cyclization of an *N*-substituted *N*-nitrosoaminoacetonitrile **15** having at least one α-hydrogen atom. This method is successful in almost every case where an *N*-nitroso compound **15** is available.

The cyclization proceeds by initial protonation at the nitrile nitrogen atom, as shown in Eq. (73).

Although *N*-nitrosoaminoacetonitrile **15** is positive to Liebermann's nitroso test and is insoluble in water or 10% hydrochloric acid, **14** is negative to the Liebermann test and easily soluble in these solvents. From this, it is evident that **14** is not the hydrochloride of **15**. The fact that **15** does not react with acetic anhydride to form an *N*-acetyl derivative of **14** shows the absence of an equilibrium between **15** and its cyclic tautomer **147**. Furthermore, the possibility of intramolecular rearrangement is excluded as **14** regenerates the starting material **15** on basification.[21]

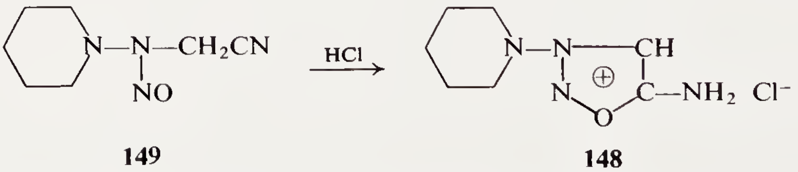


(73)

The use of a strong proton acid is necessary for the cyclization of **15**; a weak acid such as an organic carboxylic acid is ineffective.

Sydnone imine hydrochlorides are most usually prepared by treating a solution of a nitroso compound **15** in an anhydrous solvent (e.g., ether, tetrahydrofuran, acetone, alcohol, etc.) with dry hydrogen chloride. It has been reported that 3-alkylsydnone imine hydrochloride can be obtained by using aqueous hydrochloric acid.[72] Cyclization by fuming nitrous acid or nitric acid affords the corresponding nitrate.[22]

A wide variety of substituents attached to the 3- and 4-positions of sydnone imine salts **14** have been prepared on the premise that R cannot be a hydrogen atom. The groups R and R′ can be any hydrocarbon group whatsoever and may have a functional group such as halogen, hydroxyl, or dialkylamino group.[178, 179] Only one example of the synthesis of sydnone imine salts having a nonhydrocarbon functional group attached directly to the ring nitrogen is claimed in a patent[179] in which a variety of 3-(*N*,*N*-disubstituted amino)-sydnone imine hydrochlorides are presented. For example, 3-piperidinosydnone imine hydrochloride **148** is obtained from *N*-piperidinocyanomethylnitrosamine **149** by treatment with methanolic hydrogen chloride, as shown in Eq. (74).



(74)

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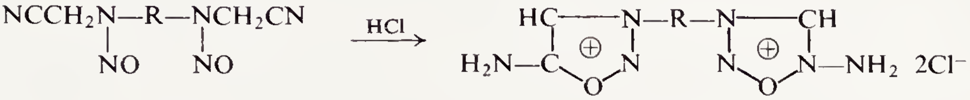
[178] V. G. Yashunskii, *Zh. Obshch. Khim.* 33, 192 (1963); *Chem. Abstr.* 59, 602 (1963).

[179] K. Masuda and Y. Imashiro, U.S. Patent 3,312,690 (1967).

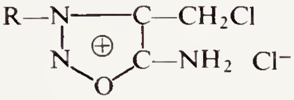
Bissydnone imine dihydrochlorides of general type **150** were synthesized[33, 72, 180, 181] from *N,N'*-dinitrosobisglycolonitriles **151**, as shown in Eq. (75).



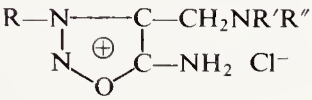
(75)

151 **150**

Recently, Zomova and Yashunskii[182] reported the synthesis of 4-chloromethyl- and 4-dialkylaminomethylsydnone imine hydrochlorides (**152** and **153**, respectively) by direct ring closure.



152



153

2. *Physical Properties*

The problem of what is the most satisfactory representation of sydnone imine derivatives (Section II,B) is closely related to the question of whether or not these compounds can be regarded as mesoionic species. This point is most adequately discussed on the basis of the physical properties of sydnone imines.

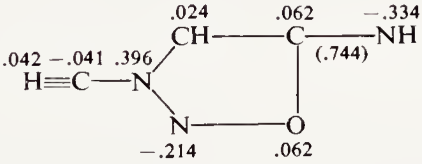


FIG. 3. Molecular orbital calculation on 3-methylsydnone imine. The number in parentheses is a bond order; the remaining numbers are charge densities. [L. B. Kier and E. B. Roche, *J. Pharm. Sci.* **56**, 149 (1967)].

Kier[12] has performed a molecular orbital calculation by a modified Hückel procedure and obtained the electron density distribution shown in Fig. 3.

[180] V. G. Yashunskii and L. E. Kholodov, *Zh. Obshch. Khim.* **32**, 865 (1962); *Chem. Abstr.* **58**, 2444 (1963).

[181] V. G. Yashunskii, V. F. Vasil'eva, L. E. Kholodov, and M. N. Shchukina, *Zh. Obshch. Khim.* **32**, 192 (1962); *Chem. Abstr.* **57**, 13749 (1962).

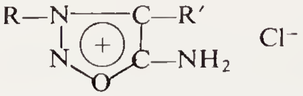
[182] S. A. Zotova and V. G. Yashunskii, *Zh. Organ. Khim.* **3**, 1889 (1967).

The *exo*-nitrogen atom is negatively charged and the N-3 atom is positively charged. This is analogous to the sydnone case.

a. Ultraviolet Spectra. The ultraviolet absorption maxima of some sydnone imine hydrochlorides are shown in Table VII.

TABLE VII

ULTRAVIOLET ABSORPTION SPECTRA OF SYDNONE IMINE HYDROCHLORIDES



R	R′	λ_{max}(ϵ or log ϵ)	Reference
Me	H	293 (6800)	*a*
i-Pr	H	288 (3.88)	*b*
		[292 (8350)]	*a*
Ph	H	308 (3.90), 260 (3.84)	*b*
		[306 (8100), 270 (6900)]	*c*
Ph	Me	314 (3.90)	*b*
Ph	Ph	324 (3.94), 242 (4.06)	*b*

[a] C. Greco, W. H. Nyberg, and C. C. Cheng, *J. Med. Pharm. Chem.* **5**, 861 (1962).

[b] V. G. Yashunskii and E. M. Peresleni, *Zh. Obshch. Khim.* **32**, 1687 (1962); *Chem. Abstr.* **58**, 9053 (1963).

[c] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2426 (1962).

No correlation could be found between the position of substituents on the phenyl ring at the 3-position of sydnone imine hydrochlorides and the absorption maxima.[72] From an analysis of their ultraviolet spectra, Yashunskii[183] concluded that sydnone imine salts have the same electronic structure as sydnones. Kier and Roche[12] found that the absorption maximum derived from an MO calculation (300 mμ) agreed closely with the observed value.

The ultraviolet absorption maxima of *N*-acylsydnone imine hydrochlorides indicated in Table VIII are at the same positions as those of the corresponding

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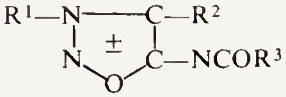
[183] V. G. Yashunskii and E. M. Peresleni, *Zh. Obshch. Khim.* **32**, 1687 (1962); *Chem. Abstr.* **58**, 9053 (1963).

TABLE VIII

ULTRAVIOLET SPECTRA OF *N*-ACYLSYDNONE IMINES[a]



			UV maxima in $m\mu(\epsilon)^b$	
R^1	R^2	R^3	Free base or hydrochloride in H_2O or EtOH	Hydrochloride in dilute HCl
Me	H	Me	238 (7100)	280 (10900)
			321 (12550)	—
Me	Me	Me	241 (8500)	215 (6000)
			328 (11700)	288 (8700)
Ph	Ph	Ph	305 (13800)	248 (15800)
			368 (16400)	306 (11100)

[a] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2441 (1962).

[b] Numbers in parentheses are molar extinction coefficients.

free bases when measured in water or ethanol. A hypsochromic shift is observed when they are measured in dilute hydrochloric acid.[184] A correlation was found between the shift and the nature of the substituent.

The positions of the absorption maxima in the longer wavelength region for *N*-acyl, *N*-carbamoyl, and *N*-thiocarbamoyl sydnone imines closely resemble those of *N*-unsubstituted sydnone imine salts.

b. Infrared Spectra. Based on the structural analogy between sydnone imine hydrochlorides and imino ether hydrochlorides and on deuteration studies, Yashunskii *et al.*[185,186] assigned the 1588–1606 cm^{-1} absorption band of the imine hydrochlorides to $-\overset{+}{N}H_2$ and the 1709–1673 cm^{-1} band to C═N stretching absorption. Mao[69] also assigned the 1709–1673 cm^{-1} to C═N stretching and the 1038–1015 cm^{-1} band to the C—H group. It was further concluded from an infrared study that sydnone imine is structurally similar to sydnone and that the electrons are delocalized over the adjacent nitrogen atoms and the C-4 atom, as shown in **154**.[185]

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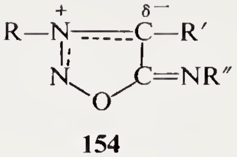
[184] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2441 (1962).

[185] V. G. Yashunskii and Yu. N. Sheinker, *Zh. Obshch. Khim.* **32**, 1681 (1962); *Chem. Abstr.* **58**, 9053 (1963).

[186] V. G. Yashunskii, E. M. Peresleni, and Yu. N. Sheinker, *Izv. Akad. Nauk SSSR, Ser. Fiz.* **26**, 1295 (1962); *Chem. Abstr.* **58**, 7520 (1963).



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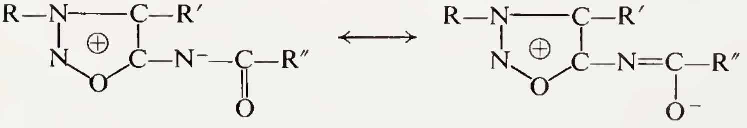
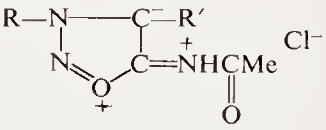
The characteristic C-4—H absorption of sydnones at 3165 cm^{-1} is diagnostic for the H-4 proton, but in the case of sydnone imine salts, this absorption cannot be used for this purpose because it is submerged by that due to the —N^{+}H$_2$ group.

The infrared carbonyl absorption of free bases of *N*-acylsydnone imines appears at 1667–1626 cm^{-1}, whereas that of the corresponding salts is shifted to 1739–1730 cm^{-1} (Nujol), the region normally populated by an ester carbonyl. Daeniker[184] interpreted this phenomenon by considering the carbonyl polarization. Thus, in the amide–imide mesomerie (**155** ↔ **156**), the contribution from form **156** is important in the free base, while in the salt such polarization is inhibited as a result of the protonation at the *exo*-nitrogen atom to give **157**. Yashunskii[187] also discussed this problem and supported the idea that the *exo*-nitrogen atom is protonated.



155 **156**



157

c. *Nuclear Magnetic Resonance Spectra.* The NMR spectra of sydnone imines shown in Table IX indicate that the signal of the proton on the 4-

TABLE IX

NUCLEAR MAGNETIC RESONANCE CHEMICAL SHIFTS (τ) OF PROTONS AT THE 4-POSITION OF SYDNONE IMINE SALTS AND SYDNONES[a]

R^3	Sydnone imine	Sydnone
Me	2.45	3.66
Ph	1.97	3.22
PhCH$_2$	2.55	3.81

[a] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2426 (1962).

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[187] V.G. Yashunskii, O. I. Samoilova, and L. E. Kholodov, *Zh. Obshch. Khim.* **34**, 2050 (1964); *Chem. Abstr.* **61**, 8299 (1964).

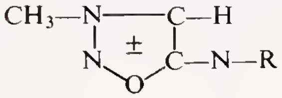
position appears at a remarkably low magnetic field.[72, 184] This was interpreted by Kier and Roche[12] as a function of the induced ring current observed with aromatic rings in general. The position of this signal may be considered as a measure of the degree of the ring's aromaticity.

The ring proton signal of 3-alkylsydnone imine salts is shifted ca. 1 ppm to lower field than that of the corresponding sydnones. That of 3-phenylsydnone imine is shifted to an even lower field. This latter shift may be a result of the combined anisotropic effect of the two aromatic rings.[12]

The 4-unsubstituted *N*-acyl, *N*-carbamoyl, and *N*-thiocarbamoyl sydnone imine salts and free bases show a signal characteristic of an aromatic ring (Table X).[184] Comparison of the spectra of free bases and salts indicates that a shift to a lower magnetic field is generally observed with salt formation. The degree of this shift is more pronounced for protons which are nearer the ring, suggesting that it is connected with the ring current of π-electrons.

TABLE X

NUCLEAR MAGNETIC RESONANCE CHEMICAL SHIFTS (τ) OF *N*-ACYLSYDNONE IMINES[a]



R	Form	C_4-H	CH_3-N
$COCH_3$	Free base	2.00	5.76
	Hydrochloride	1.28	5.52
CONHEt	Free base	2.37	5.87
	Hydrochloride	1.65	5.53

[a] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2441 (1962).

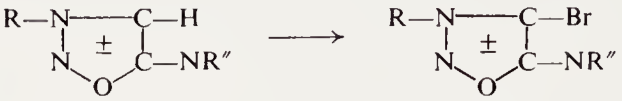
3. *Chemical Properties*

a. Substitution at the 4-Position. If sydnone imine is structurally similar to sydnone, it might be expected that the 4-position would be reactive toward electrophilic substitution. Halogenation of several sydnone imine derivatives has been attempted.

Chlorination[188] and bromination[21, 72] of sydnone imine hydrochlorides having no substituent either at the 4-position or at the *exo*-nitrogen atom

[188] V. G. Yashunskii, *Zh. Vses. Khim. Obshchestva D. I. Mendeleeva* **8**, 705 (1963); *Chem. Abstr.* **60**, 9267 (1964).

were attempted, but in every case, decomposition occurred and 4-halogeno derivatives were not isolated. On the other hand, acetyl,[21,184] benzoyl,[128a] carbamoyl,[184] methoxycarbonyl,[189] and sulfonyl[95,128] substitution at the *exo*-nitrogen atom of **158** afford the corresponding 4-bromo derivatives [Eq. (76)].



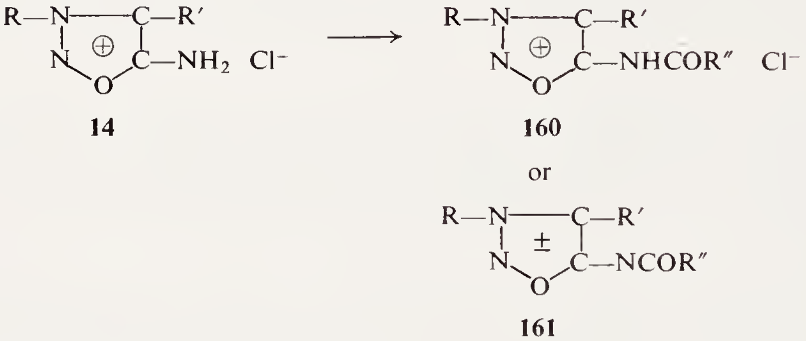
158 **159**

R″ = Ac, COPh, CONHR‴, COOMe, O_2SAr

(76)

These bromo derivatives do not seem to be lithiated, since an attempt to prepare a carboxylic acid by treating with butyllithium followed by Dry Ice was unsuccessful.[128a] The action of mercuric chloride on *N*-acetyl-3-phenylsydnone imine affords the corresponding 4-chloromercuri derivative.[21]

b. Reactions at the exo-Nitrogen Atom. The reactivity of sydnone imines is similar to that of secondary amines rather than ketimines. Sydnone imine hydrochlorides are easily acylated by the usual procedures. *N*-acylsydnone imine hydrochlorides are obtained with acid anhydride in the presence or absence of pyridine.[190–192] With acid anhydrides or acyl halides in the presence of sodium acetate, sodium carbonate, or sodium hydrogen carbonate, free *N*-acyl derivatives **161** are obtained as shown in Eq. (77).[21,128,163,184,190,193,194]



14 **160** or **161**

(77)

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[189] V. G. Yashunskii and V. S. Fedorovich, *Zh. Obshch. Khim.* **34**, 3075 (1964); *Chem. Abstr.* **61**, 16063 (1964).

[190] Belgian Patent 618,822 (1962); *Chem. Abstr.* **59**, 2840 (1963).

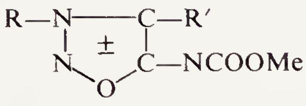
[191] Belgian Patent 618, 823 (1962); *Chem. Abstr.* **59**, 2838 (1963).

[192] Belgian Patent 618,824 (1962); *Chem. Abstr.* **59**, 2839 (1963).

[193] V. G. Yashunskii and V. G. Ermolaeva, *Zh. Obshch. Khim.* **32**, 186 (1962).

[194] V. F. Vasil'eva and V. G. Yashunskii, *Khim. Nauka Promy.* **4**, 678 (1959); *Chem. Abstr.* **54**, 8793 (1960).

The *N*-methoxycarbonyl **162** was obtained by treating sydnone imine hydrochloride with methyl chloroformate in the presence of potassium carbonate in water.[185,187,193] With diketene in the presence of sodium hydrogen carbonate in water, the *N*-acetoacetyl derivative **163** was likewise synthesized.[184]



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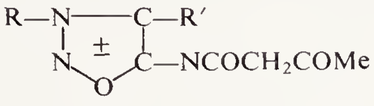
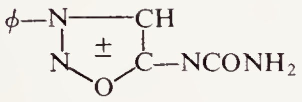
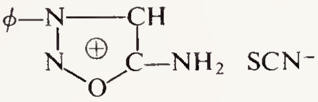


163

Combination of 3-phenylsydnone imine hydrochloride with potassium cyanate in water gives the *N*-carbamoyl derivative **164**, while with potassium thiocyanate, sydnone imine thiocyanate **165** is obtained.[195] Treatment of sydnone imine hydrochlorides with isocyanate or isothiocyanate in the presence of sodium hydrogen carbonate in water yields *N*-carbamoyl or *N*-thiocarbamoyl derivatives, respectively.[190,194,196]

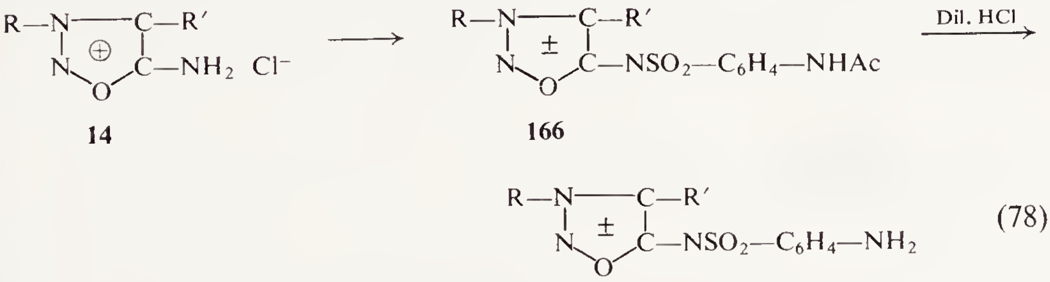


164



165

As shown in Eq. (78), *N*-sulfanilyl derivatives of sydnone imines **166** and **167** are easily obtained by the usual procedure using acetosulfanilyl chloride in pyridine. A variety of *N*-sulfanilyl sydnone imines have been synthesized for pharmacological tests.[128a,193,194,197]



167

(78)

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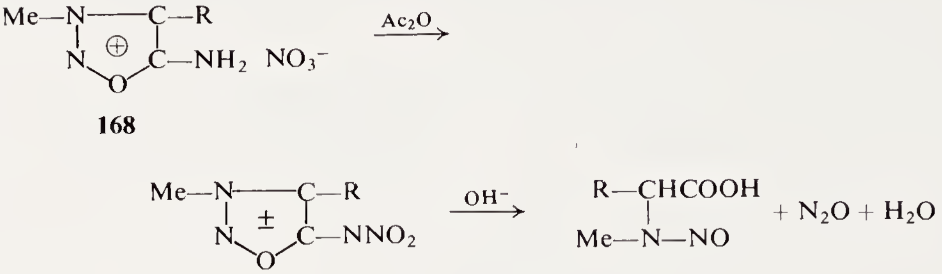
[195] M. Ohta, K. Yoshida, and S. Sato, *Bull. Chem. Soc. Japan* **39**, 1269 (1966).

[196] L. E. Kholodov and V. G. Yashunskii, *Zh. Organ. Khim.* **1**, 2063 (1965); *Chem. Abstr.* **64**, 11200 (1966).

[197] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2462 (1962).

The action of acetic anhydride on sydnone imine nitrate **168** afforded a nitroimine **169**.[22] The nitroimine **169** thus formed is stable to water and cold mineral acid but is decomposed by aqueous alkali, as shown in Eq. (79).



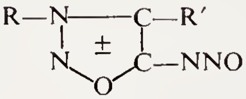
168

169

R = iso-Pr, iso-Bu

(79)

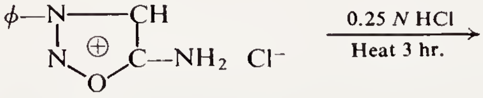
N-Nitroso derivatives **23** are formed by the action of sodium nitrite on sydnone imine hydrochlorides.[21, 190, 196, 198]



23

Interestingly, sydnones are formed [Eq. (13)] when *N*-nitrososydnone imines **23** are heated in an organic solvent,[35, 182] although the hydrolysis of sydnone imines does not produce sydnones.

c. *Reactions Involving Ring Opening. i. Hydrolysis.* Although sydnone imine hydrochlorides are generally stable toward dilute acid,[194, 199] prolonged heating with dilute hydrochloric acid causes ring cleavage. For instance, 3-phenylsydnone imine hydrochloride affords phenol, phenoxyacetic acid, and chloroacetic acid with the liberation of nitrogen, as shown in Eq. (80).



170

$$\phi OH + \phi OCH_2COOH + ClCH_2COOH + N_2 + NH_4Cl \qquad (80)$$

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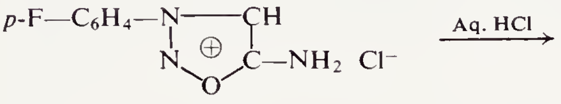
[198] L. E. Kholodov and V. G. Yashunskii, *Zh. Organ. Khim.* 3, 2047 (1967).

[199] V. G. Yashunskii, L. E. Kholodov, and O. I. Samoilova, *Collection Czech. Chem. Commun.* 30, 4257 (1965); *Chem. Abstr.* 64, 11065 (1966).

When the reaction is carried out in the presence of cuprous chloride, chlorobenzene is isolated as one of the products. It has been suggested that the reaction proceeds through a diazonium intermediate.[149, 200, 201] Participation of an aryldiazonium cation could be diagnosed using "aromatic" fluorine as a chemical label.[43] Thus, hydrolysis of *p*-fluorophenylsydnone imine **171** with boiling hydrochloric acid yields chlorobenzene, *p*-chlorophenol, and fluoride ion, as shown in Eq. (81).



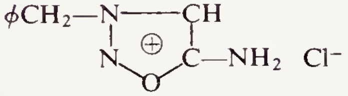
171

$$p\text{-F—C}_6\text{H}_4\text{—N}_2^+ \xrightarrow{\text{Cl}^-} \phi\text{Cl} + p\text{-Cl—C}_6\text{H}_4\text{—OH} + \text{F}^- \qquad (81)$$

Such fluorine replacement does not occur for the *m*-fluoro isomer since the *meta*-diazonium group is not effective enough in this orientation.

The mechanism mentioned above is supported by kinetic studies of the hydrolysis of sydnone imine hydrochlorides, carried out by Kholodov *et al.*[201, 202]

The acid hydrolysis of 3-benzylsydnone imine hydrochloride **172** proceeds in a similar way, as shown in Eq. (82).[200]



$$\longrightarrow \phi\text{CH}_2\text{Cl} + \text{ClCH}_2\text{COOH} + \text{N}_2 \qquad (82)$$

172

N-Acylsydnone imine hydrochlorides **160** are hydrolyzed by heating with dilute acid, yielding sydnone imine salts **14** as shown in Eq. (83). *N*-Carbamoyl derivatives are as stable as sydnone imine salts and are hydrolyzed very slowly, if at all, on heating with dilute hydrochloric acid.[184]

160 **14** (83)

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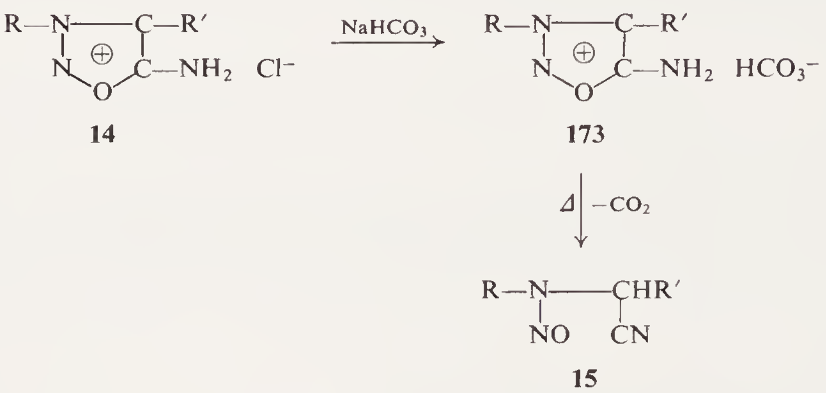
[200] L. E. Kholodov and V. G. Yashunskii, *Zh. Obshch. Khim.* **33**, 3409 (1963); *Chem. Abstr.* **60**, 4131 (1964).

[201] L. E. Kholodov and V. G. Yashunskii, *Zh. Obshch. Khim.* **37**, 670 (1967); *Chem. Abstr.* **67**, 53352 (1967).

[202] L. E. Kholodov, A. M. Khelem, and V. G. Yashunskii, *Zh. Organ. Khim.* **3**, 1870 (1967).

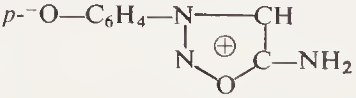
The hydrolysis of sydnone imine salts by aqueous alkali occurs differently from their acid hydrolysis. When a calculated amount of sodium hydrogen carbonate is added to an aqueous solution of sydnone imine hydrochloride **14** at 0°C, the corresponding sydnone imine hydrogen carbonate **173** is formed. In a special case, water-insoluble 3-benzylsydnone imine hydrogen carbonate can be isolated in crystalline form. The hydrogen carbonate, in general, is stable enough in solution at a low temperature for further work (e.g., preparation of *N*-acyl derivatives), but on heating it decomposes rapidly, liberating carbon dioxide and yielding *N*-nitrosoaminoacetonitrile **15**, as shown in Eq. (84).[72]



(84)

Kinetic studies of the alkaline hydrolysis of sydnone imine salts were reported by Yashunskii *et al.*[203] and by Kholodov and Yashunskii.[203,204] They showed that the ring opening reaction of 3-isopropylsydnone imine hydrochloride at 20°C and pH 7.15–9.0 is first-order with respect to sydnone imine and second-order with respect to hydroxyl ion. In addition, it was found that the ring is stabilized with decreasing substituent electronegativity at the 3- and 4-positions, and with increasing substituent size.[204]

The treatment of 3-(*p*-hydroxyphenyl)sydnone imine hydrochloride with sodium hydrogen carbonate yields a new and interesting compound **174**, having a zwitterionic structure in which the phenolic oxygen plays the role of an anionic component.[72]



174

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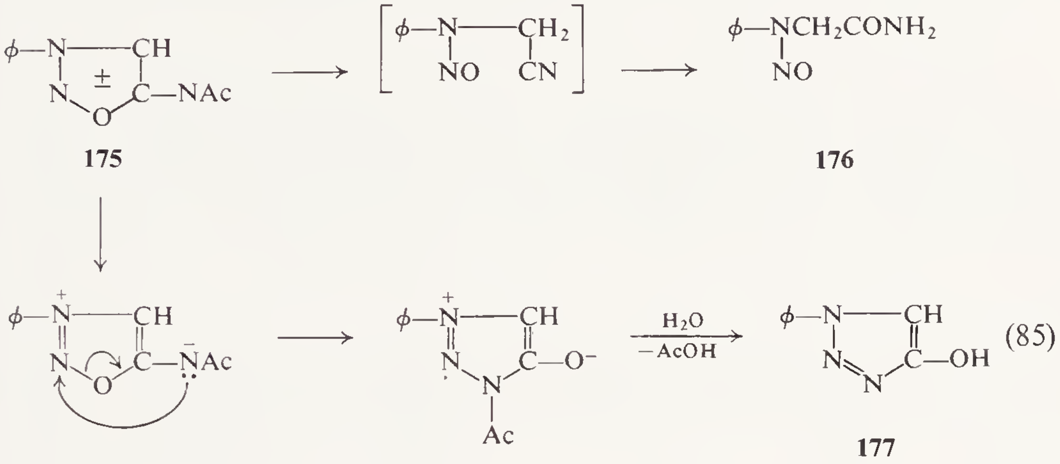
[203] V. G. Yashunskii, L. E. Kholodov, and E. M. Peresleni, *Zh. Obshch. Khim.* **33**, 3699 (1963); *Chem. Abstr.* **60**, 7886 (1964).

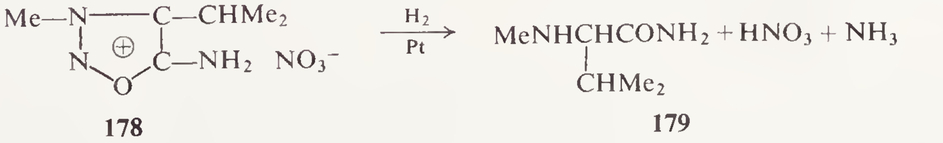
[204] L. E. Kholodov and V. G. Yashunskii, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR* p. 328 (1965); *Chem. Abstr.* **63**, 14652 (1965).

Daeniker[184,205] reported that *N*-acylsydnone imines are hydrolyzed by methanolic potassium hydroxide to a variety of products. Which of the following three reaction types occurs depends on the nature of the substituents at the 3- and 4-positions; (*1*) normal hydrolytic fission of the amide linkage affording *N*-nitrosoaminoacetonitrile or its derivatives, (*2*) cleavage between C-5 and the *exo*-N atom affording acyl amide, and (*3*) rearrangement. The last reaction is remarkable since 1,2,3-triazole derivatives are produced. In the case of *N*-acetyl-3-phenylsydnone imine **175**, *N*-nitrosoanilinoacetamide **176** and 4-hydroxy-1-phenyl-1,2,3-triazole **177** are isolated. For the formation of the latter, the rearrangement mechanism shown in Eq. (85) was postulated.



Hydrolysis of *N*-benzoyl-3,4-diphenylsydnone imine with methanolic potassium hydroxide affords benzoic acid, benzamide, and 4-hydroxy-1,5-diphenyl-1,2,3-triazole via each of the three routes mentioned above.

ii. Hydrogenolysis. Brookes and Walker[22] reported that during catalytic hydrogenation, 4-isopropyl-3-methylsydnone imine nitrate **178** takes up 2 moles of hydrogen rapidly and a third more slowly forming *N*-methylvaline amide **179** and ammonia, as shown in Eq. (86).



(86)

Daeniker and Druey[72] studied the hydrogenolysis of various sydnone imines **180** to aminoacetamides **181**. In agreement with Brookes *et al.*, they

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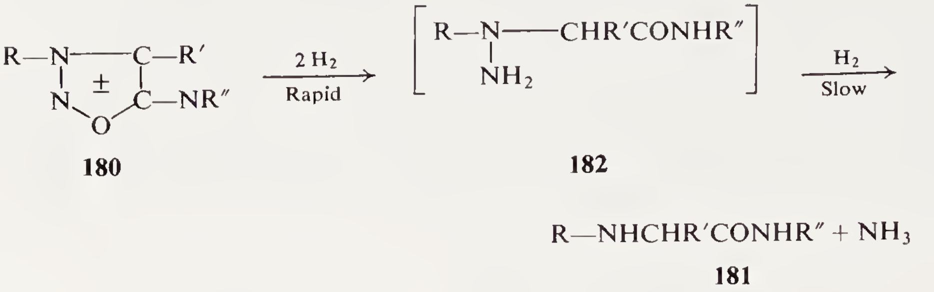
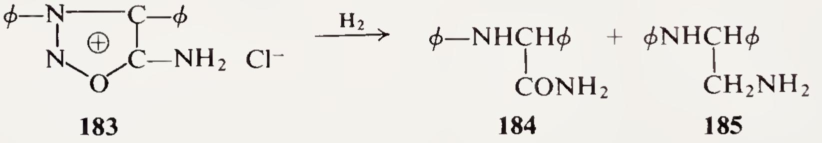
[205] H. U. Daeniker, *Helv. Chim. Acta* **47**, 33 (1964).

proposed that hydrogenation proceeds in two successive steps, with intermediate formation of hydrazinoacetamides (**182**), as shown in Eq. (87).



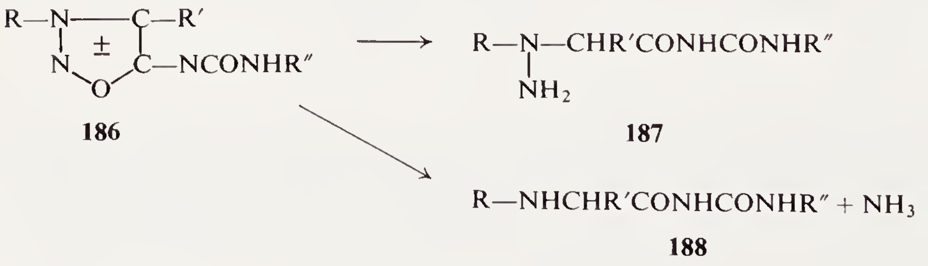
(87)

In the case of 3,4-diphenylsydnone imine hydrochloride **183**, Daeniker and Druey[72] obtained *N*,*C*-diphenylaminoacetamide **184** and another product, presumably *N*,*C*-diphenylethylenediamine **185**. The formation of the latter was attributed to ring fission between the 1- and 5-positions.



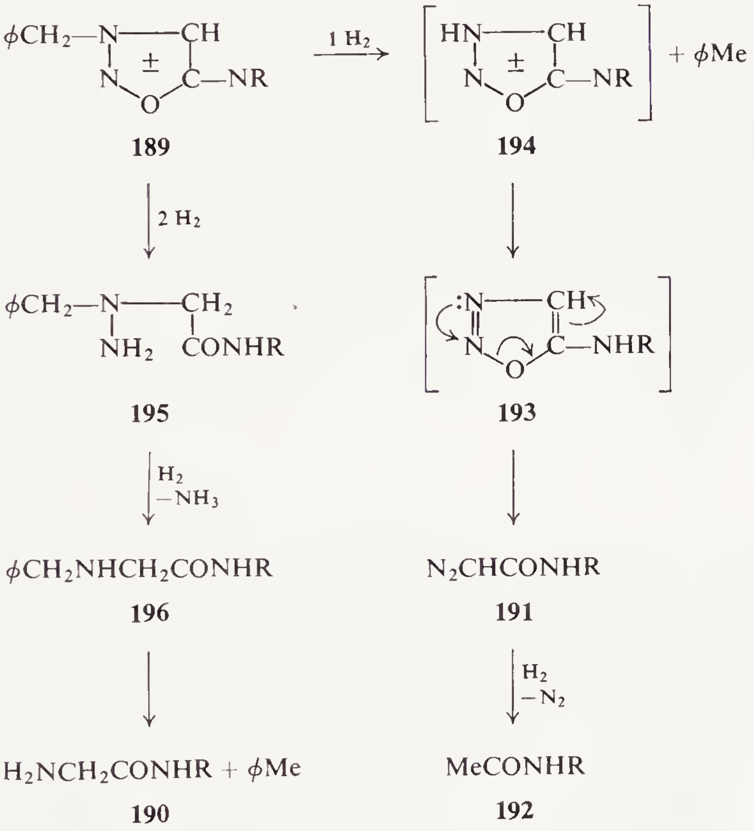
(88)

Hydrogenolysis of *N*-carbamoylsydnone imine **186** essentially follows an analogous course, except that while free base yields principally *N*-carbamoyl α-hydrazino acid amide **187**, the hydrochloride gives the amino acid amide derivative **188** by further hydrogenation. However, hydrogenolysis of *N*-phenylcarbamoyl-3-phenylsydnone imine **186** (R = R″ = Ph, R′ = H), free base or hydrochloride invariably affords amino acid amide **188** (R = R″ = Ph, R′ = H), as shown in Eq. (89).



(89)

An interesting example of sydnone imine hydrogenolysis was uncovered by Daeniker and Druey.[206] When 3-benzylsydnone imine or its *N*-acetyl derivative **189** is subjected to hydrogenolysis, debenzylation takes place and various products are obtained, depending on the nature of the starting material and reaction conditions. For example, hydrogenolysis of 3-benzylsydnone imine hydrochloride **189** ($R = H_2Cl$) in ethanol affords glycinamide **190** and chloroacetamide, while *N*-acetyl-3-benzylsydnone imine **189** (R = Ac) provides *N*-acetyldiazoacetamide **191** (R = Ac) and diacetamide **192** (R = Ac). As a possible hydrogenolysis mechanism for *N*-acetyl derivatives Daeniker and Druey postulated the formation of an unknown aromatic 1,2,3-oxadiazole intermediate **193** which isomerizes to diazoacetamide, as shown in Eq. (90).



(90)

Formation of glycinamide hydrochloride **190** from 3-benzylsydnone imine hydrochloride may be attributed to hydrogenolytic degradation of **194** or **193** via α-hydrazinoacetamide or to the sequence **189** → **195** → **196**, shown in Eq. (90), followed by debenzylation.

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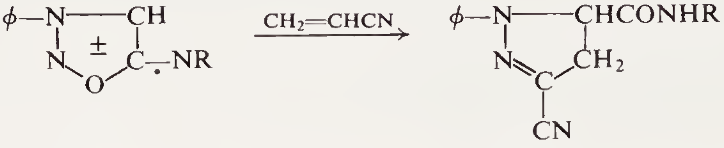
[206] H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **46**, 805 (1963).

iii. Addition. Assuming the structural analogy between sydnone and sydnone imine, it is natural to anticipate a 1,3-dipolar addition with sydnone imine. However, only one attempt, by Vasil'eva and Yashunskii,[207] has been reported. Thus, *N*-methoxycarbonyl and *N*-benzoyl-3-phenylsydnone imine **197** (R = COOMe and COPh), on heating with acrylonitrile in toluene, afford pyrazoline derivatives **198**, as shown in Eq. (91).

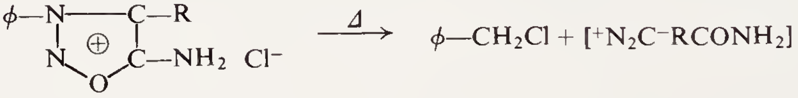


197 **198**

(91)

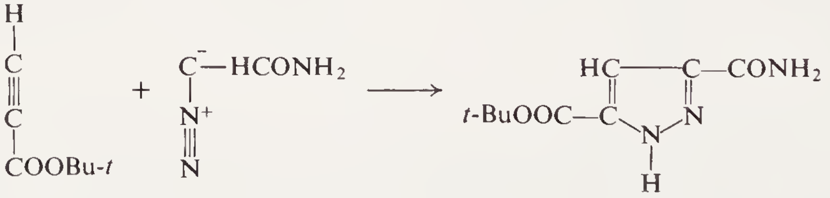
In contrast with sydnones, carbon dioxide elimination is not involved in this reaction. It has been suggested that acrylonitrile first attacks the 4-position followed by fission of the oxygen–nitrogen bond and recyclization by bond formation between the nitrogen and carbon atoms.

iv. Pyrolysis. Daeniker[208] proposed that the rate determining first step in the pyrolysis of 3-benzylsydnone imine hydrochloride **172**, in an inert solvent or without solvent, is the formation of diazoacetamide **199** [Eq. (92)]. The intermediate **199** could not be isolated and afforded chloroacetic acid, glycolic acid, or amide on subsequent reaction. The intermediacy of diazoacetamide **199** was demonstrated by heating **172** in isopropanol in the presence of *t*-butyl propiolate to form the pyrazole derivative **200** by 1,3-dipolar addition, as shown in Eq. (93).



172 **199**

(92)



200

(93)

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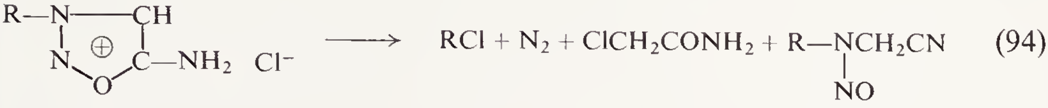
[207] V. F. Vasil'eva and V. G. Yashunskii, *Zh. Obshch. Khim.* **34**, 702 (1964); *Chem. Abstr.* 60, 13236 (1964).

[208] H. U. Daeniker, *Helv. Chim. Acta* **47**, 2421 (1964).

On the basis of kinetic studies, Kholodov[209] postulated that in the pyrolysis of sydnone imine hydrochlorides **201** in nonaqueous solvent the rate determining step is the attack of chloride ion at C-4 with fission of the N-3—C-4 bond [Eq. (94)].



201

(94)

4. *Applications*

Studies on the applications of sydnone imine derivatives are almost limited to biological or pharmacological tests. A wide variety of sydnone imine derivatives have been synthesized and examined for antifilarial,[22] antipyretic,[72, 184, 191, 192, 210] analgesic,[72, 175, 184, 191, 192, 210] antiinflammatory,[72, 184, 210] antiallergic,[211] hypotensive,[179, 210] anticonvulsive,[175, 179] spasmolytic,[175] antiblastomic,[211] chemotherapeutic,[197, 212] and anticancer activity.[169] A number of sydnone imine derivatives are reported to have marked biological activity. For example, Daeniker and Druey[72, 184] reported that sydnone imine salts and *N*-acyl derivatives possess analgesic and antipyretic activity. It is recommended that the reader refer to the recent review by Kier and Roche[12] for further details concerning the medicinal chemistry of sydnone imines.

III. Other Mesoionic Compounds

A. Mesoionic Compounds with Two Heteroatoms

1. *Mesoionic Oxazole Derivatives*

a. 4-Oxo-3,4-dihydro-1,3-oxazoles. Compounds of this type have not been prepared. An attempt to prepare a reasonable precursor **202** by the reaction of *N*-phenylbenzimidoyl chloride and glycolic acid gave instead a rearranged product **203**, as shown in Eq. (95).[213]

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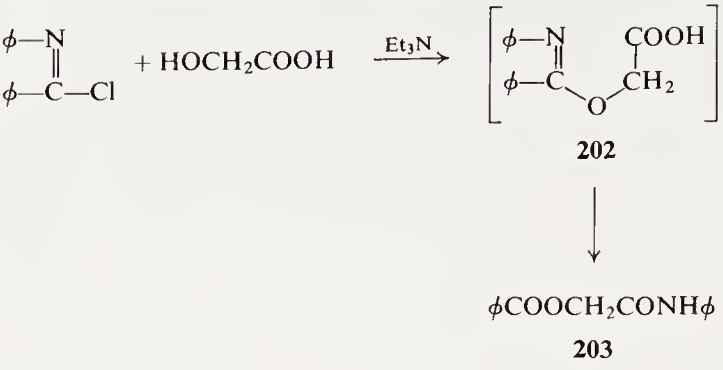
[209] L. E. Kholodov and V. G. Yashunskii, *Zh. Obshch. Khim.* **35**, 1551 (1965); *Chem. Abstr.* **63**, 17839 (1965).

[210] British Patent 962,293; *Chem. Abstr.* **61**, 9504 (1964).

[211] V. A. Chernov and V. G. Yashunskii, *Dokl. Akad. Nauk SSSR* **155**, 220 (1964).

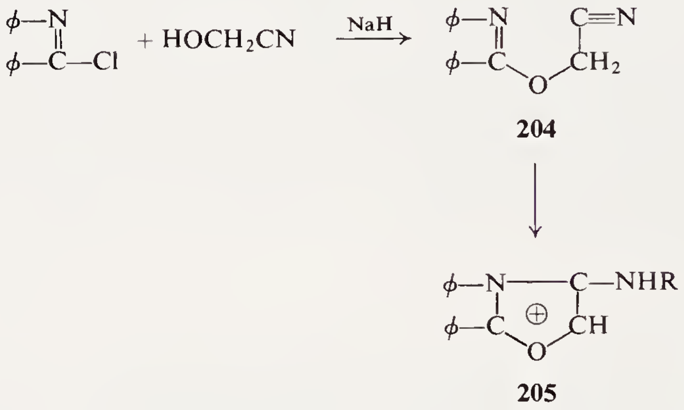
[212] W. H. Nyberg and C. C. Cheng, *J. Med. Chem.* **8**, 531 (1965); *Chem. Abstr.* **63**, 11541 (1965).

[213] Masaki Ohta and Toshiyasu Mase, unpublished work (1967).



(95)

b. 4-Imino-3,4-dihydro-1,3-oxazoles. Reaction of *N*-phenylbenzimidoyl chloride and glycolonitrile gave **204** which, when treated with hydrogen chloride, picric acid, or trichloroacetyl chloride, gave the corresponding derivatives **205** (R = H Cl^-, H $C_6H_2N_3O_7^-$, and $COCCl_3$ Cl^-), as shown in Eq. (96).[213]



(96)

c. 5-Oxo-3,5-dihydro-1,3-oxazoles. Fused mesoionic oxazolidone **206** was obtained from *N*-carboxymethylpyridone **207** and acid anhydrides [Eq. (97)]. In this reaction, the products were invariably acylated at the 3-position.[214–216]

Compound **206** decomposed with an evolution of carbon dioxide when treated with water and was converted to 2-pyridone on acid hydrolysis. Treating **206** with benzylamine also caused cleavage of the ring to give a benzylamide derivative **208**.

Monocyclic mesoionic oxazolidone **209** or **210** can similarly be formed by treating *N*-substituted *N*-acylaminoacetic acid **211** with acid anhydrides or

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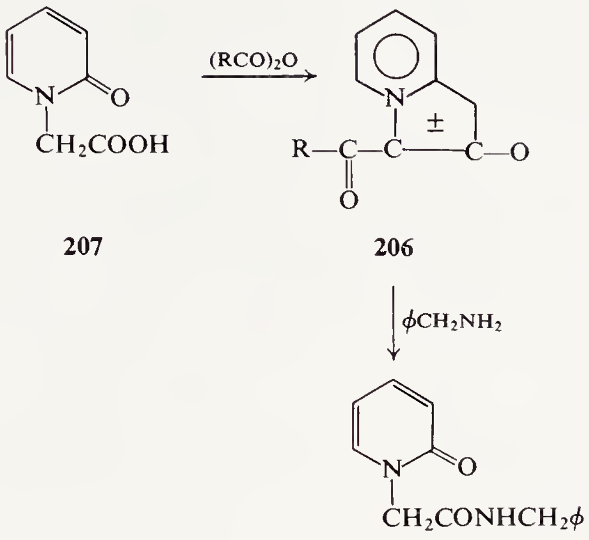
[214] A. Lawson and D. H. Miles, *Chem. Ind.* (*London*) p. 461 (1958).

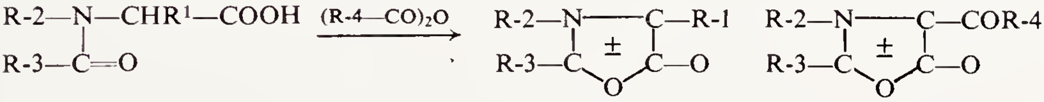
[215] A. Lawson and D. H. Miles, *J. Chem. Soc.* p. 2865 (1959).

[216] A. Lawson and D. H. Miles, *J. Chem. Soc.* p. 1945 (1960).



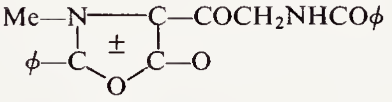
207 **206** **208** (97)

chlorides [Eq. (98)]. In this case, however, the monocyclic species appear to be less stable than the fused ring derivative **206**. Consequently, they were isolated as such only in a few exceptional cases.



211 **209** **210** (98)

Thus, the 3-methyl-2,4-diphenyl derivative **209** (R-1 = R-3 = Ph, R-2 = Me) is the only alkyl or aryl derivative which has so far been prepared.[217] When the aminoacetic acids **211** are unsubstituted on the α-carbon atom, the products are always acylated under the reaction conditions to give 4-acyl compounds **210** similar to the case of fused ring **206**. The oxazolidones substituted by a strongly electron-withdrawing acyl group appear to be relatively stable, thus, **210** with trifluoroacetyl,[213, 218, 219] chloroglyoxyloyl,[116] mono-, di-, and trichloroacetyl,[213] and methoxyglyoxyloyl[213] groups at the 4-position have been isolated. When *N*-benzoylsarcosine was treated with acetic anhydride or with dicyclohexylcarbodiimide, a compound assumed to be **212** was obtained.[219]



212

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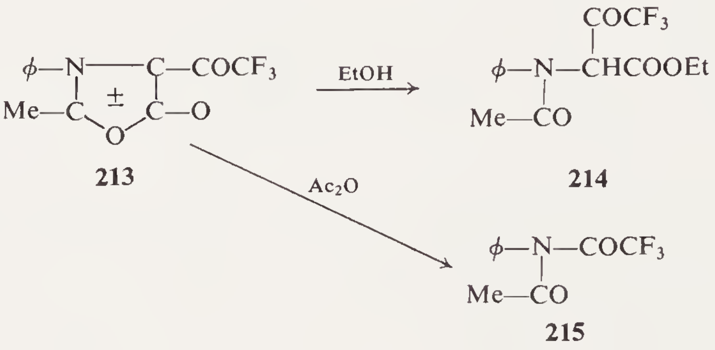
[217] R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Angew. Chem.* **76**, 185 (1964).

[218] G. Singh and S. Singh, *Tetrahedron Letters* p. 3789 (1964).

[219] C. V. Greco, R. P. Gray, and V. G. Grosso, *J. Org. Chem.* **32**, 4101 (1967).

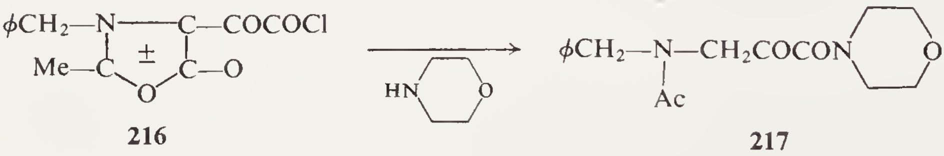
The acetylated oxazolidones of type **210** generally exhibit an ultraviolet absorption maximum at ca. 310 $m\mu$[213,219] and have two infrared bands at 1780–1880 and 1580–1620 cm^{-1}.[213,218–220] The NMR signals of the 2- and 3-methyl groups are located at ca. τ 7.5 and 6.1, respectively.[219,220]

Trifluoroacetyloxazolidone **213** reacts readily with ethanol to afford an ester **214** with ring opening, while heating with acetic anhydride causes a Dakin-West type reaction giving an *N*-acylamino ketone **215** [Eq. (99)].[218] It was suggested that the Dakin-West reaction in general proceeds through a mesoionic intermediate.[218]



(99)

Reaction of the chloroglyoxyloyl derivative **216** and aniline gives the corresponding anilide with retention of the mesoionic ring, while reaction of **216** and morpholine gives an amide **217** by ring cleavage and decarboxylation, as shown in Eq. (100).[213]



(100)

The 1,3-dipolar cycloaddition of **209** has been thoroughly investigated by Huisgen *et al.*[217] Compounds with an activated double or triple bond react with **209** at a temperature of 50°–100°C to give Δ^2-pyrroline and pyrrole derivatives (**218**[221] and **219**[217]), respectively, by the elimination of carbon dioxide as shown in Eq. (101).

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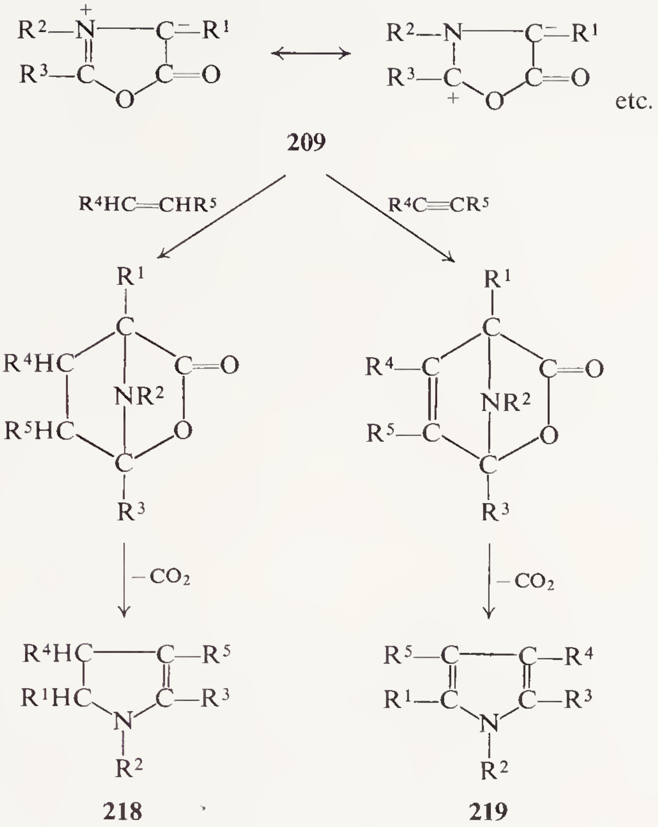
[220] W. D. Burrows, *J. Org. Chem.* **31**, 3435 (1966).

[221] H. Gotthardt, R. Huisgen, and F. C. Schaefer, *Tetrahedron Letters* p. 487 (1964).



(101)

The 3-methyl-2,4-diphenyl derivative **220** reacts similarly with carbonyl compounds,[222] but the oxazoline **221** formed initially by decarboxylation of an intermediate **222** rearranges further to give *N*-benzoylalkenylamine **223** [Eq. (102)]. Reaction with an excess of diethyl mesoxalate gives a bicyclic bisadduct **224**, which must have been formed by addition of another molecule of mesoxalate to the intermediate ylid **221**, as well as a compound of type **223**. Compound **224** is converted to β-lactone **225** by mild acid treatment. When **220** is treated with acetaldehyde at 0°C, bisadduct **226** is formed without expelling carbon dioxide. The formation of **226** presumably involves the addition of another molecule of acetaldehyde to intermediate **222** to give **227**, followed by its rearrangement.

Reactions of **220** with a variety of heteromultiple bonds other than carbonyl have been reported [Eq. (103)].[223] For example, **220** reacts with carbon disulfide at a temperature as low as 20°C to give a high yield of a mesoionic thiazolidine-5-thione **228**. It reacts similarly with carbon oxysulfide and phenyl isothio-

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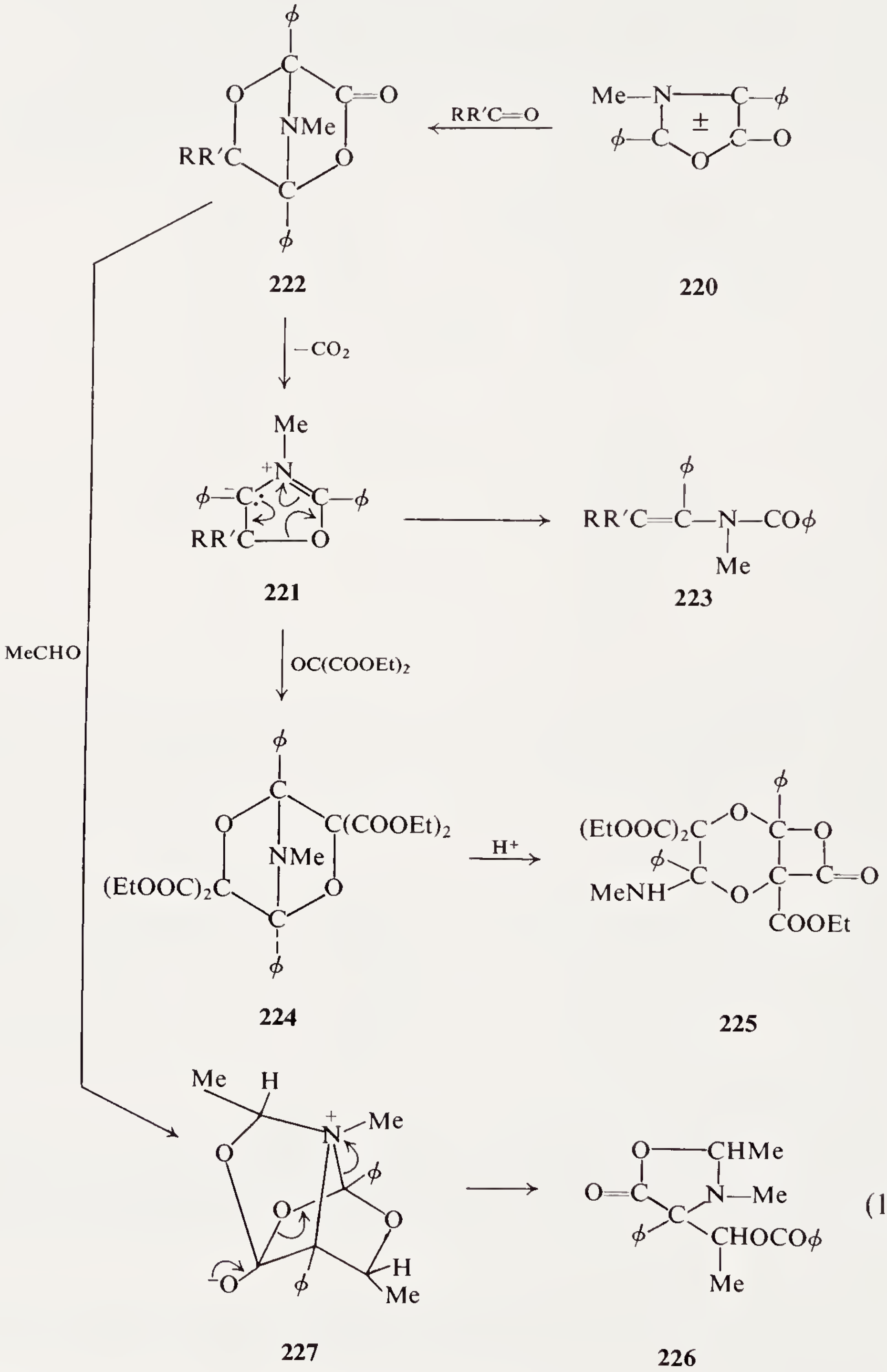
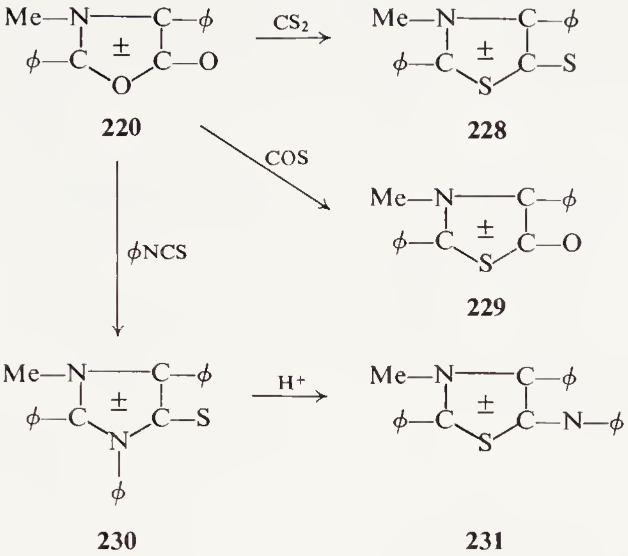
[222] R. Huisgen and E. Funke, *Angew. Chem.* **79**, 320 (1967).

[223] R. Huisgen, E. Funke, F. C. Schaefer, H. Gotthardt, and E. Brunn, *Tetrahedron Letters* p. 1809 (1967).

cyanate to give mesoionic oxothiazole **229** and mesoionic imidazoline-4-thione **230**, respectively. The latter rearranges to mesoionic iminothiazole **231** upon treatment with hydrochloric acid.

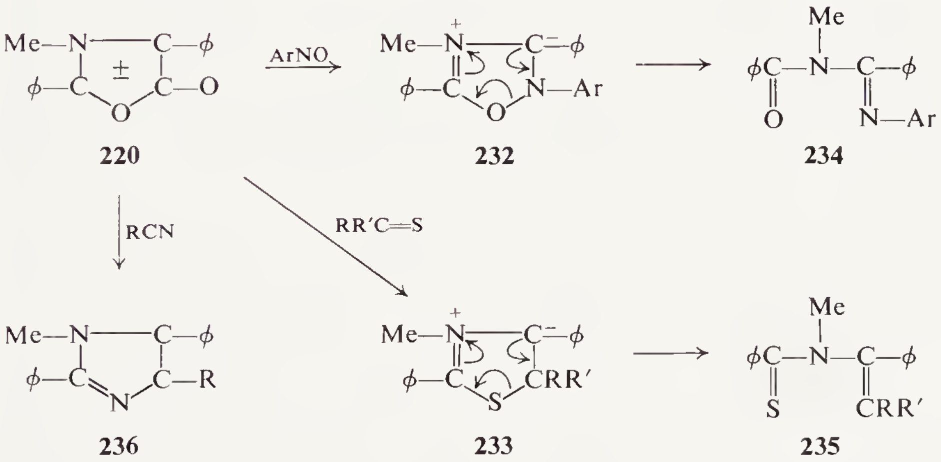


(102)



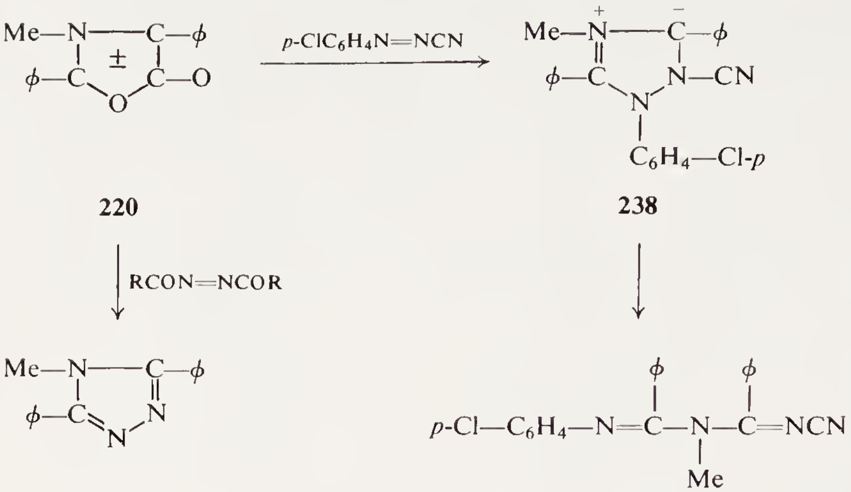
(103)

In reactions of **220** with nitrosobenzene and thiocarbonyl compounds, the intermediate ylids **232** and **233** rearrange to give **234** and **235**, respectively. Nitriles react analogously with **220**, giving the corresponding imidazole derivatives **236** [Eq. (104)]. Interestingly, the reaction of **220** and *p*-nitrobenzonitrile affords an *N*-acylamidine **234** (Ar = *p*-NCC_6H_4—), a reaction parallel to that with nitrosobenzene, showing that addition takes place at the nitro rather than the nitrile group.



(104)

Reacting **220** and *p*-chlorobenzenediazocyanide gives the ring-cleaved product **237** from the intermediate ylid **238**, whereas reaction with azocarboxylates and similar compounds gives triazole derivatives **239** via loss of acyl groups as shown in Eq. (105).

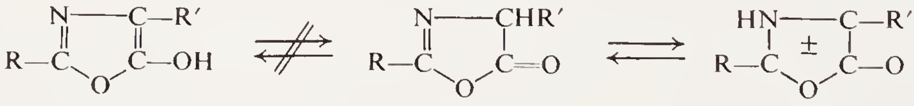


220 **238** **239** **237**

(105)

Inasmuch as **209** is generally unstable it is usually not isolated in these reactions but is most often prepared by warming a mixture of acylaminoacetic acid and acid anhydride in the presence of a 1,3-dipolarophile, and reacted *in situ.* Consequently, it may be concluded that 1,3-dipolar cycloaddition proceeds more readily than the Dakin-West reaction. Since high yields are generally attained in these dipolar addition reactions, they may prove to be important pathways for the preparation of a variety of heterocyclic compounds.

Azlactones **240** likewise react with compounds possessing activated double or triple bonds to give the corresponding pyrrolines and pyrroles[224,225] at a slightly higher temperature than observed for mesoionic oxazole **209**. It has been proposed that azlactone **240** is in equilibrium with its mesoionic isomer **241**, as shown in Eq. (106), and that the latter, present in low concentration, reacts as the 1,3-dipole to give the addition products.



242 **240** **241**

(106)

The possibility that azlactone **240** or its enol form **242** reacts with a dipolarophile could be ruled out since 4,4-disubstituted azlactone did not react with acetylenedicarboxylate even at higher temperatures. A Diels-Alder rather than

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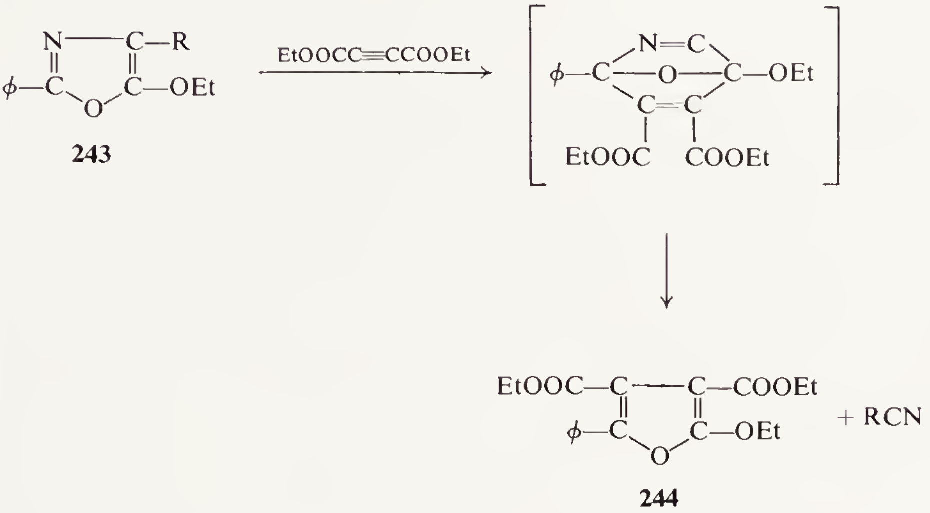
[224] R. Huisgen, H. Gotthardt, and H. O. Bayer, *Angew. Chem.* 76, 185 (1964).

[225] R. Huisgen, H. Gotthardt, and H. O. Bayer, *Tetrahedron Letters* p. 481 (1964).

a 1,3-dipolar addition took place in the reaction of ethoxyoxazole **243** and acetylenedicarboxylate, giving a furan derivative **244**, as shown in Eq. (107).



(107)

A most interesting and entirely new type of reaction, suggesting that the mesoionic oxazolidone **209** is in equilibrium with an open-chain isomer [Eq. (108)], has been found to occur.[226] When **220** is heated with an azomethine, an azetidinone **245** is formed. Similarly, the reaction of **220** and diisopropylcarbodiimide gives an azetidinone imine **246**. These results are reasonably interpreted only when an equilibrium between **220** and an acylaminoketene **247** is postulated.[226] Further, the reaction of **220** and an enamine gives **248**, the formation of which may similarly be considered to involve the generation of **249** by addition of enamine to acylaminoketene **247** followed by ring cleavage to **248**. Heating **220** in xylene gives an allene derivative **250**, which may be regarded as the fragmentation product of dimer **251** from **247**. The presence of ketene tautomer **247**, however, could not be observed spectroscopically. In this connection, it may be worthwhile to recall that an analogous ketene formulation has been regarded as an important contributor to the resonance hybrid of sydnone (Section II,A,2,*e*).

d. 5-Imino-3,5-dihydro-1,3-oxazoles. Compounds of this type have been proposed as intermediates in some reactions of Reissert compounds, but they appear remarkably unstable. Attempts at isolation and characterization of these substances, their derivatives, or their salts have not been successful.[151,227]

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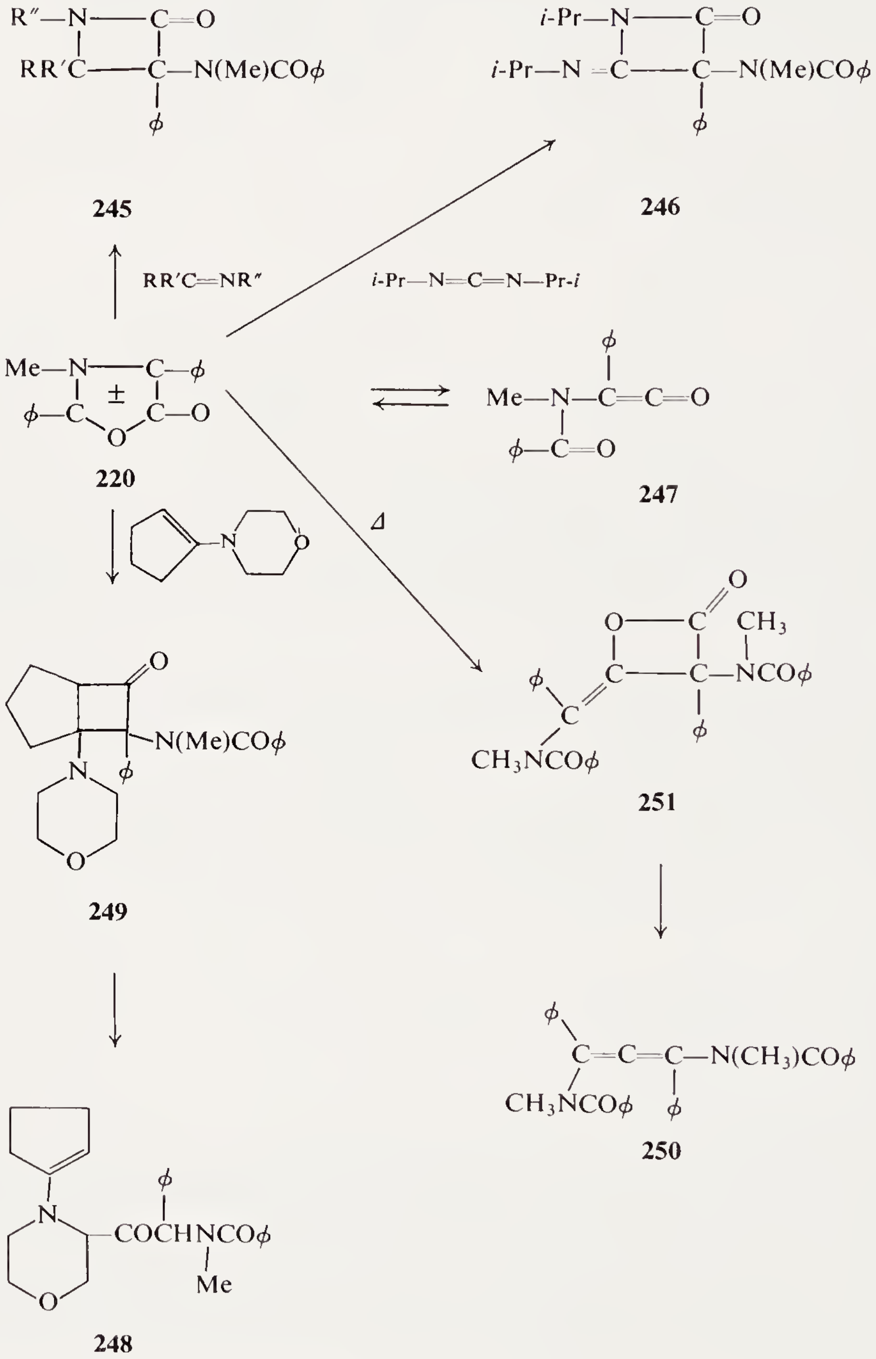
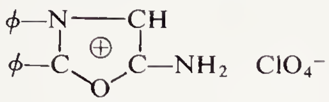
[226] R. Huisgen, E. Funke, F. C. Schaefer, and R. Knorr, *Angew. Chem.* **79**, 321 (1967).

[227] R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.* **77**, 5024 (1955); T.-K. Liao and W. E. McEwen, *J. Org. Chem.* **26**, 5257 (1961); E. K. Evanguelidon and W. E. McEwen, *ibid.* **31**, 411 (1966).

Recently, however, a crystalline perchlorate which appears to be represented by **252** could be isolated when *N*-benzoylanilinoacetonitrile was treated with hydrogen chloride followed by silver perchlorate.[213]



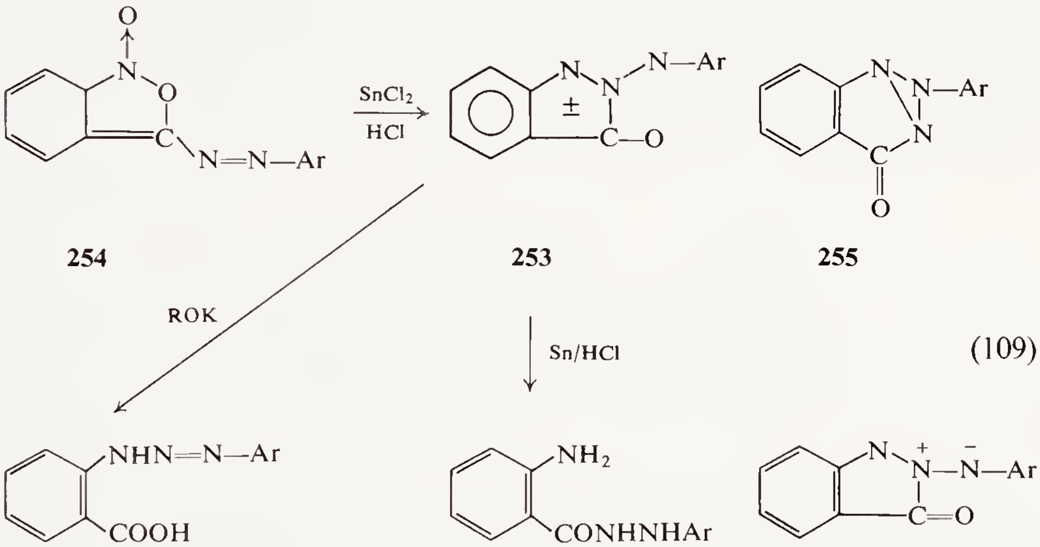
(108)



252

2. *Mesoionic Pyrazole Derivatives*

a. Fused 3-Oxopyrazole. A mesoionic structure **253** was proposed[228] for the compounds formed by stannous chloride reduction of 3-arylazoanthranil 1-oxides **254**. A bridged structure **255** was originally assigned [Eq. (109)].[229] The substances do not seem to satisfy the mesoionic requirement as defined by Baker *et al.*[8] Thus, it appears doubtful that mesoionic structure **253** conforms to the observed properties more adequately than a betaine structure **256**. The compounds show a polarized infrared carbonyl band at 1655 cm^{-1}. They are soluble in hot concentrated sulfuric, hydrochloric, and nitric acids; the free base is regenerated on dilution. The action of alcoholic potassium hydroxide gives diazoaminobenzenecarboxylic acid **257**, while tin and hydrochloric acid give aminobenzoylarylhydrazines **258**.



254 **253** **255**

(109)

257 **258** **256**

3. *Mesoionic Imidazole Derivatives*

a. 4-Oxo-3,4-dihydro-1H-imidazoles. A red compound **259** (Besthorn's red), prepared by heating quinaldic acid **260** with acetic anhydride, has been known for a long time [Eq. (110)].[230]

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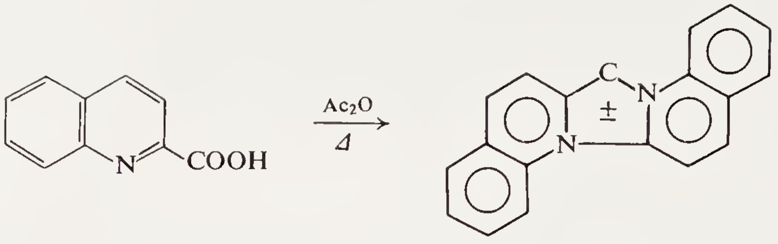
[228] M. S. Gibson, *Tetrahedron* **15**, 1377 (1962).

[229] F. D. Chattaway and A. J. Walker, *J. Chem. Soc.* p. 323 (1927).

[230] E. Besthorn and J. Ibel, *Ber.* **37**, 1236 (1904).

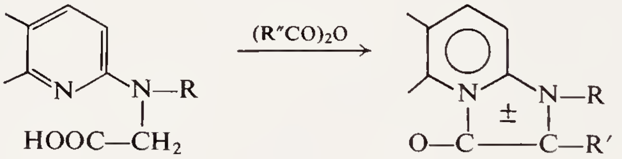


(110)

260 **259**

Knollpfeiffer and Schneider[231] first suggested that **259** would best be represented by a resonance hybrid of a number of betaine structures. This view was supported by Hammick and Roe[232] following a study of its infrared spectrum, which shows a polarized carbonyl band at 1624 cm^{-1}. In contrast, its hydrochloride has a carbonyl band at 1724 cm^{-1} arising from *N*-protonation and consequent reduction of carbonyl polarization.

Similar fused rings **261** are formed when *N*-substituted *N*-2-pyridyl- (or quinolyl-) glycines are treated with acid anhydride, as shown in Eq. (111).[215] The principal products are those in which the 2-position is acylated (**261**, R′ = COR″). In the case of quinolyl derivatives, ring closure can be effected by heating with hydrochloric acid instead of acid anhydride to give **261** (R = H). This shows the remarkable stability of **261**.



(111)

262 **261**

Reacting phenacylisoquinolinium betaine **263** and phenyl isocyanate gives another betaine **264**, which, when treated with potassium ferricyanate, affords a fused mesoionic ring **265**, isomeric with **261** [Eq. (112)].[233] The infrared band of the *exo* carbonyl of **265** appears at 1670 cm^{-1} while that of the carbonyl group of the benzoyl substituent is shifted to below 1600 cm^{-1} as a result of strong polarization. Compound **265** is stable and was unchanged by heating with hydrochloric acid or sodium hydroxide.

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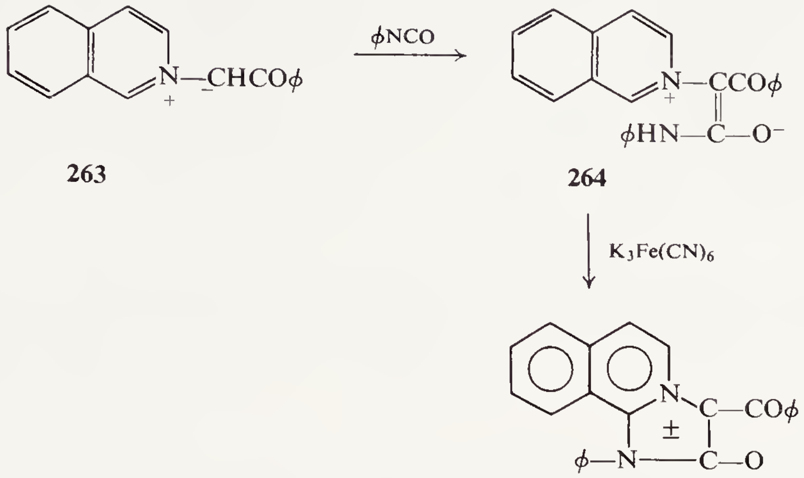
[231] F. Knollpfeiffer and K. Schneider, *Ann.* **530**, 34 (1937).

[232] D. L. Hammick and A. M. Roe, *Chem. Ind.* (*London*) p. 900 (1953).

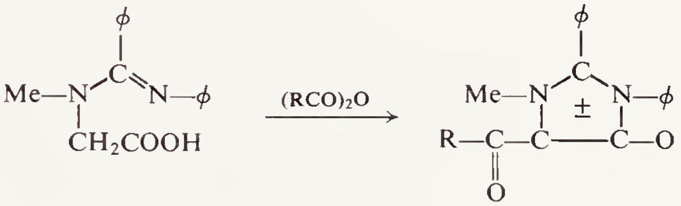
[233] M. Ohta and S. Sato, unpublished work (1966).



263 **264** **265**

(112)

The corresponding monocyclic compound **266** is similarly formed by heating *N*-(*N′*-phenylbenzimidoyl)glycine **267** with acid anhydride, as shown in Eq. (113).[215] The monocyclic **266** is also very stable. It is recovered unchanged when heated with acids, alkali, or benzylamine.

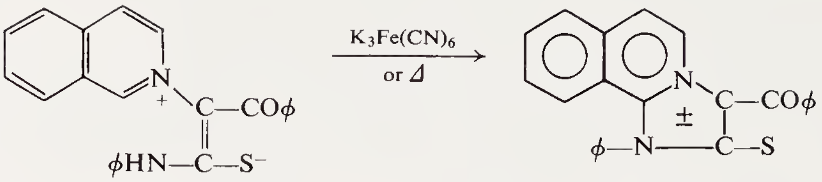


267 **266**

(113)

b. 3,4-Dihydro-1H-imidazole-4-thiones. The formation of the title compound **230** by cycloaddition of mesoionic oxazolidone **220** and phenyl isothiocyanate and its subsequent rearrangement to an iminothiazole **231** has been described (Section III,A,1,*c*).

Addition of phenyl isothiocyanate to phenacylisoquinolinium betaine **263** gives another betaine **268**. The latter undergoes cyclization and dehydrogenation when heated in toluene or treated with ferricyanate to give a fused mesoionic imidazolinethione **269**, as shown in Eq. (114).[233]

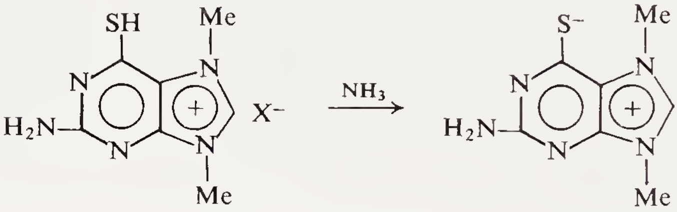


268 **269**

(114)

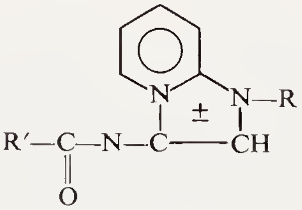
Compound **269** is orange colored and shows an infrared band at 1300 cm^{-1} which may be assigned to the thiocarbonyl group. It is stable and is unchanged by heating with acid or alkali. A methiodide is formed by treating it with methyl iodide.

Treating a purinium salt **270** with ammonia gives betaine **271**[234] which may be regarded as a mesoionic compound in which the *exo* thiocarbonyl group is external to the mesoionic imidazole ring.



270 **271**

c. *4-Imino-3,4-dihydro-1H-imidazoles.* Bristow *et al.*[235] have prepared a fused mesoionic ring of type **272** by treating *N*-2-pyridylaminoacetonitrile **273** or its corresponding aldoxime **274** with acid anhydrides or chlorides.



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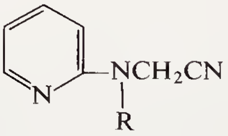

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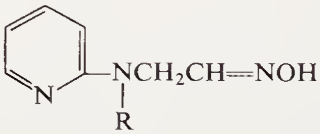

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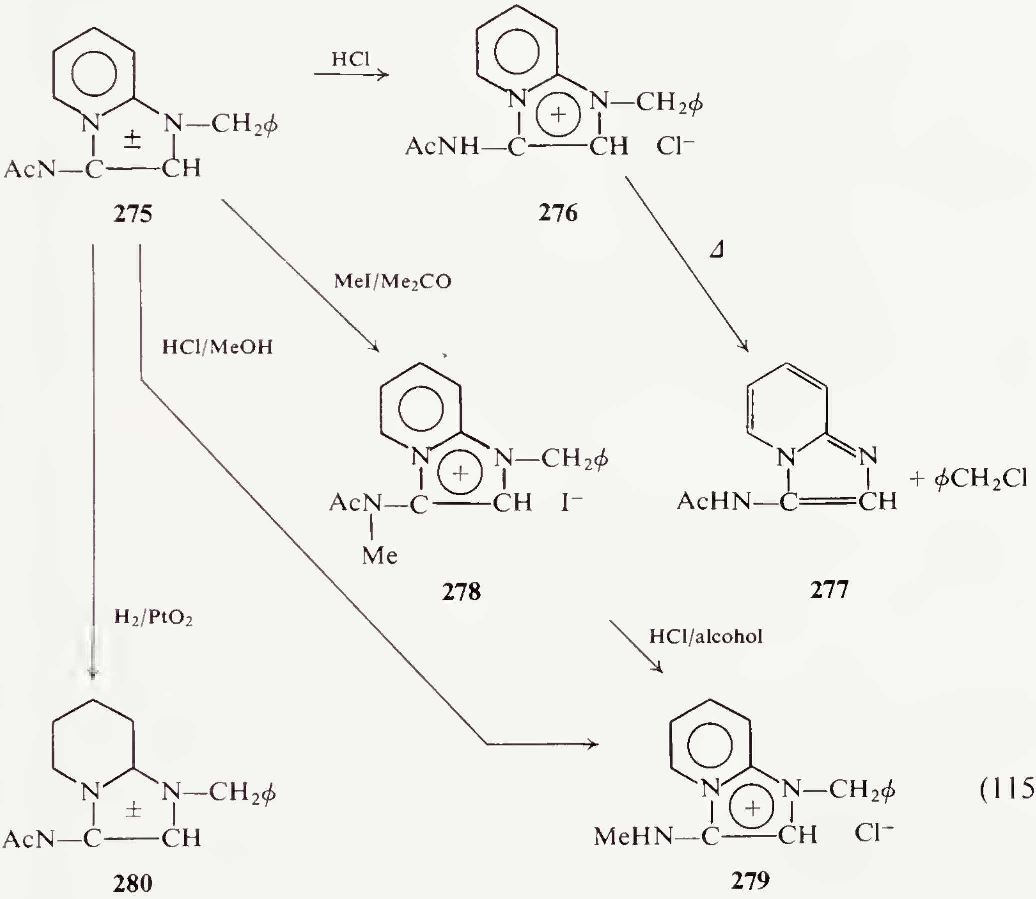
[234] H. Bredereck, H. Heise, O. Christmann, and P. Schellenberg, *Angew. Chem.* **74**, 183 (1962).

[235] N. W. Bristow, P. T. Charlton, D. A. Peak, and W. F. Short, *J. Chem. Soc.* p. 616 (1954).

Treating **273** with benzenesulfonyl chloride likewise effects cyclization, giving the corresponding *N*-benzenesulfonyl derivative **272** (R′CO = $PhSO_2$). *N*-acetyl-1-benzyl derivative **275** is stable to alkali but it regenerated the open-chain nitrile **273** (R = $PhCH_2$) upon mild acid hydrolysis. It gives a hydrochloride **276** which is pyrolyzed to benzyl chloride and pyridoimidazole derivative **277**. The methiodide **278** splits off the acetyl group on treatment with alcoholic hydrochloric acid to give pyridoimidazolium salt **279**, which is also formed by reacting **275** with methyl iodide in methanol. The pyridine ring of **275** is preferentially reduced by platinum oxide-catalyzed hydrogenation to give **280** [Eq. (115)].



(115)

4. *Mesoionic Thiazole Derivatives*

a. 4-Oxo-3,4-dihydro-1,3-thiazoles. Duffin and Kendall[236] have established the structure of the dehydration product **281** by reacting (2-pyridylthio)acetic

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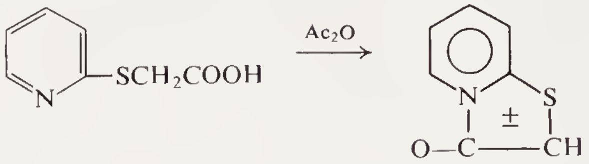
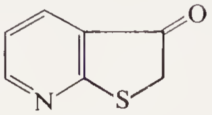
[236] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.* p. 734 (1951).

acid **282** with acetic anhydride [Eq. (116)]. Earlier, a pyridothiophene (**283**)[237] and then a ketene (**284**)[238] structure had been proposed.



(116)

282 **281**



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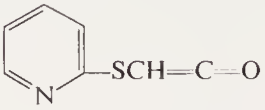
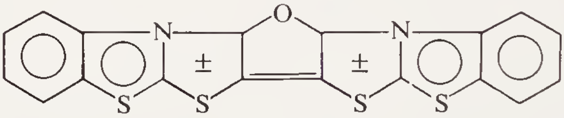


284

Analogous ring formation has since been applied to quinoline,[236] imidazole,[239,240] benzimidazole,[239] and thiadiazole[241,242] derivatives, and the corresponding fused mesoionic rings have been isolated. This ring closure reaction is accelerated by the presence of bases such as pyridine and triethylamine.[236,241] With thiazole derivatives, cyclization to mesoionic compounds could only be effected in the presence of a base; in its absence a pigment of unknown structure was formed. Structure **285** was recently proposed for the pigment formed from (benzothiazolylthio)acetic acid.[242]



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In the case of (pyridazinylthio)acetic acid, even the action of a mixture of acetic anhydride and pyridine gave a pigment, while the mesoionic ring was formed only when it was treated with a mixture of acetic anhydride, pyridine, and triethylamine.[243] No ring formation occurs from oxadiazole, benzoxazole, or triazole derivatives.[241]

[237] E. Koenig and H. Geisler, *Ber.* **57**, 2076 (1924).

[238] A. E. Tschitschibabin and N. N. Woroshtzow, Jr., *Ber.* **66**, 364 (1933).

[239] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.* p. 361 (1956).

[240] P. M. Kochergin, *Zh. Obshch. Khim.* **31**, 3267 (1961); *Chem. Abstr.* **57**, 2208 (1962).

[241] M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Japan* **33**, 1394 (1960).

[242] N. Cagnoli and V. Bellavita, *Gazz. Chim. Ital.* **95**, 615 (1965).

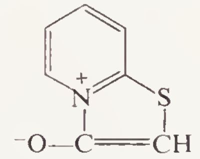
[243] M. Ohta and K. Kishimoto, *Bull. Chem. Soc. Japan* **34**, 1402 (1961).

Compound **281** could be prepared by reacting 2-acetylthiopyridine **285** and monochloroacetic acid or monochloroacetamide, or by reacting pyridylthioacetamide **287** and acetyl chloride [Eq. (117)].[244, 245] The synthesis fails with **287** and acetic anhydride.[236]

(117)

286 **287**

These fused mesoionic thiazoles have an infrared carbonyl band at 1630–1650 cm^{-1}.[241, 243] The positions of their ultraviolet absorption maxima are sensitive to solvent polarity,[239, 246] and it has been proposed that in the resonance of **281** (**288** ↔ **289** ↔ **290**, etc.) an important contribution is made by **290**. However, it was pointed out that structures **288** and **289** are of lower energy than **290**.[246]



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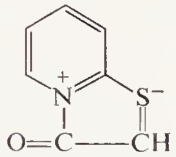

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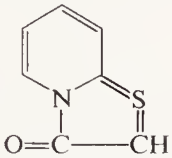

290

This proposal and the properties of similar compounds led Duffin and Kendall[247] to favor structures such as **290** as representative and to suggest that they should no longer be classified as mesoionic compounds. However, although the contribution of structure **290** may certainly be important, contributions from other forms such as **288** and **289** also appear not to be negligible. These species are consequently classified as mesoionic compounds in this review.

The reactions of compounds of this type have been most extensively investigated with benzimidazole derivatives **291**, as shown in Eq. (118).[239] While **291** is unchanged on heating with water, acid-catalyzed ethanolysis causes ring cleavage to give the ethyl ester of the starting material **292**. Acid-catalyzed hydrolysis yields a compound believed to be **293**, and **292**. Alkaline hydrolysis provides mercaptobenzimidazole **294** and benzimidazolidone **295**. Reduction of **291** with zinc and hydrochloric acid proceeds readily, furnishing

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[244] H. Kato, K. Tanaka, and M. Ohta, *Bull. Chem. Soc. Japan* **39**, 1248 (1966).

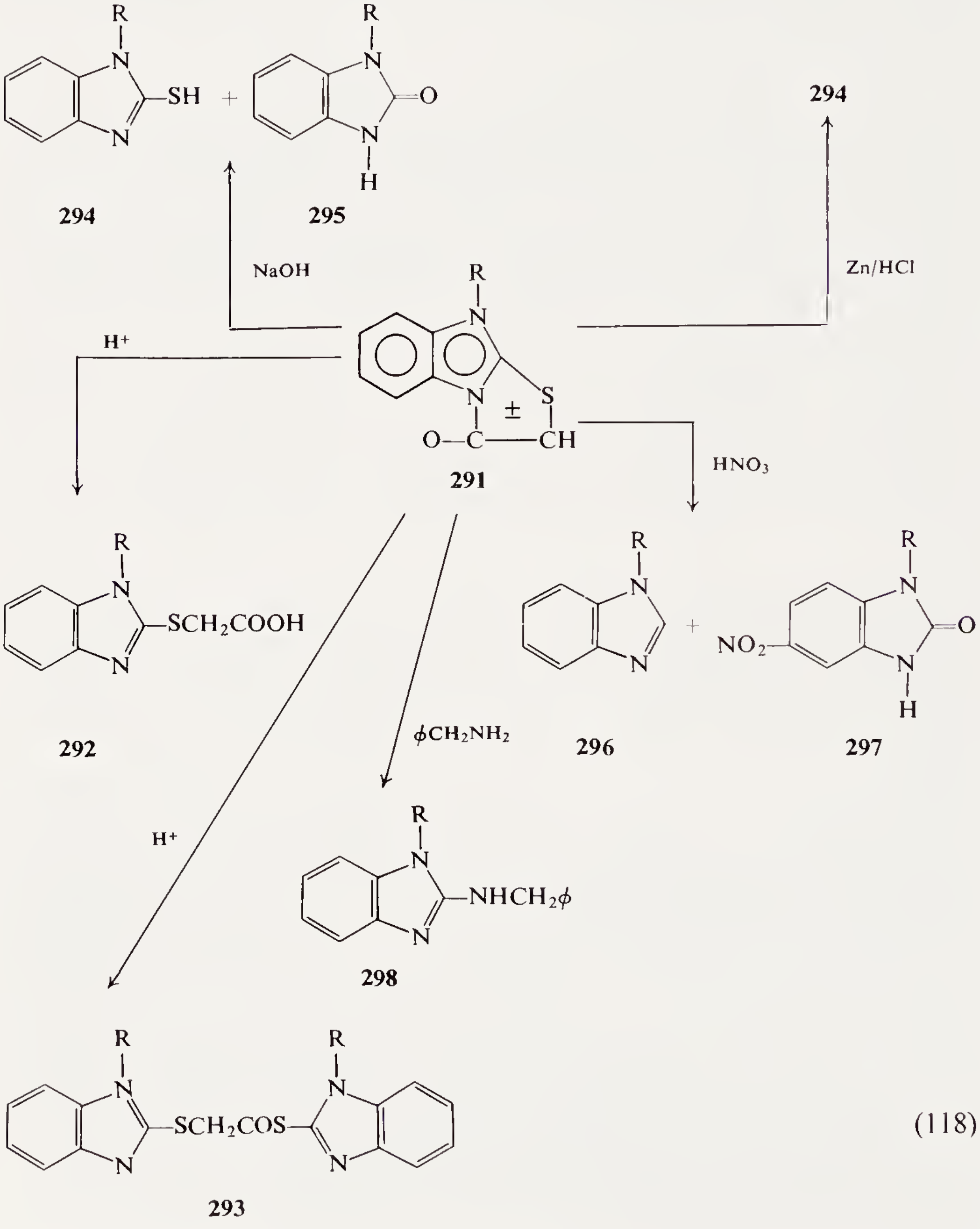
[245] H. Kato, K. Tanaka, and M. Ohta, *Bull. Chem. Soc. Japan* **35**, 1901 (1962).

[246] E. B. Knott, *J. Chem. Soc.* p. 937 (1955).

[247] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.* p. 3189 (1956).

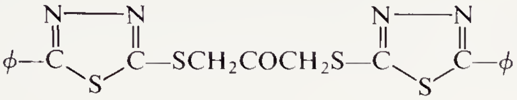
294. The mesoionic ring is not nitrated by nitric acid, but the ring cleaves to give benzimidazole **296** and nitrobenzimidazolidone **297**. The action of benzylamine also causes ring cleavage, producing benzylaminobenzimidazole **298**.

Similar reactions seem to occur with other fused mesoionic thiazoles,[236] but the thiazolo and benzothiazolo analogs, when treated with 50% aqueous sulfuric acid or heated with pyridine, give symmetrical ketones of type **299**.



(118)

Reaction of the pyridazo analog and phenylhydrazine is reported to give pyridazinylthioacetohydrazide **300**.[243]



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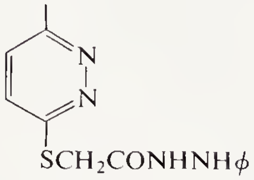
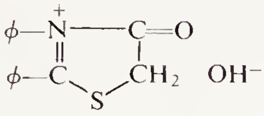


300

A monocyclic compound closely related to this type of ring system, a quaternary salt formed **301** by reacting thiobenzanilide and bromoacetic acid, has been described.[248] The correct structure of this compound was found to be (benzoylthio)acetanilide **302**.[249]

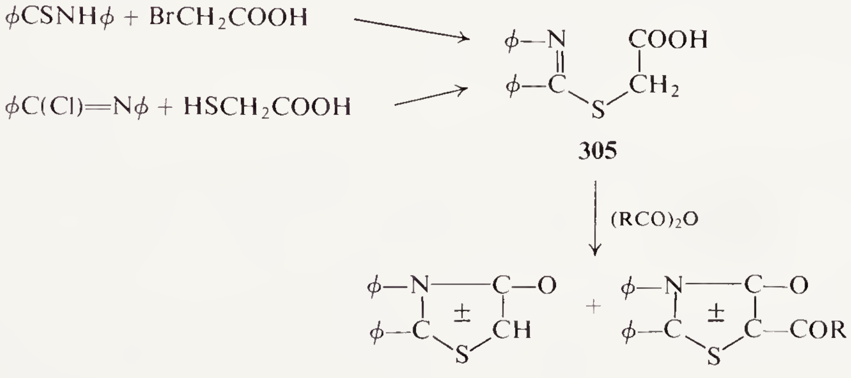


301

$\phi COSCH_2CONH\phi$

302

Monocyclic mesoionic thiazoles **303** and/or **304** were formed by treating **305** with acid anhydride. Compound **305**, in turn, was formed by reacting thiobenzanilide and bromoacetic acid, or *N*-phenylbenzimidoyl chloride and thioglycolic acid, as shown in Eq. (119).[249] In the first reaction, when either acetic anhydride or chloroacetic anhydride is employed as the only condensation reagent, the product is always acylated at the 5-position to give **304**. Both the unacylated product **303** and **304** are obtained by the action of acetic anhydride



(119)

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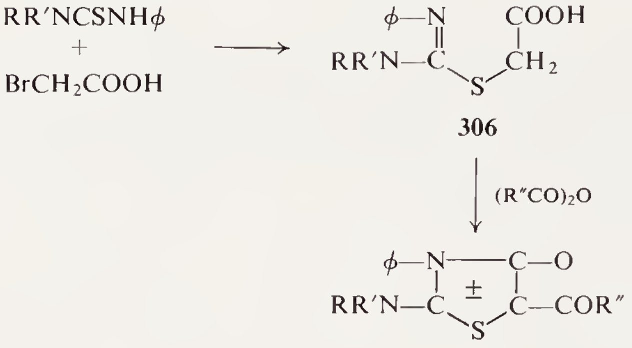
[248] B. Holmberg, *Arkiv. Mineral Geol.* **24A**, 17 (1947); *Chem. Abstr.* **45**, 581 (1957).

[249] M. Ohta, H. Chosho, C. Shin, and K. Ichimura, *Nippon Kagaku Zasshi* **85**, 440 (1964).

and pyridine. Unacylated **303** is the sole product when acetic anhydride and triethylamine are used. Other variously substituted derivatives have been prepared by similar methods.[249, 250]

As shown in Eq. (120), the reaction of *N*-phenyl-*N*,*N*′-disubstituted thiourea and bromoacetic acid gives intermediate **306**, which, on treatment with acid anhydride in the presence or absence of triethylamine, affords 2-disubstituted amino-5-acyl derivative **307**.[251]

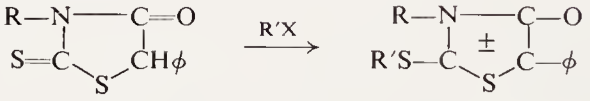


306

307

(120)

When the anion of *N*-substituted rhodanine **308** is alkylated with methyl iodide or benzyl chloride, a mesoionic ring **309** with a methylthio or benzylthio group at the 2-position is formed, as shown in Eq. (121).[252]



308 **309**

(121)

The structure of **309** ($R = NH_2$, $R' = Me$) was unambiguously established by X-ray analysis. The bond distance thus obtained is shown in Fig. 4.[252] The following points merit special mention:

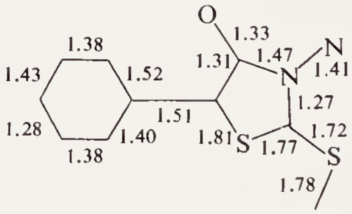


FIG. 4. Bond distance of 4-oxo-3-amino-2-methyl-5-phenyl-3,4-dihydro-1,3-thiazole. [G. Isaksson and J. Sandström, *Acta Chem. Scand.* **21**, 442 (1967)].

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[250] Z. Takayanagi, H. Kato, and M. Ohta, *Bull. Chem. Soc. Japan* **40**, 2930 (1967).

[251] M. Ohta and S. Sato, *Nippon Kagaku Zasshi* **89**, 199 (1968).

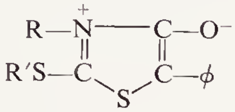
[252] G. Isaksson and J. Sandström, *Acta Chem. Scand.* **21**, 442 (1967).

(*1*) The C-4—C-5 bond length (1.31 Å) almost equals that of a normal C=C double bond.

(*2*) The C-4—O-8 bond length (1.33 Å) is remarkably long, in strong contrast to the bond length of the exocyclic C—O bond of sydnone (1.20 Å).

(*3*) The C-2—N-3 bond (1.27 Å) is very close in length to a normal double bond on the one hand, while the N-3—C-4 bond (1.47 Å) has a length similar to a normal single bond.

From these results, one may conclude that of the many canonical forms such as **310–315** which are considered to contribute to the resonance of **309**, contributions from **310–312** are important with the most important contribution from **310**.



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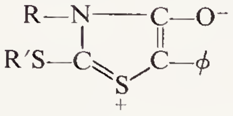

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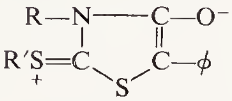

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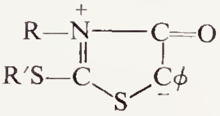

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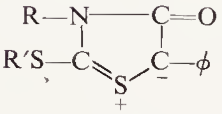

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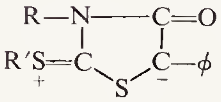


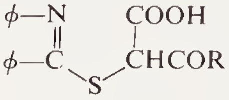
315

The bond orders and charge distributions of **309**, calculated by MO methods, agree well with the X-ray analysis results. However, the experimental dipole moment value for **309** (R = R′ = Me) was found to be 5.21 D, which deviates markedly from the value obtained by MO methods (15.3 D) and calculated for structure **310** (ca. 12 D). It has been suggested that in compounds with large separated charges, such as **310**, back polarization of the σ-bond plays an important role.

The ultraviolet spectrum of **309** is bathochromically shifted relative to rhodanine **308**, while the infrared carbonyl absorption bands of **309** (1685 cm^{-1}) are shifted to a lower frequency than those of **308** (1725–1730 cm^{-1}). When compound **309** forms a complex with sodium iodide, the infrared carbonyl absorption band is shifted to as low as 1605 cm^{-1}, indicating that sodium iodide coordinates with the carbonyl group.

The physical properties of **303** and **304** differ markedly with substitution. For example, 2,3-diphenyl and 3,5-diphenyl-2-methyl derivatives show only end absorption in the ultraviolet and show a high frequency infrared carbonyl band at 1725 and 1710 cm^{-1}. 2,3,5-Triphenyl, 2,5-diphenyl-3-benzyl and 2,3-diphenyl-5-acyl derivatives on the other hand, are highly colored, show an infrared carbonyl band in the relatively low frequency region (1620–1670 cm^{-1}), and have basic properties, suggesting that they have betaine-like structures with highly polarized carbonyl groups.[250]

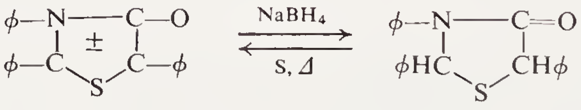
Treating **303** with acetic anhydride gives the corresponding 5-acetyl derivative **304** (R = Me). However, **303** was not acylated when it was treated with acid anhydride under conditions identical to those of cyclization to **304**. Accordingly, it was proposed that formation of acylated product **304** in the preparation of mesoionic thiazole is not a result of the acylation of **303**; rather, the acylation takes place before the ring closure. The intermediate **316** thus formed gives the products **303** and **304** by dehydration or decarboxylation, respectively. The bases present in the reaction mixture determine the course of these elimination reactions.[249]



316

Reaction of **304** (R = Me) with bromine or *N*-bromosuccinimide gives a compound, the elemental analysis of which agrees in composition with either the hydrobromide of a bromo derivative or the bromine addition product of **304**. Interestingly, when this bromo compound is treated with thiourea, the 5-benzoyl derivative **304** (R = PhCO) is formed; no reasonable explanation has been found for this anomalous reaction.[253]

Reduction of the triphenyl derivative **317** with sodium borohydride affords the corresponding triphenylthiazolidine-4-one **318**, which regenerates **317** when heated with sulfur [Eq. (122)].[253]



317 **318**

(122)

As shown in Eq. (123), 2,3-diphenyl-5-acetyl derivative **319** is similarly reduced to **320**. The 5-ethylidene derivative **321**, obtained by dehydrating **320**, is isomeric with mesoionic 5-ethylthiazole derivative **322**. If **321** can be stabilized by mesomerism, it may be in equilibrium with **322** under suitable

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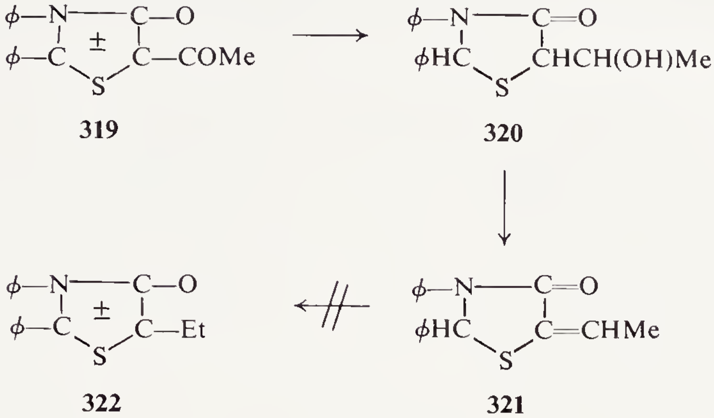
[253] Z. Takayanagi and M. Ohta, unpublished work (1965).

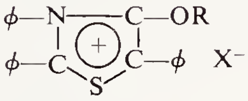
conditions. Attempts to detect such a tautomerization, however, have so far been unsuccessful.[253]



319 **320** **321** **322**

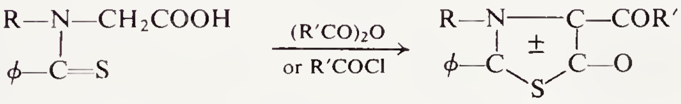
(123)

The triphenyl derivative **317** is weakly basic and is soluble in concentrated hydrochloric acid. With perchloric acid, acetyl perchlorate, and trimethyloxonium fluoroborate, the corresponding 4-hydroxy-, 4-acetoxy- and 4-ethoxythiazolium salts **323** (R = H, Ac, Et) are formed.[250]



323

b. 5-Oxo-3,5-dihydro-1,3-thiazoles. Lawson and Searle[254] prepared 4-acyl derivatives of this type (**324**) by treating *N*-substituted *N*-thioacylaminoacetic acid **325** with acid anhydride or chloride, as shown in Eq. (124).[255]



325 **324**

(124)

The unacylated ring could be obtained by treating **325** with acetic anhydride in the presence of triethylamine.[255]

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[254] A. Lawson and C. E. Searle, *J. Chem. Soc.* p. 1556 (1957).

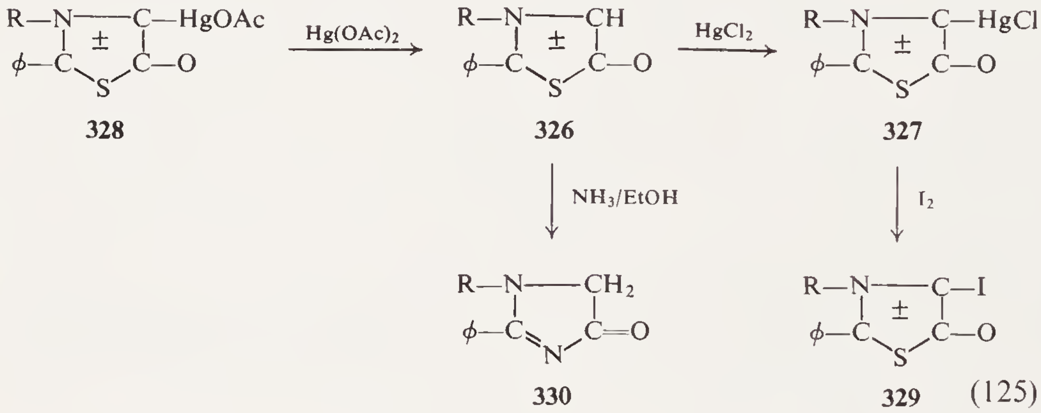
[255] M. Ohta and C. Shin, *Bull. Chem. Soc. Japan* **38**, 704 (1965).

Formation of mesoionic 5-oxo-thiazole **229** by reacting mesoionic 5-oxo-oxazole **220** and carbonyl sulfide[223] has already been described (Section III,A,1,*c*).

The infrared carbonyl band of unacylated **324** appears at 1620–1630 cm^{-1}.[255] This represents a shift to considerably lower frequencies compared to common thiol esters.

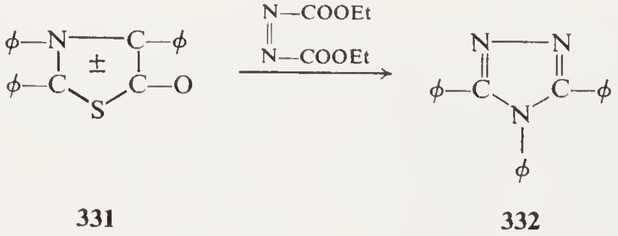
Hydrolysis of **324** (R = Me) with hydrochloric acid gives sarcosine,[254] while hydrolysis of unacylated **326** (R = Me) with hydrochloric acid regenerates *N*-thiobenzoylsarcosine **325** (R = Me). Compound **326** (R = Ph) is unaffected by hydrochloric acid.[255]

The 4-position of **326** is active to electrophilic reagents and affords 4-acyl **324**, 4-chloromercuri **327**, and 4-acetoxymercuri **328** derivatives on treatment with acid anhydride or chloride, mercuric chloride, and mercuric acetate, respectively. The chloromercuri derivative **327** gives the corresponding 4-iodo derivative **329** upon reaction with iodine.[255] Treating **326** (R = Me) with hot ammonia causes ring cleavage followed by recyclization to give imidazolinone **330**[216] [Eq. (125)].



328 **326** **327** **330** **329** (125)

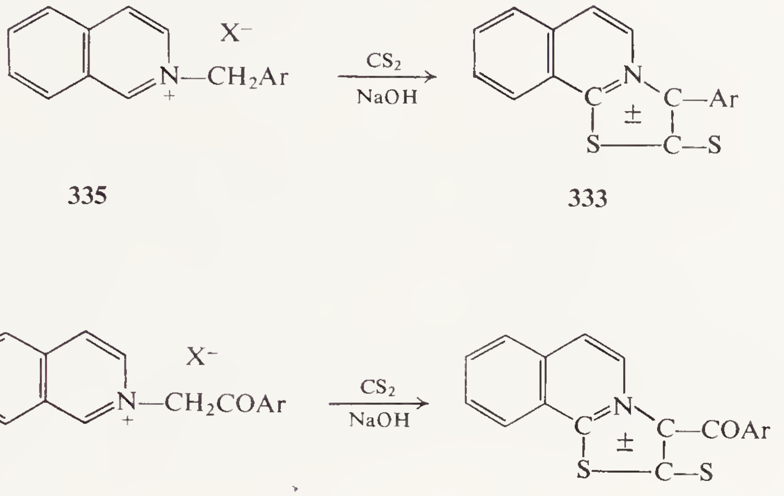
The triphenyl derivative **331** undergoes 1,3-dipolar cycloaddition with azocarboxylate furnishing triphenyltriazole **332**, as shown in Eq. (126).[223]



(126)

331 **332**

c. 3,5-Dihydrothiazole-5-thiones. Kröhnke and Steuernagel[24,256] prepared fused mesoionic ring of types **333** and **334** by treating *N*-arylmethyl- and *N*-acylmethylisoquinolinium salts **335** and **336**, respectively, with carbon disulfide and alkali. 1,3-Dipolar cycloaddition is followed by dehydrogenation, as shown in Eq. (127).



(127)

335 **333**

336 **334**

The structure of **333** was established by X-ray analysis.[257] Compound **333** shows an infrared band at 1350 cm^{-1} which may be assigned to the thiocarbonyl group. It is a stable compound, unaffected by sodium hydroxide or concentrated hydrochloric acid. It readily forms a methiodide, a complex with Cu^{2+}, Co^{2+}, and Pb^{2+}, and a hydrochloride in ether which regenerates **333** on contact with water.[256] Compound **333** ($Ar = p\text{-}NO_2C_6H_4$) is recrystallized as yellow needles from a deep-blue pyridine solution. It is recovered from dioxane as red plates.[256]

The formation of monocyclic thiazolinethione **228** by the interaction of mesoionic oxazolidone **220** and carbon disulfide[223] has been described (Section III,A,1,*c*). Performic acid converts **228** to thiazolesulfonic acid betaine **337**, which gives thiazole **338** on treatment with hydrochloric acid, as shown in Eq. (128).[223]

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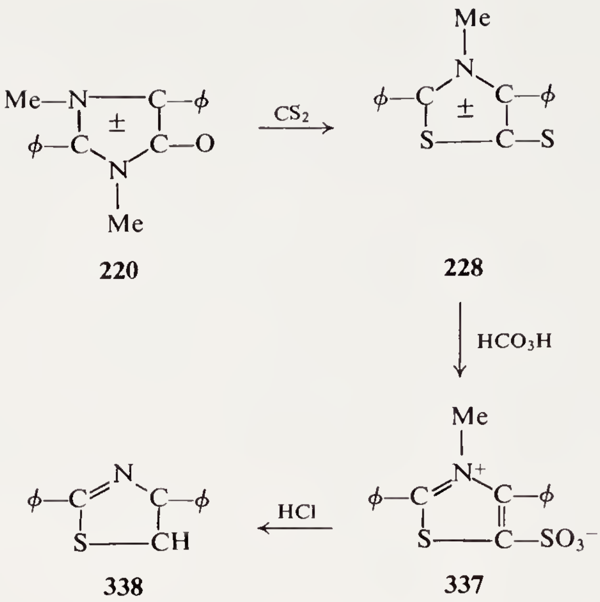
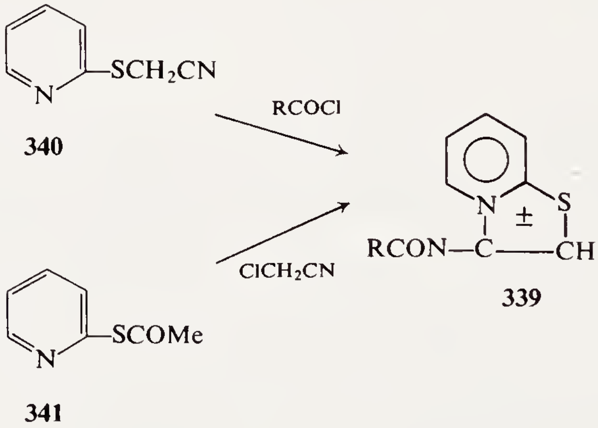
[256] F. Kröhnke and H. H. Steuernagel, *Ber.* 97, 1118 (1964).

[257] J. E. Baldwin, M. C. McDaniel, M. Newton, and I. C. Paul, *Tetrahedron Letters* p. 4239 (1966).



(128)

d. 4-Imino-3,4-dihydrothiazoles. A fused mesoionic ring of type **339** was prepared by heating (2-pyridylthio)acetonitrile **340** with acid chloride, or by treating 2-acetylthiopyridine **341** with chloroacetonitrile, as shown in Eq. (129).[245,258]



(129)

Mesoionic compounds fused to an isoquinoline ring were prepared similarly, but not from the lepidyl derivative. Failure with the last compound is presumably due to steric hindrance between the hydrogen atom at the 8-position of the ring and the acyl substituent.[258] Such ring closure cannot be effected by acetic anhydride or hydrogen chloride.

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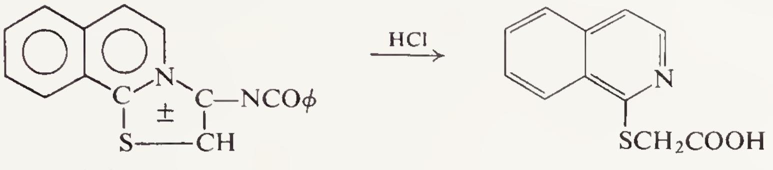
[258] H. Kato and M. Ohta, *Bull. Chem. Soc. Japan* **39**, 1253 (1966).

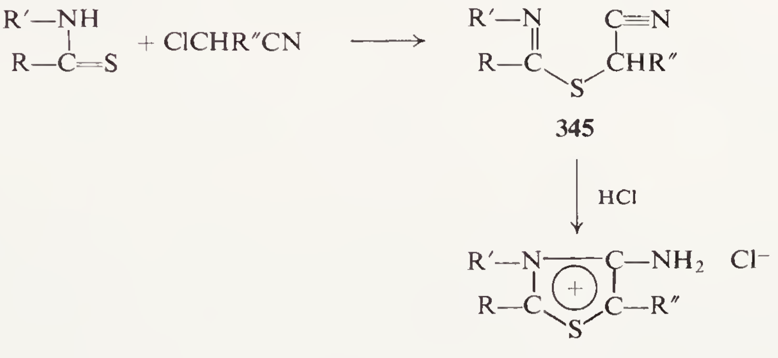
Compounds of this type are very stable. The isoquinolyl derivative **342** is unaffected by treatment with phenylhydrazine, aniline, chromic acid, or by reduction with zinc dust and hot acetic acid, but is decomposed to (isoquinolylthio)acetic acid **343** and benzoic acid when heated with hydrochloric acid, as shown in Eq. (130).[258]



342 **343**

(130)

As shown in Eq. (131), monocyclic rings of this type (**344**) are formed by similarly treating an intermediate **345**, prepared by the reaction of a thioamide and chloroacetonitrile.[259] Cyclization can be promoted by acid chlorides, hydrogen chloride, *p*-toluenesulfonic acid, acetic anhydride and boron trifluoride, or picric acid to give the corresponding salts or salts of *N*-substituted products. Acid anhydrides alone or phenyl isocyanate are uneffective.[259] The hydrochloride **344** can also be formed by heating thioamides with chloroacetonitrile at a suitable temperature, with or without solvent.[195, 259]



345

344

(131)

The treatment of intermediate **346**, prepared by the reaction between dithiocarbamate and chloroacetonitrile, gives 2-alkylthio derivative **347** with acid chloride. Compound **347** reacts readily with secondary amines to give 2-disubstituted amino derivative **348**. Amino derivative **348** can also be formed by treating intermediate **349** with acid chloride. Compound **349**, in turn, is prepared by the reaction of *N*-trisubstituted thiourea and chloroacetonitrile [Eq. (132)].[260]

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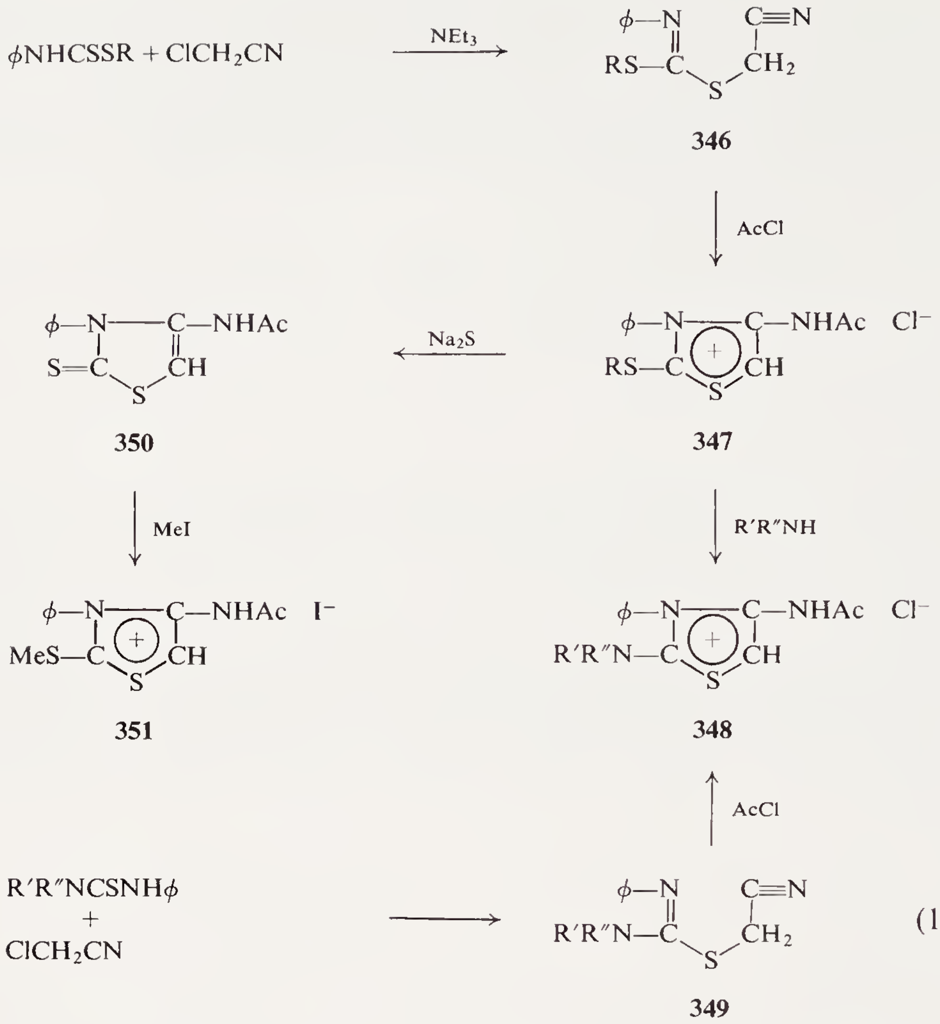
[259] H. Chosho, K. Ichimura, and M. Ohta, *Bull. Chem. Soc. Japan* 37, 1670 (1964).

[260] K. Ichimura and M. Ohta, *Bull. Chem. Soc. Japan* 38, 707 (1965).

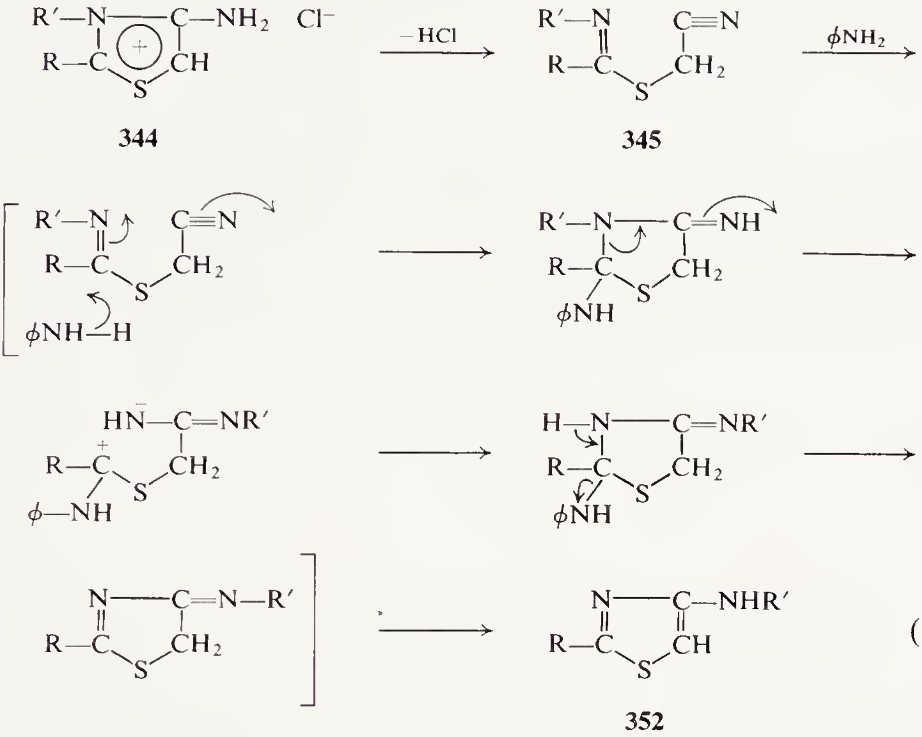


(132)

Treatment of **347** with sodium sulfide yields thiazolidine-2-thione **350**, which regenerates mesoionic 2-methylthio-4-acetiminothiazole hydroiodide **351** when treated with methyl iodide.[260]

The infrared spectra of these compounds show bands at ca. 3000 and ca. 1630 cm^{-1}, assignable to an NH and a C=N group, respectively. Although the infrared carbonyl absorption band of the hydrochlorides of the *N*-acyl derivatives appear at ca. 1700 cm^{-1}, that of the corresponding free base cannot be detected, probably because of a shift to a low frequency region caused by strong polarization of the carbonyl group.

The mesoionic iminothiazoles are isolated only as salts or *exo*-*N*-substituted derivatives; the treatment of hydrochloride **344** with alkali usually regenerates the intermediate **345**.[195] When the hydrochloride of 2,3-diphenyl derivative **344** (R = R′ = Ph) is treated with aniline or toluidine, 4-anilino-2-phenylthiazole **352** (R = R′ = Ph) is formed. Since the same **353** is obtained by treating intermediate **345** (R = R′ = Ph) with aniline (but not with a tertiary amine), this rearrangement may be considered to involve the stages shown in Eq. (133).[261]



(133)

Both the hydrochlorides **353** and *N*-acyl derivatives **354** are easily hydrolyzed by hydrochloric acid to give amide **355**.[259] The hydrochlorides **353** give the corresponding *N*-acyl (**354**) and amidino **356** derivatives on heating with acid anhydrides or chlorides and urea, respectively. In addition, they furnish carbamoyl derivatives **357** and **358** when treated with cyanate ion and phenyl isocyanate, and yield thermally stable,[195] unrearranged thiocyanates with thiocyanate ion. Compound **353** reacts with neither alkyl halides nor dimethyl sulfate [Eq. (134)]. It is interesting that all of these *N*-carbonyl derivatives form hydrochlorides.

The *N*-acyl derivatives **354** are reduced by sodium borohydride to give the corresponding acylaminothiazolidines **359**.[250]

As shown in Eq. (135), the 2-methylated *N*-acyl derivative in the form of its hydrochloride **360** is active enough to condense with benzaldehyde to give the corresponding styryl derivative **361**.[253]

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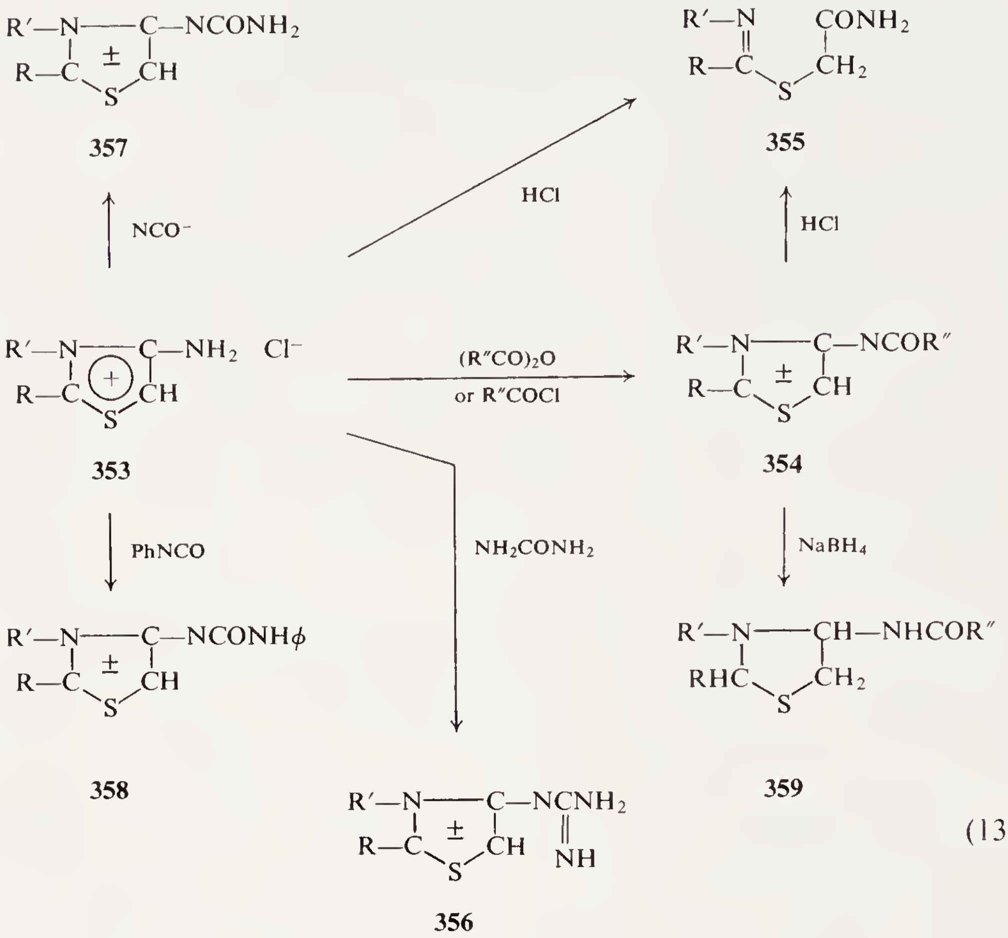
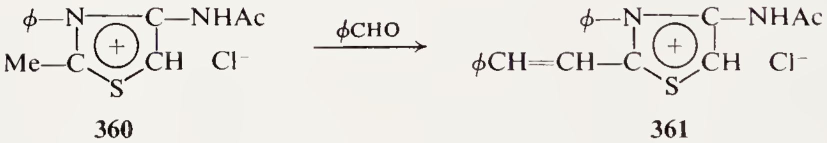
[261] M. Ohta and S. Sato, unpublished work (1965).



(134)



(135)

The thermal instability of 3-benzylsydnone imine hydrochloride has been described previously (Section II,B,3,*c*). A similar pyrolysis takes place with 3-benzyl-4-iminothiazoles. For example, 2-phenyl-3-benzyl-4-iminodihydrothiazole hydrochloride **362** (R = H) or its *N*-acyl derivatives (**362**, R = R′CO) is readily thermolyzed to benzyl chloride and the 4-amino-2-phenylthiazole derivative **363**, as shown in Eq. (136).[262] This reaction may be a convenient procedure for the preparation of 4-aminothiazole derivatives.

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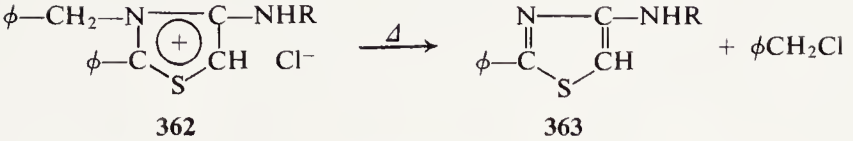
[262] C. Shin and M. Ohta, *Bull. Chem. Soc. Japan* **38**, 1816 (1965).

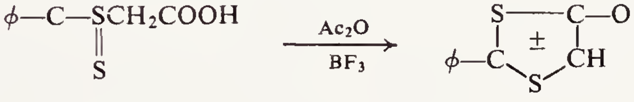


362 363 (136)

e. 5-Imino-3,5-dihydrothiazoles. The rearrangement of imidazolinethione **230** to title compound **231** by hydrochloric acid is described in Section III,A,1,*c*.

5. *Mesoionic Dithiole Derivatives*

a. 4-Oxo-4H-1,3-dithioles. All the mesoionic compounds so far described contain at least one nitrogen atom in the mesoionic ring. A mesoionic compound **364** which contains no nitrogen atom in the ring was prepared by heating carboxymethyl dithiobenzoate **365**. The latter was obtained from potassium dithiobenzoate and chloroacetic acid, with acetic anhydride in the presence of boron trifluoride, as shown in Eq. (137).[263]



365 364 (137)

The ring formation cannot be effected by acetic anhydride alone or by acetic anhydride and an organic base. Compound **364** is colored bright red and shows an infrared carbonyl band at 1690 cm^{-1} which is a region normally expected for a thiol ester. This absorption is shifted to a higher frequency compared to 1,2-dithiol-3-ones, which generally show a band at 1640–1650 cm^{-1}.[264] The PMR signal of the 5-proton of **364** appears at a high magnetic field ($\tau = 6$), which suggests a low aromatic ring current and/or high electron density at this position.

b. 4-Imino-4H-1,3-dithioles. Treatment of thiobenzoylthioacetonitrile **366** with hydrogen chloride or acid chlorides afforded **367**, either as its hydrochloride or its *N*-acyl derivatives, as shown in Eq. (138).[263,265] This ring formation can also be effected by nitric or sulfuric acid to give the corresponding salts.

366 367 (138)

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[263] M. Ohta and M. Sugiyama, *Bull. Chem. Soc. Japan* **38**, 598 (1965).
[264] L. F. Boberg and J. Knoop, *Ann.* **708**, 148 (1967).
[265] M. Ohta and M. Sugiyama, *Bull. Chem. Soc. Japan* **36**, 1437 (1963).

The hydrochloride of *N*-acyl derivatives of **367** are pale yellow. On heating, they develop the bright red color of the free base but are reversibly converted to the pale yellow species on cooling.

The infrared spectrum of the hydrochloride of *N*-acyl derivatives **367** shows a carbonyl band at 1650–1675 cm^{-1}, while the hydrochloride of *N*-unsubstituted **367** shows infrared bands of a primary amine at 3200 and 3100 cm^{-1}. This suggests that protonation occurs at the *exo* nitrogen atom to give aminodithiolium chloride **367** (R = H).

Although the *N*-unsubstituted hydrochloride **367** (R = H) is stable to acids, it is instantly decomposed on contact with bases.

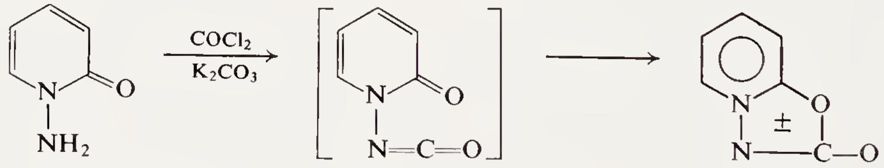
B. MESOIONIC COMPOUNDS WITH THREE AND FOUR HETEROATOMS

1. *Mesoionic Oxadiazole Derivatives*

a. 2-Oxo-2,4-dihydro-1,3,4-oxadiazoles (Isosydnones). Compounds of this type are of special interest, since this ring system differs from the sydnones only in the reversal of the —CO—O— grouping.

An early attempt to prepare isosydnones by methods analogous to the preparation of mesoionic thiazoline-2-thione (Section III,B,2,*d*) was unsuccessful.[14] The failure was due mainly to the instability of intermediate carbamic acids; every attempt to obtain *N′*-carboxy-*N*-acyl-*N*-phenylhydrazine was unsuccessful.

Later, Hoegerle[266] was successful in isolating a fused isosydnone **368** by treating *N*-amino-2-pyridone **369** with phosgene in chloroform in the presence of potassium carbonate. An isocyanate intermediate **370**, as shown in Eq. (139), is probably involved.



369 **370** **368**

(139)

The synthesis of monocyclic isosydnones **17** was reported first by Hashimoto *et al.*[23] and later by Roche and Kier.[267] Both used the same type of reaction [Eq. (140)]. The reaction conditions were essentially the same as those Baker *et al.*[14] had used unsuccessfully.

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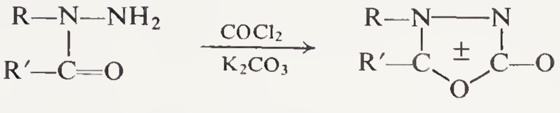
[266] K. Hoegerle, *Helv. Chim. Acta* **41**, 548 (1958).

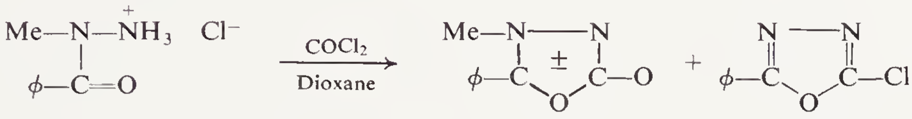
[267] E. B. Roche and L. B. Kier, *J. Pharm. Sci.* **54**, 1700 (1965).



17

(140)

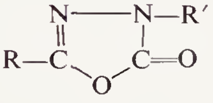
When *N*-benzoyl-*N*-methylhydrazine **371** was heated with an excess of phosgene in dioxane in the absence of potassium carbonate, 2-chloro-5-phenyl-1,3,4-oxadiazole **372** was formed besides the expected mesoionic **373**, as shown in Eq. (141).[268]



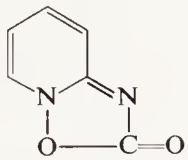
371 **373** **372**

(141)

A value of 7.58 D was obtained for the dipole moment of **373**,[268] which is close to those of sydnones. The infrared spectrum of **17** shows a carbonyl band usually in the range of 1750–1755 cm^{-1}.[23,267,268] This value is almost identical with the carbonyl band of sydnones. It is shifted to a slightly lower frequency than the carbonyl band (1795–1775 cm^{-1}) of 2,4-disubstituted Δ^2-1,3,4-oxadiazolin-5-one **374**, which has the same skeleton but is not mesoionic.[269] The carbonyl absorption of fused ring **368** and its derivatives appears within the range of 1786–1767 cm^{-1}, in close agreement with the carbonyl absorption band at 1773 cm^{-1} of a nonmesoionic isomer **375**.



374



375

The NMR spectrum of **373** shows a methyl proton signal at τ 6.05[268] which is shifted to a lower magnetic field than the proton signal (τ 6.5) of the methyl group of an isomer **374**, and is rather close to that of 3-methyl-4-phenylsydnone (τ 5.87).

These data suggest that the contribution from a polarized carbonyl group such as **376** to the resonance [Eq. (142)] is not too important, and that the nitrogen atom at the 4-position is positively charged. These results, in turn,

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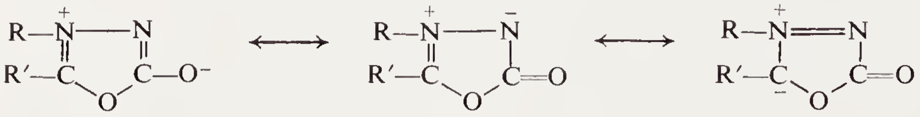
[268] C. Ainsworth, *Can. J. Chem.* **43**, 1607 (1965).

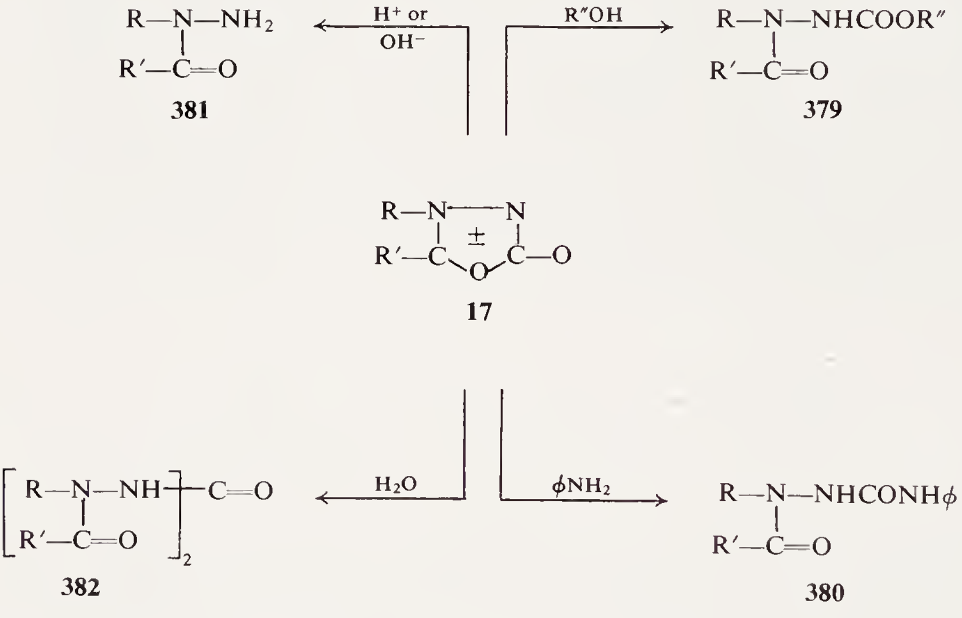
[269] A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. II, p. 229. Academic Press, New York, 1963.

suggest that canonical structures **377** and **378** are important contributors to the resonance of **17**.



376 **377** **378** (142)

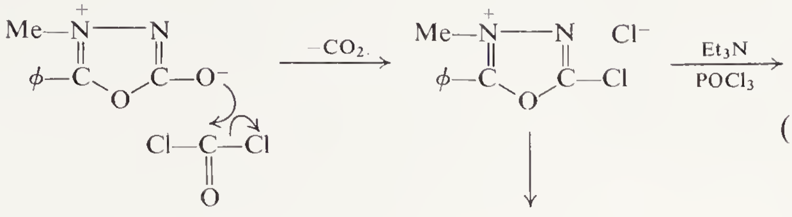
Monocyclic isosydnones **17** are considerably less stable than the isomeric sydnones and, as shown in Eq. (143), they are converted to the corresponding urethanes **379** upon warming with alcohol for a short time. They are converted to amides **380** with amines. They regenerate starting material **381** with acid and alkali and are converted to urea derivatives **382** on warming with water.[23,268]



(143)

Although sydnones provide a variety of heterocyclic compounds by 1,3-dipolar cycloaddition, isosydnone **17** does not react with acetylenedicarboxylate, phenyl isocyanate, or phenyl isothiocyanate, either by heating or by irradiation.[233]

The by-product oxadiazole **372** described above is also formed by reacting **373** and phosgene, presumably by the pathway shown in Eq. (144).[268]

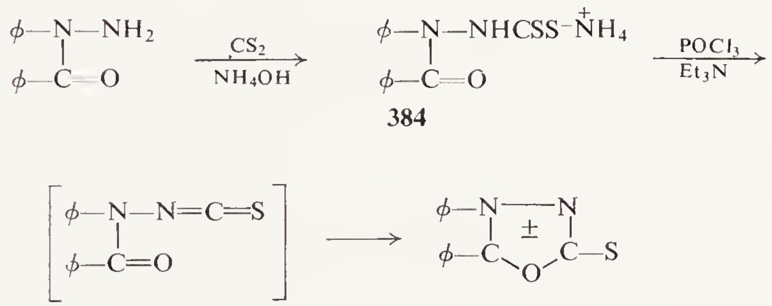


372

(144)

The fused oxadiazolidones **368** appear to be more stable than the monocyclic **17**; they can be recrystallized from ethanol, and are converted to the corresponding urethans only when heated with ethanol for 3 days.

b. 2,4-Dihydro-1,3,4-oxadiazole-2-thiones. The diphenyl derivative of the title compound **383** was prepared as shown in Eq. (145) by the action of phosphorus oxychloride on ammonium *N*-benzoyl-*N*-phenyldithiocarbazate **384** in the presence of triethylamine. Compound **384** was obtained from *N*-benzoyl-*N*-phenylhydrazine and carbon disulfide.[270] The infrared spectrum of **383** shows an absorption band at 1445 cm^{-1} which may be assigned to the C═S group.



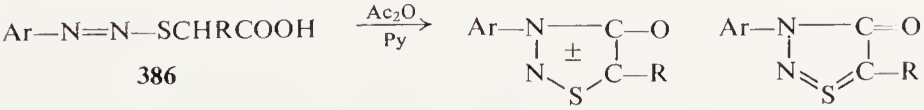
384

383

(145)

2. *Mesoionic Thiadiazole Derivatives*

a. 4-Oxo-3,4-dihydro-1,2,3-thiadiazoles. Duffin and Kendall[247] prepared compounds of type **385** by treating (arylazothio)acetic acid **386** with a mixture of acetic anhydride and pyridine, as shown in Eq. (146). The presence of pyridine is essential for ring formation. Compound **385** is not formed at all when it is absent.



386

385

387

(146)

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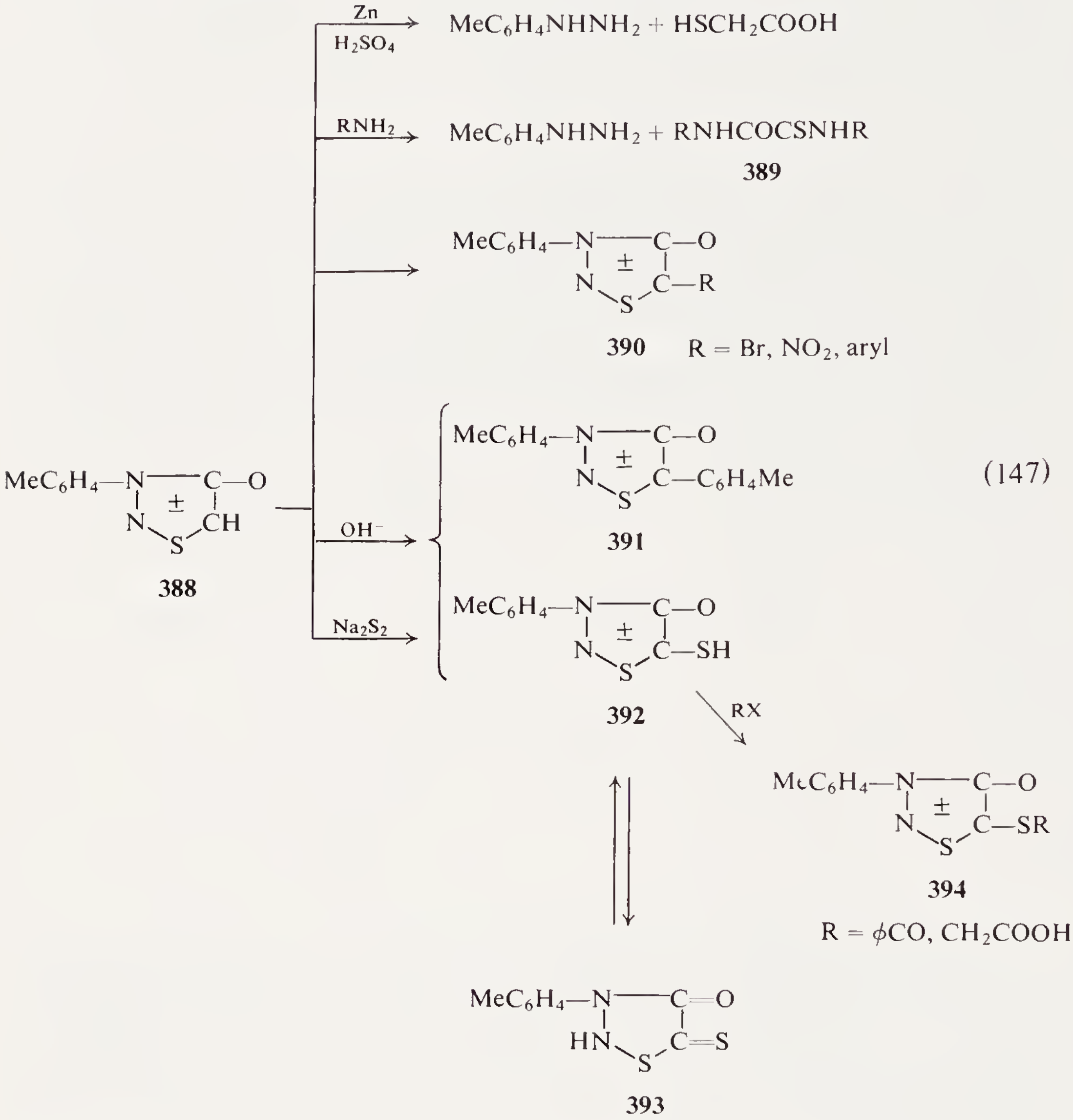
[270] A. Ya. Lazaris, *Zh. Org. Khim.* 3, 1902 (1967).

Compound **385** is a thermally stable yellow substance. It is weakly basic and forms acid salts, which, however, dissociate readily on contact with water or heating. A complex is formed between **385** and mercuric chloride. In this respect, it resembles nonmesoionic 1,2,3-thiadiazoles.

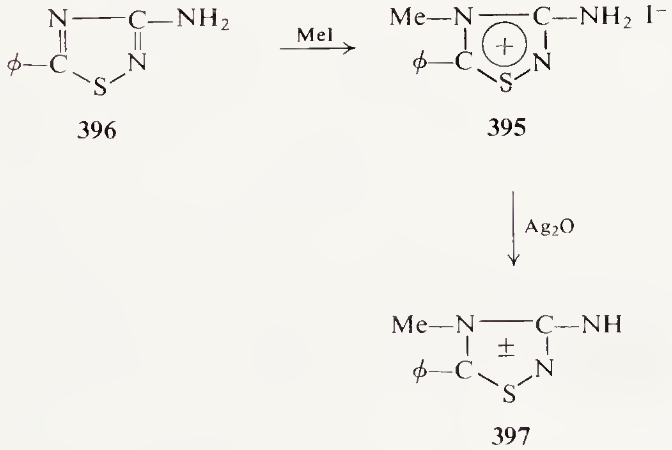


(147)

The ultraviolet absorption spectra of **385** show two absorption maxima at around 270 and 370 mμ; the position of the longer maximum is shifted bathochromically with decreasing solvent polarity. This fact led Duffin and Kendall to regard this compound type as having a covalent structure **387** which undergoes *dsp*^{2} hybridization of the sulfur atom rather than having a mesoionic structure **385**. At the present time, while the structures of these compounds are still obscure, they are represented by structure **385** and are classified as mesoionic compounds in this text.

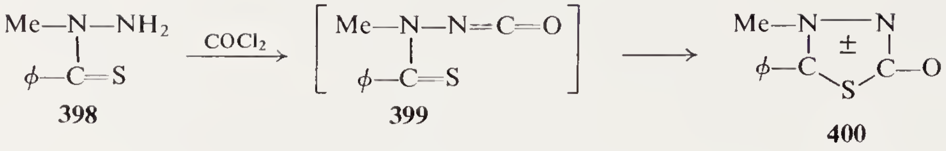
The chemical properties of **385** were most extensively studied through the 3-*p*-tolyl derivatives **388** and are summarized in Eq. (147). Reduction of **388** with zinc and sulfuric acid gives *p*-tolylhydrazine and thioglycolic acid; chromic acid oxidation of **388** furnishes a *p*-toluenediazonium salt. Although **388** is stable towards strong acids and alkali, it reacts with amines to give tolylhydrazine and monothioxamide **389**. Compound **388** behaves as a typical aromatic toward electrophilic reagents and is brominated and nitrated with ease at the 5-position providing **390** (R = Br) and **390** (R = NO_2). An aryl group can be introduced at the 5-position by reacting an aryldiazonium salt with **388** to give **390** (R = aryl). The treatment of **388** with alcoholic sodium hydroxide or ethoxide affords 5-tolyl and 5-mercapto derivatives **391** and **392**, presumably as a result of partial decomposition of **388** to toluenediazonium salt. The mercapto derivative **392** is also formed by heating **388** with sodium disulfide. It is interesting to note that the mercapto derivative **392** thus formed, which may equilibrate with a thione structure **393** with normal valency, is unstable. In contrast, the *S*-derivatives of **388**, such as **394** which can have only a mesoionic structure, are stable.

b. 3-Imino-3,4-dihydro-1,2,4-thiadiazoles. Treating the methiodide (**395**) of 3-amino-5-phenyl-1,2,4-thiadiazole (**396**) with silver oxide affords a free base which may be regarded as a mesoionic compound **397**, as shown in Eq. (148).[25]



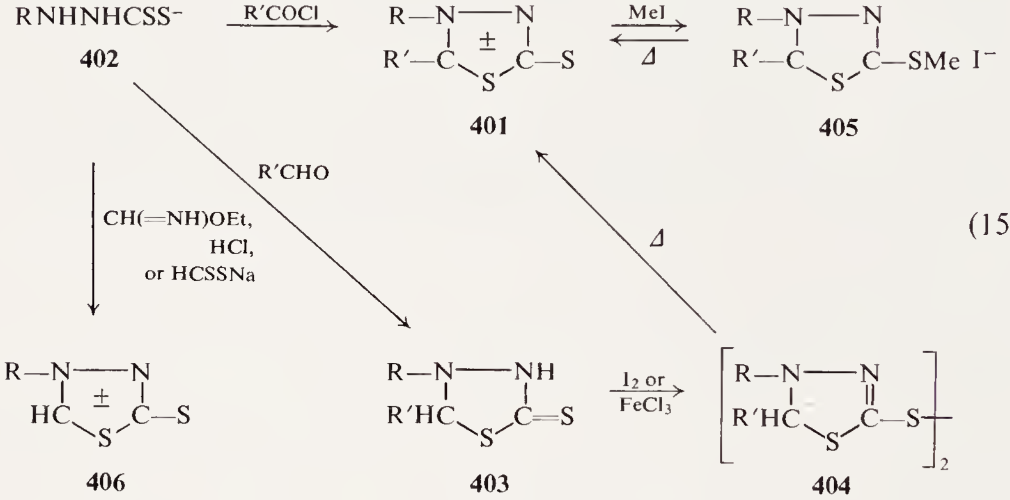
(148)

c. 2-Oxo-2,4-dihydro-1,3,4-thiadiazoles. The treatment of *N*-thiobenzoyl-*N*-methylhydrazine **398** with phosgene gives, presumably via isocyanate **399**, a mesoionic oxo-thiadiazole **400** in 86% yield [Eq. (149)].[270] It shows an infrared carbonyl band at 1660 cm^{-1}.



(149)

d. 2,4-Dihydro-1,3,4-thiadiazole-2-thiones. A large number of compounds of type (**401**) were prepared by Busch *et al.* by a variety of methods summarized in Eq. (150). The methods of preparing **401** are (*1*) reacting dithiocarbazate **402** and acid chloride,[171,272] (*2*) heating potassium dithiocarbazate **402** with an aldehyde,[272] (*3*) oxidizing 1,3,4-thiadiazolidine-2-thione **403** to disulfide **404**, followed by its thermal disproportionation to **401** and **403**,[273–275] (*4*) pyrolyzing methiodide **405**,[271] and (*5*) reacting dithiocarbazate **402** and ethyl formimidate[276] or sodium dithioformate[277] to give 5-unsubstituted product **406**. Although all of these procedures are simple, the yields of **401** achieved are generally low.



(150)

Busch[273] originally assigned a bicyclic structure **407** ("isodithiobiazoline") to the product, and later[271] favored an alternative bridged structure **408** ("*endo*-thiodihydrothiadiazole"). Both of these structures are hardly acceptable in view of the stability of these compounds.

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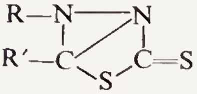
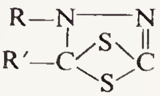
[271] M. Busch and H. Munker, *J. Prakt. Chem.* **60**, 217 (1899).
[272] M. Busch, *J. Prakt. Chem.* **67**, 201 (1903).
[273] M. Busch, *Ber.* **28**, 2635 (1885).
[274] M. Busch, *J. Prakt. Chem.* **60**, 25 (1899).
[275] M. Busch and F. Best, *J. Prakt. Chem.* **60**, 225 (1899).
[276] M. Busch and S. Schneider, *J. Prakt. Chem.* **67**, 246 (1903).
[277] W. Baker, W. D. Ollis, A. Phillips, and T. Strawford, *J. Chem. Soc.* p. 289 (1951).

Later, Schönberg[278] proposed that they be represented as resonance hybrids of a number of zwitterionic forms such as **409** and **410**. This view was supported by the fact that compounds of this type have relatively large dipole moments.[279] Baker[8,277] amplified this idea and wrote that they ought to be considered members of the mesoionic compound class.

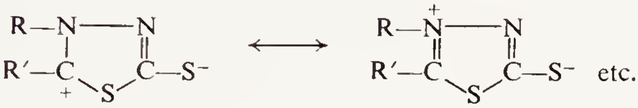


407



408

Compounds **401** in general are yellow crystals with high melting points, and usually show two ultraviolet absorption maxima at 260–280 and 350–360 mμ.[280] The infrared absorption spectra of **401** show a band at 1325–1350 cm^{-1}, which may be assigned to the thiocarbonyl grouping.[280,281] The methyl PMR signal of **401** (R = Ph, R′ = Me) appears at the rather low field of τ 7.03. Likewise, the proton of 5-unsubstituted **406** appears at the surprisingly low field of τ −0.45.[282] This is probably due to the combined effect of an aromatic ring current and the deshielding effect of the adjacent nitrogen and sulfur atoms.



409 **410**

Compound **401** forms a stable methiodide **405** with methyl iodide, which dissociates to **401** and methyl iodide on heating. Compound **401** is neither desulfurized by mercuric oxide nor oxidized to the corresponding sulfone. Though stable to acids, **401** decomposes to dithiocarbazate and carboxylic acid in alkali. Reacting **401** and ammonia or aliphatic amines causes ring cleavage to give hydrogen sulfide, carboxylic acid, and thiosemicarbazide **411**. Reaction with aromatic amines gives a mesoionic triazoline-2-thione **412**,[281–283] for which an *endo*-bicyclo structure **413** had erroneously been proposed by Busch.[272] Triazolinethione **412** can also be formed by reacting the quaternary

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[278] A. Schönberg, *J. Chem. Soc.* p. 824 (1938).

[279] K. A. Jensen and F. Friediger, *Kgl. Danske Videnskab. Selskab. Mat. Fys. Medd.* **20**, 1 (1943); *Chem. Abstr.* **39**, 2068 (1965).

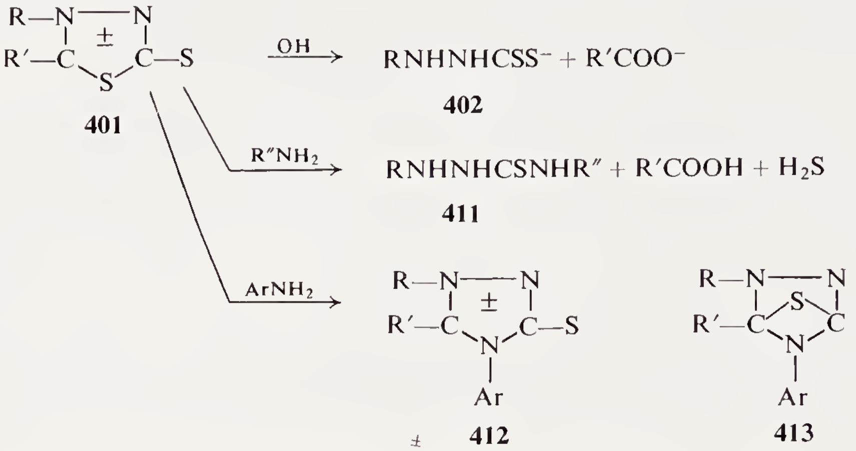
[280] T. G. Stewart and L. B. Kier, *J. Pharm. Sci.* **54**, 731 (1965).

[281] M. Ohta, H. Kato, and T. Kaneko, *Bull. Chem. Soc. Japan* **40**, 579 (1967).

[282] G. W. Evans and B. Milligan, *Australian J. Chem.* **20**, 1779 (1967).

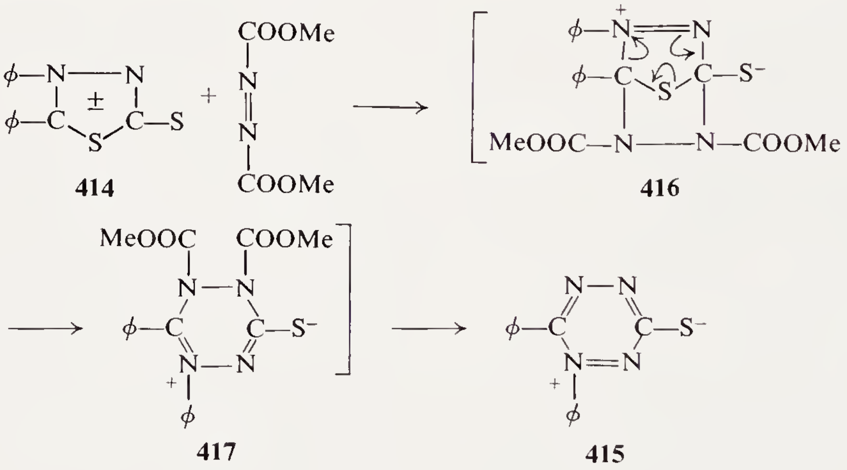
[283] K. T. Potts, S. K. Roy, and D. P. Jones, *J. Org. Chem.* **32**, 2245 (1967).

salt **405** and both aromatic and aliphatic amines.[272,281,284] Substitution reactions with 5-unsubstituted **406** have not been studied [Eq. (151)].



(151)

When the 4,5-diphenyl derivative **414** was heated with dimethyl azodicarboxylate in benzene, a reaction formally analogous to Diels-Alder reaction occurred to give a six-membered mesoionic compound **415**, presumably via **416** and **417**, as shown in Eq. (152).[285]



(152)

Since compounds **401** are isoelectronic with sydnones, Stewart *et al.*[280,286] anticipated that they might also be isobiosteric with sydnones. Indeed, they found that five lower alkyl-4-phenyl derivatives of **401** act as growth inhibitors of some gram-positive organisms and have low acute intraperitoneal toxicity.

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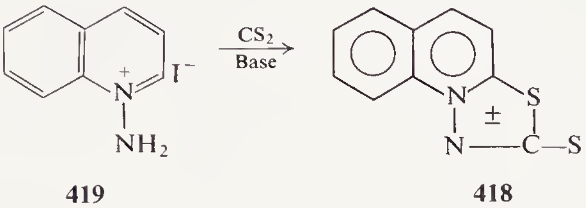
[284] M. Busch, E. Opfermann, and H. Walther, *Ber.* **37**, 2318 (1904).

[285] R. M. Moriarty, J. M. Kliegmann, and R. B. Besai, *Chem. Commun.*, p. 1045 (1967).

[286] L. B. Kier, M. C. Dodd, P. Sapko, and T. G. Stewart, *Nature* **204**, 697 (1964).

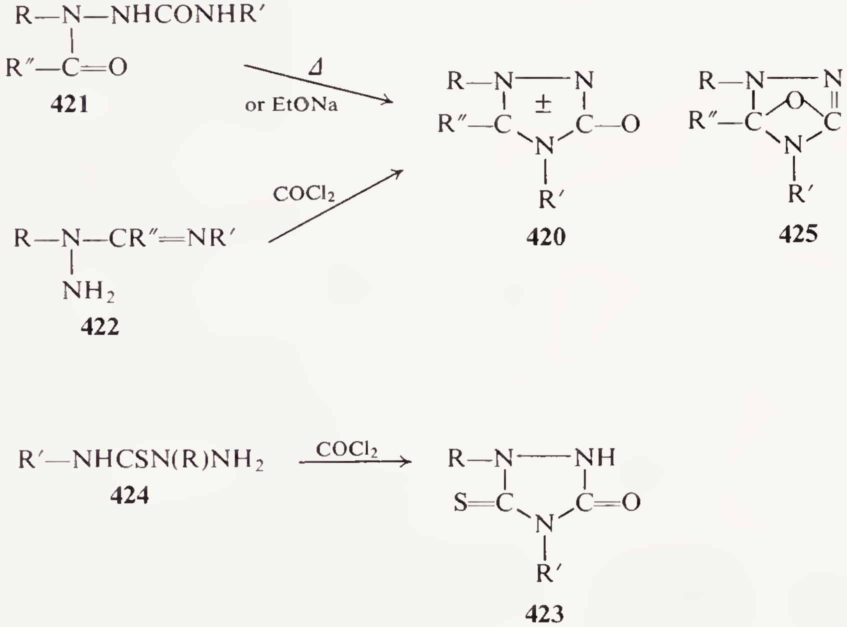
A fused mesoionic ring **418** of this system was prepared in high yield as a deep yellow substance by treating 1-aminoquinolinium salt **419** with carbon disulfide in the presence of a base, as shown in Eq. (153).[287]



(153)

3. *Mesoionic Triazole Derivatives*

a. 3-Oxo-1,3-dihydro-1,2,4-triazoles. Compounds of this type (**420**) can be prepared merely by heating or by treating *N*-acylsemicarbazide **421** with alkoxide,[272] treating *N*-aminobenzamidine **422** with phosgene,[288, 289] or methylating or oxidating triazolidin-3-one-5-thione **423**, prepared from thiosemicarbazide **424** and phosgene[289] [Eq. (154)].



(154)

The formation of a mesoionic oxotriazole **88** by the 1,3-dipolar addition of phenyl isocyanate on 3-phenylsydnone **21** is described in Section II,A,3,*d* [Eq. (35)].

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[287] R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Letters* p. 387 (1962).

[288] M. Busch and R. Ruppenthal, *Ber.* **43**, 3001 (1910).

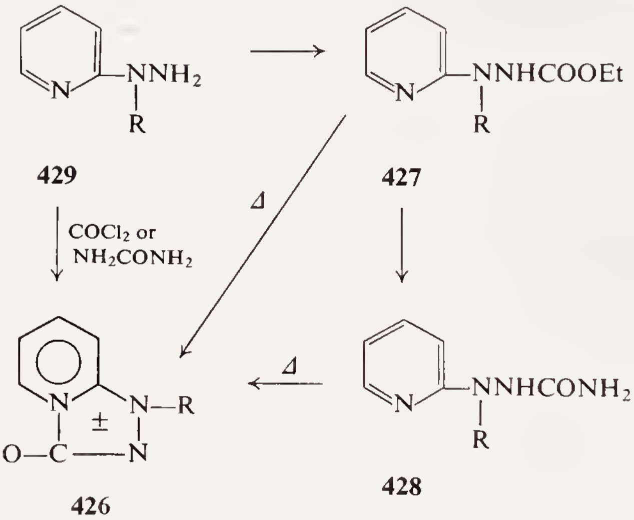
[289] M. Busch and H. Holzmann, *Ber.* **34**, 320 (1901).

A bridged "*endo*-oxytriazoline" structure **425** had originally been assigned to these compounds by Busch *et al.*[272, 288, 289] Although this structure was repeatedly questioned, it was difficult to determine which of the two heteroatoms, nitrogen and oxygen, is *exo* to the ring, and its correct structure was established only recently.[282, 283, 290]

The ultraviolet absorption maximum of **420** (R = R′ = Me, R″ = Ph) appears at 270 mμ. It shows a carbonyl infrared absorption at 1660–1680 cm^{-1}. The PMR spectrum of **420** (R = R′ = Ph, R″ = H) possesses a signal for the 5-proton at a very low magnetic field, τ ca. 0.[282, 283]

Compound **420** does not give methiodide. Its triphenyl derivative (R = R′ = R″ = Ph) decomposes to diphenylsemicarbazide and benzoic acid on heating with sodium hydroxide.[283, 290] It is not brominated on the mesoionic ring and does not react with 1,3-dipolarophiles.[283]

A fused mesoionic compound of this type, 3-oxo-1,3-dihydro-1,2,4-triazolo[4,5-a]pyridine (**426**), was prepared by Palazzo and Baiocchi[291] by pyrolysis of pyridylcarbazate **427** or pyridylsemicarbazide **428**, or by heating *N*-substituted *N*-pyridylhydrazine **429** with phosgene or urea [Eq. (155)].



(155)

2-Oxo-1,2-dihydro-1,3,4-triazolo[4,5-a]pyridine (**430**), which is isomeric with **426**, was prepared by Palazzo and Baiocchi,[292] by treating *N*-substituted pyridylaminocarbamoyl chloride **431** with sodium azide. It shows two ultraviolet absorption maxima at 270 and 306 mμ and an infrared carbonyl band at

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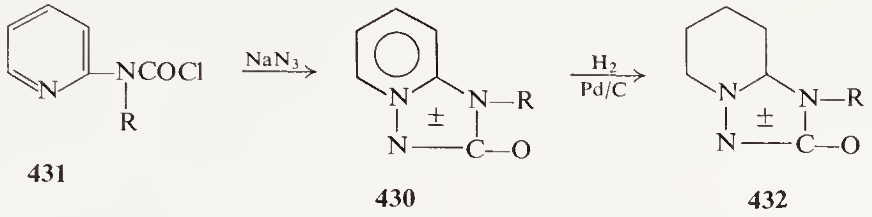
[290] K. T. Potts, S. K. Roy, and D. P. Jones, *J. Heterocyclic Chem.* **2**, 105 (1965); *Chem. Abstr.* **63**, 2966 (1965).

[291] G. Palazzo and L. Baiocchi, *Ann. Chim.* (*Rome*) **55**, 935 (1965); *Chem. Abstr.* **63**, 19335 (1965).

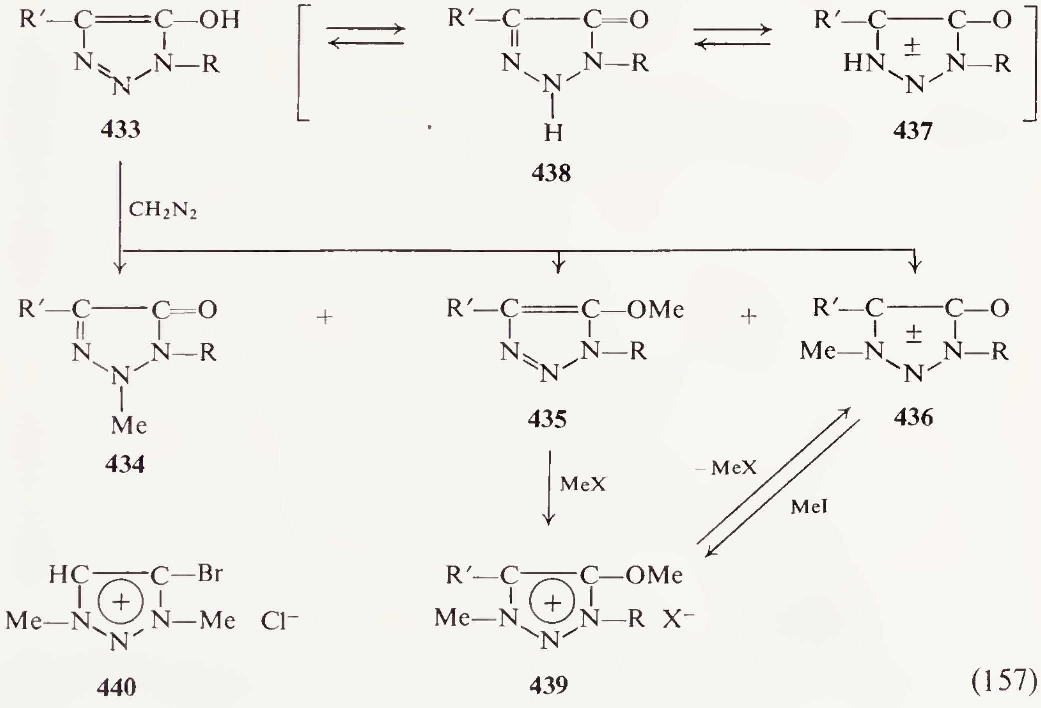
[292] G. Palazzo and L. Baiocchi, *Ann. Chim.* (*Rome*) **56**, 1020 (1966).

1670 cm^{-1}. Only the pyridine ring of **430** (R = Et) was reduced by hydrogenation over palladium charcoal to give the piperidine derivative **432**. The latter shows an infrared carbonyl band at 1650 cm^{-1}.



431 **430** **432** (156)

b. *4-Oxo-3,4-dihydro-1H-1,2,3-triazoles.* As shown in Eq. (157), the methylation of 3-substituted 4-hydroxytriazole **433** by diazomethane gave three compounds **434–436**, one of which (**436**) was shown by Begtrup and Petersen[26, 293] to have a mesoionic structure. That relatively high yields of **436** (24–62%) are usually obtained may suggest that contribution from a mesoionic tautomer **437** is important even in a system where nonmesoionic tautomers such as **433** and **438** can exist.



433 **438** **437** **434** **435** **436** **440** **439** (157)

Methylation of **433** (R = R′ = Ph) was earlier investigated by Scarpati *et al.*,[294] but they erroneously proposed structure **434** (R = R′ = Ph) for the product.

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[293] M. Begtrup and C. Petersen, *Acta Chem. Scand.* **19**, 2022 (1965); **20**, 1555 (1966).

[294] R. Scarpati, D. Sica, and A. Lionetti, *Gazz. Chim. Ital.* **93**, 90 (1956).

Heating methoxytriazoles **435** with alkyl halides in chloroform appears to give quaternary salts **439** as judged by examination of NMR spectra. However, salts **439** in general are very unstable and are not isolated as such. They decompose under the reaction conditions to mesoionic compounds **436** in high to quantitative yields. In this way, mesoionic compounds **436** with various substituents on the 1-position can be prepared. The fact that quaternary salts **439** decompose very readily to give mesoionic **436** instead of methoxytriazoles **435**, which are typically aromatic rings, indicates the stability of mesoionic **436**.

Although the 1,3-dimethyl substituted **436** reacts with methyl iodide, giving the corresponding methoxytriazolium salts **439**, other **436** derivatives do not.

Mesoionic **436** (R = Me, R′ = H) is also formed by reacting 1,3-dimethyl-4-bromotriazolium chloride **440** and sodium methoxide, presumably by way of **439**.

All compounds **436** are colorless hygroscopic solids and generally show an infrared carbonyl band at 1627–1646 cm^{-1}. The infrared carbonyl band of the corresponding 4-triazolinones **434** appears at 1660–1675 cm^{-1}, suggesting that the carbonyl group of **436** is slightly more polarized than that of **434**.

The nuclear magnetic resonance spectra of **436** derivatives show a proton signal for the 5-ring proton at around 3.2 τ. This is shifted to a slightly higher magnetic field than those of triazolinones **434** (τ 2.9) and methoxytriazoles **435** (τ 2.8–2.9) and is shifted to a considerably higher magnetic field than those of triazolium salts **439** (τ 0.5–1.1). The signal of the 4-methyl protons of **436** (τ ca. 6), however, is shifted to a considerably lower magnetic field than those of the methyl groups at the 2- and 3-positions of triazolinones **434** (τ 6.5–6.7). Further, these resonances are rather close to those of methyl groups at the 3-position of methoxytriazoles **435** (τ 6.1) and triazolium salts **439** (τ 5.7), suggesting that the nitrogen atom on the 1-position is positively charged.

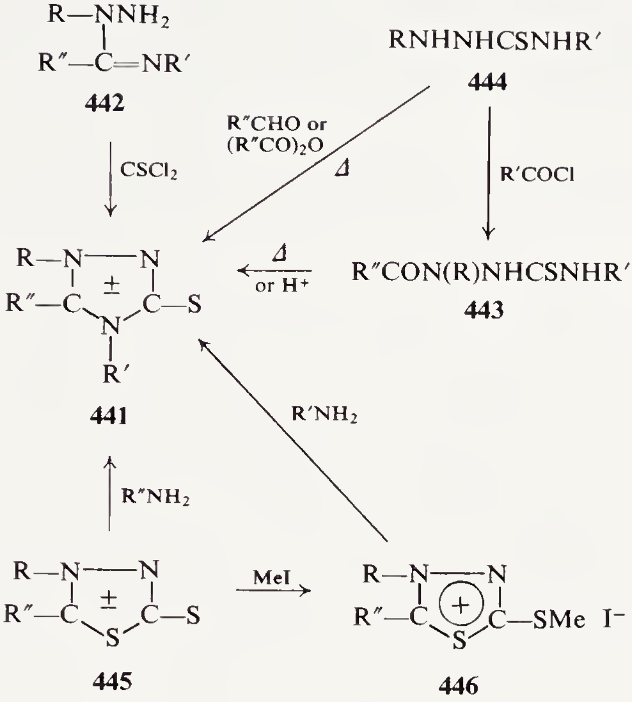
c. 1,3-Dihydro-1,2,4-triazole-3-thiones. Compounds of this type (**441**) are prepared as summarized in Eq. (158), by treating *N*-aminoamidines **442** with thiophosgene,[289] by heating[293] or acid treating[295] *N*-acylthiosemicarbazides **443**, or by heating thiosemicarbazides **444** with acid anhydrides[295] or aldehydes.[284, 296] They are also formed by treating mesoionic 1,3,4-thiadiazoline-3-thiones **445**, their hydrochlorides, or their quaternary salts **446** with amines.[272, 284]

The unlikely structure **447** was originally suggested for these compounds by Busch *et al.*[272, 284, 289, 295, 296] Structure **441** was only recently established.[281–283]

It has been reported[283] that treating 1,4-diphenylthiosemicarbazide with acetic anhydride, heating acetyl-1,4-diphenylthiosemicarbazide, or heating or

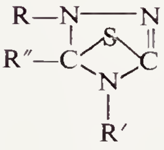
[295] M. Busch and W. Renner, *Ber.* **67**, 384 (1934).

[296] M. Busch, *J. Prakt. Chem.* **124**, 301 (1930).



(158)

treatment of 3-mercapto-1,4-diphenyl-5-methyltriazolium chloride **448** with pyridine leads to 1,3,4-triazoline-4-thione **449** instead of **441** by phenyl migration.



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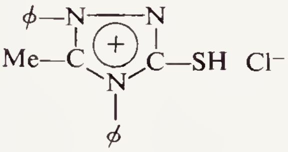

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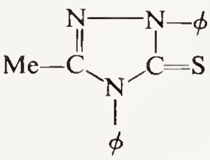
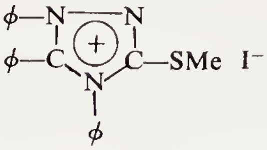


449

Compounds **441** appear to be very stable. In the reaction of certain thiosemicarbazides and acid chlorides, the intermediate acyl derivatives **443** could not be isolated but spontaneously cyclized to give mesoionic compounds **441** under the acylation conditions.[283] Although **441** can be converted to hydrochlorides and methiodides, the reaction is easily reversed either by heating or by treating pyridine.[272,281,283] It has been claimed[272] that the reaction between the methylthiotriazolium salt **450** and ammonia gives a bridged compound **451**, the correct structure of which is very probably a mesoionic iminotriazole described in Section III,B,3,*d*.

Compound **441** does not react with dipolarophiles; nitration occurs on a phenyl substituent instead of the mesoionic ring, even when the 5-position is unsubstituted.[283]



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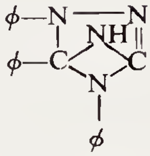
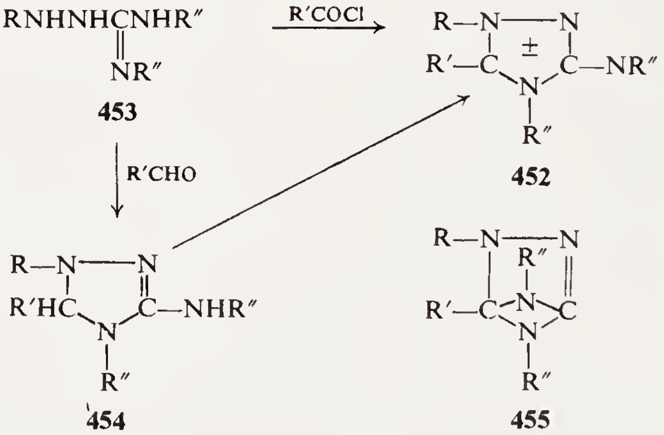


451

The ultraviolet absorption maxima of **441** usually appear at ca. 300 and 240 $m\mu$. A strong infrared absorption, which may be assigned to the C=S grouping, is found at 1350 cm^{-1}.[281, 283]

Two values (τ 0.10 and 1.02) are reported for the 5-proton NMR signal of **441** ($R = R' = Ph$, $R'' = H$).[282, 283] These low values may reasonably be explained in terms of an aromatic ring current and the positively charged mesoionic ring.

d. 3-Imino-1,3-dihydro-1,2,4-triazoles. Nitron (**452**, $R = R'' = Ph$, $R' = H$), a representative mesoionic compound of this type, has long been known as a precipitant of nitric acid. It is prepared by treatment of *N*-aminoguanidine **453** with acid anhydrides or with formic acid,[297, 298] or by oxidation of aminotriazoline **454** with nitric acid or ferric chloride. Compound **454**, in turn, is prepared by treatment of **453** with aldehydes [Eq. (159)].[298, 299]



(159)

The probable formation of **452** by the action of ammonia on 3-methylthiotriazolium salt **450** is described in Section III,B,3,*c*.

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[297] M. Busch, *Ber.* **38**, 856 (1905).

[298] M. Busch, *J. Prakt. Chem.* **74**, 533 (1906).

[299] M. Busch and G. Mehrtens, *Ber.* **38**, 4049 (1905).

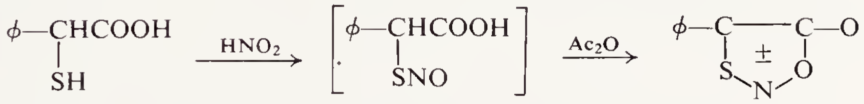
A bridged bicyclic structure **455** was originally given for these compounds.[297] Later, Schönberg[278] proposed that they could best be represented as resonance hybrids of a number of iminotriazole betaines. This view is supported by the dipole moment of nitron[300] (7.2 D).

The proton magnetic resonance spectrum of nitron shows the 5-ring proton signal at τ 0.47. The 5-methyl derivative signal appears at τ 7.42. Both of these values are at lower magnetic fields relative to similar protons in common heterocyclic compounds.

Nitron is a strong base. It readily forms the methiodide and even yields a stable salt with carbon dioxide. The hydrolysis of nitron with potassium hydroxide gives *N*-aminoguanidine **453**.

4. *Mesoionic Oxathiazole Derivatives*

a. 5-Oxo-5H-1,3,2-oxathiazoles. Only a single compound of this type is known. Bacchetti and Alemagna[301] prepared the 4-phenyl derivative **456** by the reaction between 2-mercaptophenylacetic acid **457** and nitrous acid, followed by treating the reaction product with acetic anhydride in the cold, as shown in Eq. (160).



457 **456** (160)

Compound **456** is soluble without decomposition in 50% sulfuric acid, whereas it is decomposed by concentrated sulfuric acid or by sodium hydroxide, and is pyrolyzed to sulfur, benzonitrile, carbon dioxide, and nitrous oxide. Reduction of **456** with zinc and hydrochloric acid affords phenylacetic acid.

A dipole moment of 4.5 D was obtained for **456**, a relatively low value in comparison with other mesoionic compounds.

5. *Mesoionic Oxatriazole Derivatives*

a. 5-Oxo-3,5-dihydro-1,2,3,4-oxatriazoles. Compounds of this type (**458**) are formed by decomposing diazonium nitroformates **459**, which in turn are formed by reacting nitroform and diazonium salts [Eq. (161)].[302–304]

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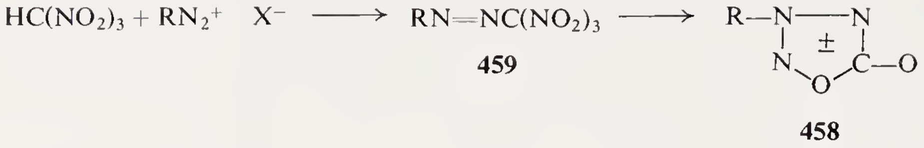
[300] F. L. Warren, *J. Chem. Soc.* p. 1100 (1938).

[301] T. Bacchetti and A. Alemagna, *Atti Accad. Naz. Lincei, Rend. Classe Sci. Fis. Mat. Nat.* **28**, 646 (1960).

[302] A. Quilico, *Gazz. Chim. Ital.* **62**, 912 (1932); *Chem. Abstr.* **27**, 1348 (1933).

[303] G. Ponzio, *Gazz. Chim. Ital.* **63**, 471 (1933); *Chem. Abstr.* **28**, 748 (1934).

[304] J. H. Boyer and S. A. Hernandez, *J. Am. Chem. Soc.* **78**, 5124 (1956).



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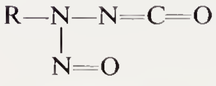

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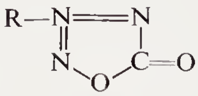
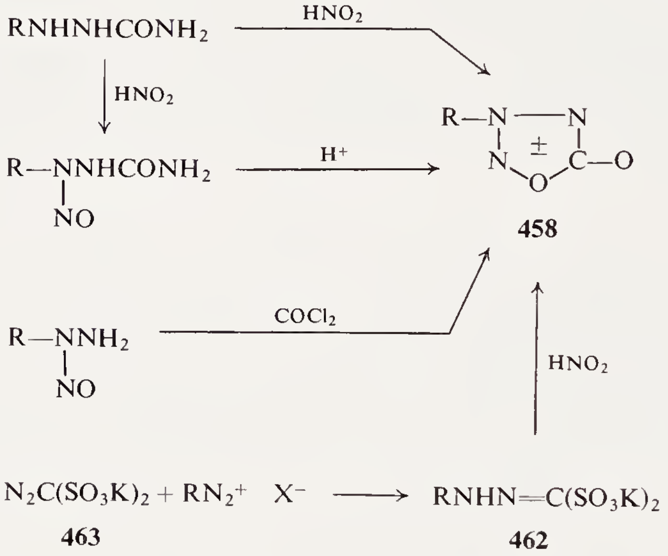


461

Quilico[302] originally assigned a "nitrosocarbonylphenylhydrazine" structure **460** to the product, which was later revised to **461** by Ponzio.[303]

Other synthetic methods for **458** include: (R = alkyl) treating semicarbazides with nitrous acid,[305] treating *N*-substituted *N*-nitrososemicarbazides with acid,[19, 304] and treating *N*-substituted *N*-nitrosohydrazines with phosgene;[306] (R = aryl) treating potassium hydrazonomethanedisulfonates **462**, prepared by the reaction between potassium diazomethanedisulfonate **463** and diazonium salts,[307] with nitrous acid [Eq. (162)].



(162)

Compound **458** is stable to boiling alcohol or dilute acids. However, the 3-cyclohexyl derivative of **458** (R = cyclohexyl) is decomposed to carbon dioxide, ammonia, and cyclohexanol when heated with strong acid.[19] It is claimed that the 3-phenyl derivative **458** (R = Ph), on heating with acid, decomposes to carbon dioxide and phenyl azide.[302] Treatment with potassium

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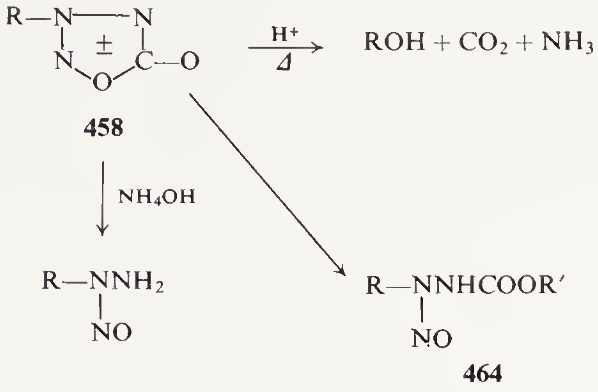
[305] J. H. Boyer and F. C. Carter, *J. Am. Chem. Soc.* **77**, 1280 (1955).

[306] M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Japan* **35**, 766 (1962).

[307] W. V. Farrar, *J. Chem. Soc.* p. 906 (1964).



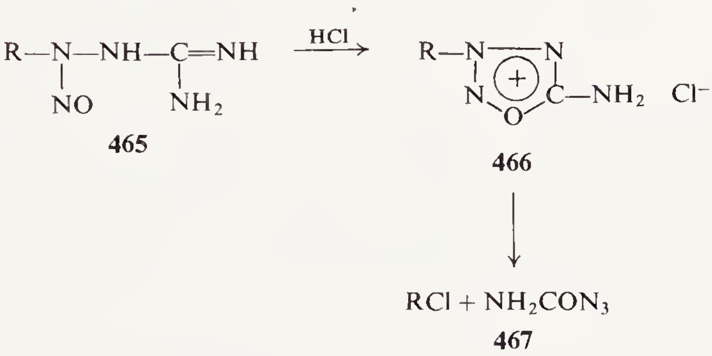
(163)

alkoxide in the cold gives *N*-nitrosohydrazinourethan **464**[303] while ammonia produces *N*-substituted *N*-nitrosohydrazine, as shown in Eq. (163).[19]

Compounds **458** show an infrared carbonyl band at ca. 1780 cm^{-1}; the phenyl derivative has two ultraviolet absorption maxima at 218 and 275 mμ.[19, 305–307]

Some derivatives of **458** are reported to have a hypotensive effect.[177]

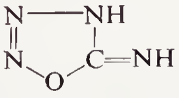
b. 5-Imino-3,5-dihydro-1,2,3,4-oxatriazoles. Treating 1-cyclohexyl-2-guanyl-1-nitrosohydrazine **465** (R = cyclohexyl) with concentrated hydrochloric



(164)

acid gives the hydrochloride of mesoionic iminooxatriazole **466** (R = cyclohexyl), as shown in Eq. (164).[19]

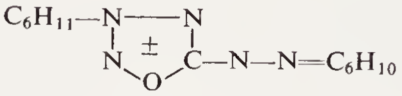
Heating **466** with acid gives cyclohexyl chloride and carbamoyl azide **467**, probably by way of iminooxatriazoline **468**. When **466** is heated with benzoic



468

acid, cyclohexene is formed. The 3-benzyl derivative of **466** appears very unstable. The mesoionic **466** could not be isolated from **465** ($R = PhCH_2$); instead, benzyl chloride, ammonium chloride, and carbamoyl azide were formed. Interestingly, benzyl chloride was not found when the 1-benzyl-2-methyl derivative of **465** [$PhCH_2N(NO)N(Me)c(NH_2){=}NH$] was treated with hydrochloric acid. Possibly, the mesoionic ring corresponding to **466** cannot be formed as an intermediate in this case.

Mesoionic cyclohexylidene-3-cyclohexyl-1,2,3,4-oxatriazolidone hydrazone (**469**) forms as a free base when cyclohexylidene-1,2-diamino-3-cyclohexylaminoguanidinium chloride (**470**) is treated with nitrous acid and then with base.



469

$C_6H_{11}NHNH\underset{\displaystyle NNH_2}{\underset{|}{C}}NHN{=}C_6H_{10}\quad HCl$

470

6. *Mesoionic Tetrazole Derivatives*

a. 5-Oxo-3,5-dihydro-1H-tetrazoles. Treating potassium diazomethanedisulfonate **463** with a benzenediazonium salt gives an unstable intermediate **471**, which decomposes at pH 8–10 to a 1,3-diphenyl derivative of **472** in moderate yield.[307] This compound was found to be identical with the product obtained by reacting diphenylthiosemicarbazide with nitrous acid followed by alkali treatment. Bicyclic structures **473** and **474** were originally proposed for this material by Busch.[308] Compound **472** was also identical with the product obtained by reacting bisethylsulfonylmethane (**475**) and a benzenediazonium salt under alkaline conditions. A bisphenylazomethanal structure **476** was originally suggested by Backer[309] [Eq. (165)].

It has been suggested that one of the several dimethyltetrazole derivatives obtained by treating 5-hydroxytetrazole or its *N*-monomethyl derivatives with diazomethane may be a mesoionic compound **472** ($Ph = CH_3$).[310]

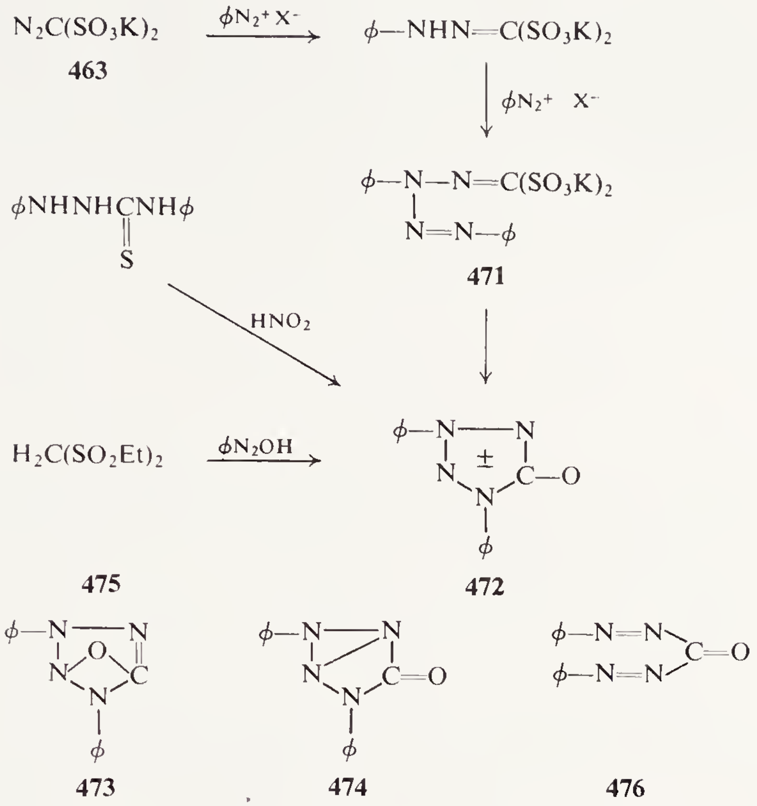
Compound **472** exhibits three ultraviolet absorption maxima at 225, 261, and 325 mμ and an infrared carbonyl band at 1695 cm^{-1}.[25] It does not show ketonic properties, is stable to acids and alkalis even at 100°C,[309] and forms a hydrochloride in concentrated hydrochloric acid.

The latter hydrochloride regenerates the free base **472** on dilution with water.[308]

[308] M. Busch and W. Schmidt, *Ber.* **62**, 1449 (1929).

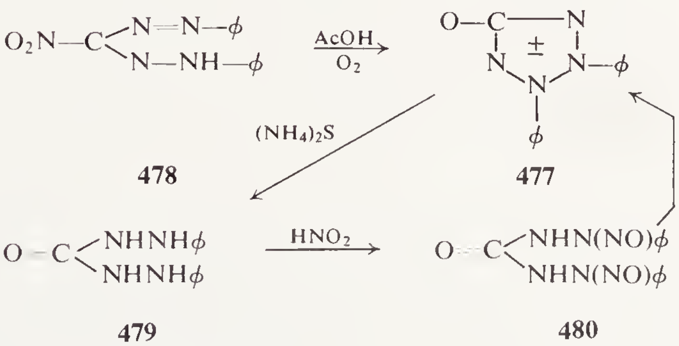
[309] H. J. Backer, *Rec. Trav. Chim.* **70**, 733 (1951).

[310] K. Hattori, E. Lieber, and J. P. Horwitz, *J. Am. Chem. Soc.* **78**, 411 (1956).



(165)

b. 5-Oxo-3,5-dihydro-2H-tetrazoles. Bamberger *et al.*[311,312] reported the formation of a betaine, which is probably more adequately represented by a mesoionic structure **477**, by boiling nitroformazyl **478** with acetic acid. The hydrochloride of **477**, prepared by treating **477** with concentrated hydrochloric acid, regenerates the free base **478** on treatment with water, demonstrating that **477** is weakly basic. The reduction of **477** with ammonium sulfide cleaves the ring to give diphenylcarbazide **479**. Its dinitroso derivative **480** is unstable and readily cyclizes to **477** [Eq. (166)].



(166)

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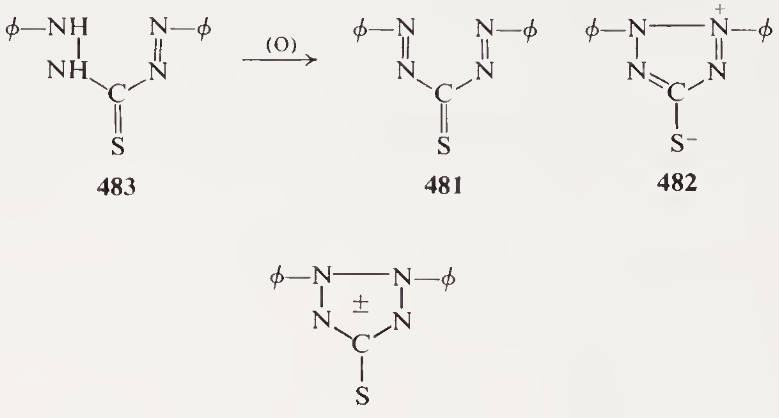
[311] E. Bamberger, *Ber.* **44**, 3743 (1911).

[312] E. Bamberger, R. Padova, and E. Ormerod, *Ann.* **446**, 260 (1926).

c. 3,5-Dihydro-2H-tetrazole-5-thione. Structure **481** and then a betaine structure **482** were proposed for dehydrodithizone, an oxidation product of dithizone (**483**).[20, 312, 313] The compound is best represented by a mesoionic structure **484** [Eq. (167)].



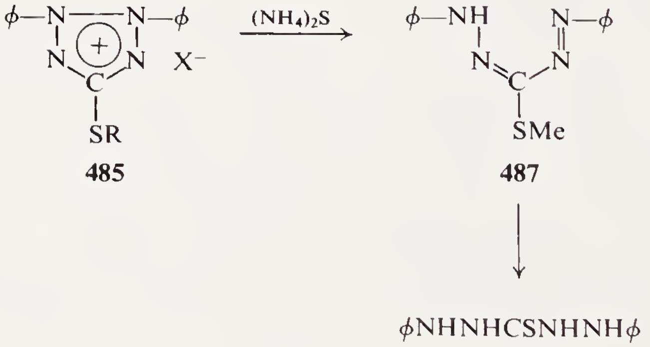
483 **481** **482**

484

(167)

Because of its polar nature, **484** is more soluble than **483** in polar solvents. In contrast to the deep red color of **483**, **484** shows only weak absorption at 400 mμ, besides a strong absorption at 254 mμ in accord with other mesoionic tetrazoles.

Tetrazole **484** reacts rapidly with methyl iodide and chloroacetic acid, giving the corresponding tetrazolium salts **485**, which are readily cleaved by mild reducing agents. For example, the methiodide **485** (R = Me) is reduced by ammonium sulfide to diphenylthiocarbazide **486** via intermediate **487**. When **484** is heated in acetic acid, reddish-bronze crystals, which are isomeric with **484**, are formed. Structure **481** has been proposed for these.



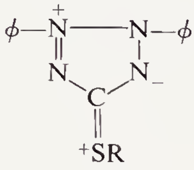
485 **487**

ϕNHNHCSNHNHϕ (168)

486

[313] P. Grammaticakis, *Compt. Rend. Acad. Sci.* **234**, 528 (1952).

The protonated form of **484** is strongly acidic (p$K_a = -1.57$), as is 1-carboxymethylthiotetrazolium chloride **485** ($R = CH_2COOH$) (p$K_a' = 2.47$). This shows that the contribution from canonical form **488** is important in the resonance of **485**, and further suggests that even for unprotonated **484**, structure **489** may contribute more importantly than structures **482** and **490**.[314]



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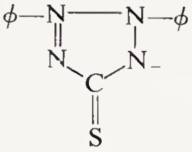

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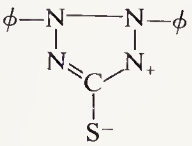
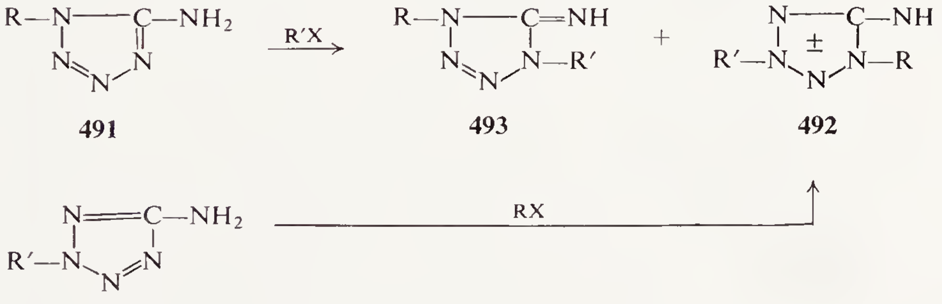


490

Compounds of this type, having very low pK_a values but high polarizabilities, may be expected to be highly nucleophilic toward sp^3 carbons but poorly so toward ester sp^2 carbons. This expectation was substantiated by the failure of **484** to undergo a displacement reaction with *p*-nitrophenyl acetate.[315]

d. 5-Imino-3,5-dihydro-1H-tetrazoles. Alkylation of 1-substituted 5-aminotetrazole **491** gives mesoionic 1,3-disubstituted tetrazoles, for which the 1-substituted 5-alkylaminotetrazole structure was originally proposed.[316] Alkylation of 1-substituted 5-aminotetrazole **491** by benzyl chloride or methyl benzenesulfonate gives a mesoionic 1,3-derivative **492** as well as the 1,4-derivative **493**. Mesoionic **492** is the main alkylation product of 2-substituted 5-aminotetrazoles **494** [Eq. (169)]. Further alkylation of **492** gives 5-alkylamino derivatives.[317, 318] The structure of **492** was confirmed by X-ray analysis[318, 319] and by the fact that an identical alkylation product **492** is obtained by alkylating suitably substituted aminotetrazoles **491** and **494**.



491 **493** **492**

494

(169)

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[314] J. W. Ogilvie and A. H. Corwin, *J. Am. Chem. Soc.* **83**, 5023 (1961).

[315] J. W. Ogilvie, V. K. Miyamoto, and T. C. Bruice, *J. Am. Chem. Soc.* **83**, 2493 (1961).

[316] R. Herbst, C. Roberts, and E. Harvill, *J. Org. Chem.* **16**, 139 (1951).

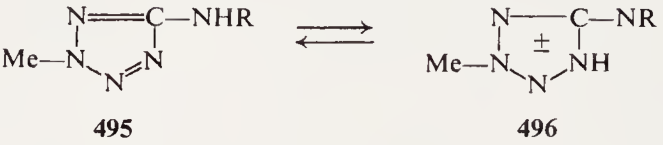
[317] R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.* **76**, 2894 (1954).

[318] J. H. Bryden, R. A. Henry, W. G. Finnegan, R. H. Boschan. W. S. McEwen, and R. W. van Dolah, *J. Am. Chem. Soc.* **75**, 4863 (1953).

[319] J. H. Bryden, *Acta Cryst.* **8**, 211 (1955); *Chem. Abstr.* **49**, 10000 (1955).

In general, 5-alkylaminotetrazoles are weak bases and react only sluggishly with phenyl isothiocyanate. Mesoionic **492** species are strong bases and combine readily with phenyl isothiocyanate.

Although tetrazoles usually have only end absorption in their ultraviolet spectra, **492** shows an absorption maximum at 254–258 mμ. Interestingly, the ultraviolet spectra of 2-methyl-5-alkylaminotetrazoles **495** closely resemble those of **492**, although 1-methyl-5-aminotetrazoles show only end absorption. This suggests that **495** exists mainly as its mesoionic tautomer **496**, as shown in Eq. (170) above.



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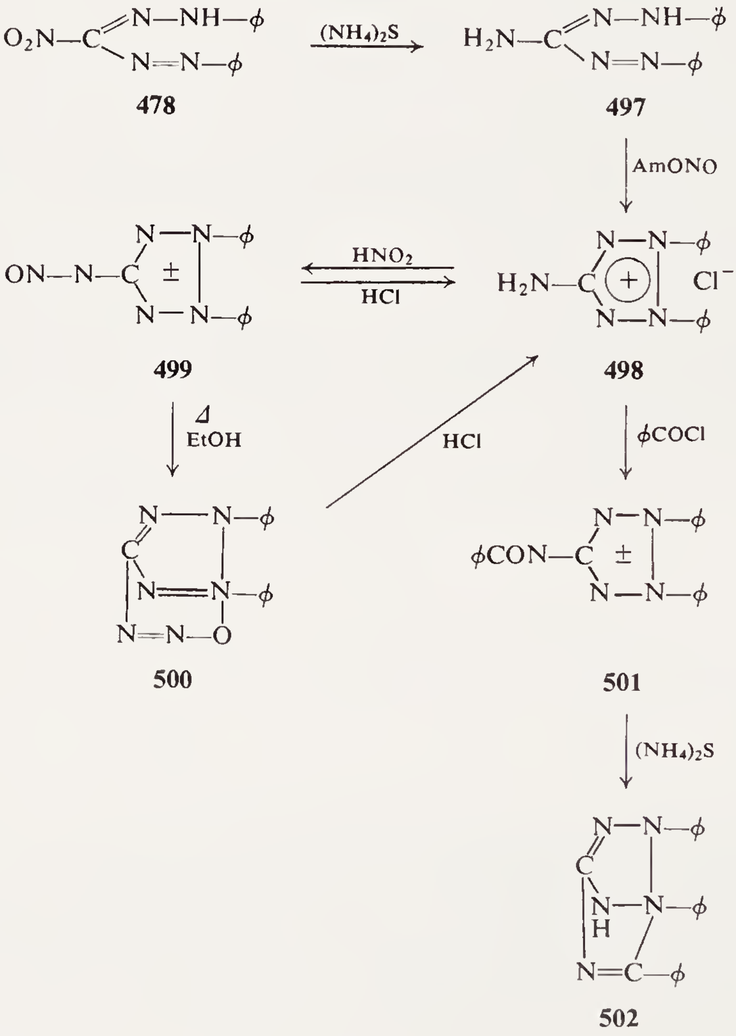
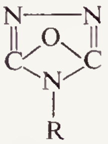


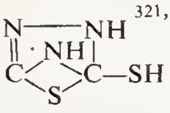
(171)

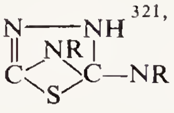
e. 5-Imino-3,5-dihydro-2H-tetrazoles. Nitroformazyl **478** is reduced by ammonium sulfide to aminoformazyl **497**, which, on treatment with amyl nitrite, yields the mesoionic iminotetrazole hydrochloride **498**.[312] The *exo* imino group of the tetrazolium salt **498** is nitrosated by nitrous acid to give unstable **499**, which on brief treatment with hydrochloric acid regenerates **498**. Heating **499** in ethanol results in its rearrangement to a stable isomer which regenerates **498** only when heated with hydrochloric acid for a long time. The doubtful structure **500** was proposed for this isomer. Benzoyl chloride acylates **498** to give **501**. The latter is still basic and converts to its hydrochloride, similarly to other imino type mesoionic compounds. Reduction of **501** with ammonium sulfide gives an oxygen-free compound to which structure **502** has been assigned [Eq. (171)].

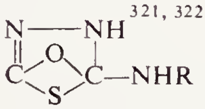
7. "*Bridged Heterocyclic Compounds*"

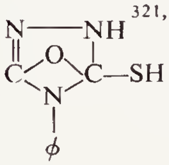
Although many compound structures once assigned an *endo*-heteroatom bridged formulation have been revised and corrected, there still remain in the literature further examples, as shown below. The structures of these substances have not yet been elucidated.

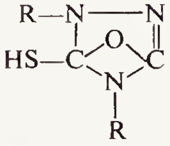

[320, 321, 322]

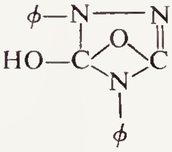

[321, 322, 323]


[321, 322]


[321, 322]


[321, 322]


[289, 324]


[289]

509

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[320] P. C. Guha and P. C. Sen, *Quart. J. Indian Chem. Soc.* **4**, 43 (1927); *Chem. Abstr.* **21**, 2900 (1927).

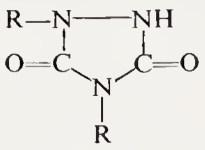
[321] S. L. Janniah and P. C. Guha, *J. Indian Chem. Soc.* **16A**, 19 (1933).

[322] S. L. Janniah and P. C. Guha, *Chem. Abstr.* **27**, 3712 (1933).

[323] S. L. Janniah and P. C. Guha, *J. Am. Chem. Soc.* **52**, 4860 (1930).

[324] M. Busch and E. Opfermann, *Ber.* **37**, 2333 (1904).

All of these structures violate Bredt's rule and thus are considered here to have a monocyclic five-membered ring structure. From the fact that different physical constants have been reported for some compounds with the same structural formulas, it appears that they exist in many of their tautomeric forms. For example, six tautomeric forms **503–508** are conceivable even for compound **509** which, in principle, has fewer tautomeric forms than the other compounds. It may be a difficult but worthwhile task to elucidate the correct structures, and to find out if **509**, for example, can exist as its mesoionic tautomeric forms **505** or **508**.



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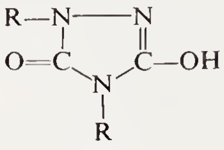

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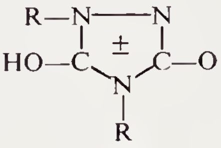

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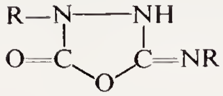

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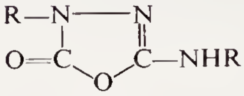

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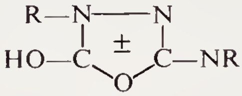

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IV. Structure and Aromaticity of Mesoionic Compounds

Although the physical and chemical properties of the individual mesoionic compounds have been enumerated in considerable detail in the preceding sections, it appears worthwhile to discuss the structures of these compounds with an emphasis on their aromaticity, a major concern of this series.

An appraisal of the properties of these compounds leads to the conclusion that they are stabilized to a certain extent. The main problem here, however, is whether their stability is associated with aromatization resulting from delocalizing six π-electrons in the ring, analogous to the tropone electronic distribution, as suggested by Baker and Ollis,[8] Thomas,[325] and Bieber;[18] or, as originally suggested by Baker *et al.*,[3, 326] whether it is simply a result of resonance among a large number of betaine canonical forms in which six delocalized π-electrons are not necessarily a *sine qua non*. In either case, it is possible that only a single canonical form contributes importantly to the resonance hybrid and the remaining ones contribute but slightly or negligibly. In such cases, the substances are best regarded as betaines since their structures can be represented

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[325] W. J. O. Thomas, *Chem. Ind.* (*London*) p. 533 (1955).

[326] W. Baker and W. D. Ollis, *Nature* **158**, 703 (1946).

satisfactorily by a principal betaine canonical contributor. It may be meaningless to classify such compounds as mesoionic merely because they formally conform to mesoionic requirements. In this connection, it may be desirable to discuss briefly in this section the definition, methods of representation, and nomenclature of mesoionic compounds.

Before entering into a discussion on the aromaticity of mesoionic compounds, the criteria for aromaticity should be clarified. Sydnone, an extensively studied representative mesoionic compound, is certainly aromatic insofar as one views an aromatic species as a stable, fully unsaturated, cyclic compound. Furthermore, it can chemically be regarded as aromatic because it readily undergoes a wide variety of electrophilic substitution reactions which are typical of aromatic substrates (Section II,A,3). No unanimous conclusion, however, can be drawn from the existing data regarding the aromaticity of sydnone if an aromatic compound is defined as one having a large delocalization energy or an aromatic ring current associated with the delocalization of six π-electrons. For example, the ultraviolet spectra, dipole moments, polarographies, diamagnetic susceptibilities, and theoretical calculations at least do not contradict the notion of sydnone aromaticity and, in fact, support it. On the other hand, the NMR spectrum of sydnone may cast doubt on the presence of an aromatic ring current. Moreover, its infrared spectrum and X-ray analysis results favor a structure with considerable bond localization (Section II,A,2).

What is more perplexing, the properties of many known mesoionic ring systems have not been fully elucidated. Furthermore, the electronic structures of these formal mesoionic compounds appear to differ considerably from one another, depending on the kinds and arrangements of atoms which constitute the ring and the exocyclic heteroatoms. Thus, a unified argument cannot be generally applied to all the mesoionic compounds. For example, the contribution from tropone-like canonical forms with a polarized *exo*-carbonyl group is not likely to be considerably greater in sydnones and other oxo-type mesoionic compounds in general than in typical oxo-type heterocylic compounds.[327] Although difficulty is encountered in analyzing imino-type mesoionic compounds because the free *exo-N*-unsubstituted bases are usually not isolable, the infrared carbonyl absorption bands of *N*-acylated derivatives suggest a considerable polarization of the acyl carbonyl group. This, together with the fact that the *N*-acyl derivatives readily form mineral acid salts at the *exo*-nitrogen atom, appears to indicate that the exocyclic C=N bond is considerably polarized in the imino-type mesoionic compounds. Not much systematic study has been performed on thione type compounds, and at

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[327] A. conspicuous exception is found with mesoionic 5-oxo-2-alkylmercaptothiazoles **309**, for which a remarkably long C—O bond distance is reported.[252]

present, one would best refrain from drawing any conclusion about polarization with compounds of this type.

Thus, the main problem with oxo-type mesoionic compounds, such as sydnone is to learn to what extent the tropone-like structural formulas are acceptable. Similarly, the question concerning the imino-type mesoionic compounds is the degree of polarization of the exocyclic C=N bond, and the degree of delocalization of the positive charge within the heterocyclic ring. The latter and their salts may satisfactorily be represented by typical betaine and quarternary salt structures if they are greatly polarized and if the degree of positive charge delocalization is small. They may be adequately represented by tropone and tropylium salt-type structures if the positive charge is considerably localized.

The next problem which arises is whether or not a compound of this type is represented satisfactorily by one covalent structural formula, and if not, how they are to be represented and named. Here, as pointed out by Baker, the adverb "satisfactorily" should be accorded special attention. For example, some delocalization of positive charge within a mesoionic ring is reasonably anticipated even though it may never be as evenly distributed as it is in tropylium salts. On the other hand, the charge will rarely be localized on a single atom in a heterocyclic ring which can be represented by a quaternary or a betaine structural formula.

In this connection, one should probably consider the adequacy of merely naming and classifying vast numbers of heterocylic compounds having such variable properties as mesoionic compounds. The word mesoionic was originally proposed to indicate resonance among zwitterionic structures (mesomerie + ionic)[3] and had nothing to do with the concept of the tropone-like structures later proposed by Baker and Ollis.[8] The present authors feel it more adequate to define the term in a wider sense than that intended by Baker, and to apply the term in its original sense to all neutral compounds which are resonance hybrids solely or mainly of zwitterionic structures, with or without aromatic character. When the electronic structures of these compounds are more fully understood they may be reclassified as sydnoid or sydnone-like, troponoid, aromatic mesoionic compounds, etc.

Many proposals have been made for representing mesoionic compounds as sydnones, such as **2**–**6** (Section I,B). They are also frequently represented as simple heterocylic betaines such as **7**. The structural formulas **2** and **3** were once widely applied, but the tropone-like structure **4** is now accepted by The Chemical Society (London).[328]

The electronic structure of **4** tends to overemphasize the polarization and the positive charge delocalization, leading to the misunderstanding that there is an

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[328] W. Baker, *Proc. Chem. Soc.* p. 75 (1959).

almost complete delocalization of six π-electrons and that all the atoms comprising the ring are positively charged. At present, since the electronic structures of these compounds have not been adequately elucidated, and since the polarization of the *exo* carbonyl group and the presence of an aromatic sextet are still doubtful, we personally prefer to use the less definite ± symbol in **3** if use of such a special symbol is applicable.

Finally, one should also consider the nomenclature for these systems. As a premise, one should avoid as far as possible the use of trivial names such as sydnone. To this end, there should be a certain systematic nomenclature for these compounds which conforms to IUPAC rules. One method now used by Chemical Abstracts is to adopt the nomenclature for betaines and to name these compounds as anhydro compounds derived from hypothetical quaternary hydroxides.[5,15] In this way, sydnone, for example, is named anhydro-3-substituted 5-hydroxy-1-oxa-2,3-diazolium hydroxide. This nomenclature, though simple, may not be satisfactory for considering mesoionic compounds as derivatives of hypothetical quaternary hydroxides (e.g., **10**) and, thus, may lead to the misunderstanding that sydnone, for example, exists as a betaine structure **7**.

Another nomenclature system is the one proposed by Baker,[3] according to which mesoionic compounds are named as derivatives of unsubstituted aromatic heterocycles. Thus, 3-phenylsydnone, for example, is named as ψ-3,5-dihydro-3-phenyl-5-keto-1-oxa-2,3-diazole, the prefix ψ being used to indicate mesoionic nature. Although Baker and Ollis[8] later abandoned this system and agreed to name them as anhydro compounds, his nomenclature also follows IUPAC rules. Furthermore, it appears to be almost bias-free concerning the charge distribution. We have used this nomenclature in this review with a slight modification. Namely, the prefix keto is replaced by oxo,[329] and the prefix ψ is omitted since it is not yet clear if the compounds really have mesoionic structure as defined by Baker and Ollis.[8] Moreover, only one structure is possible for the compound represented by this nomenclature, regardless of the presence or absence of the prefix ψ.

In addition to the above-described, nomenclatures, a conventional one for heterocyclic compounds, such as naming 3-phenylsydnone as 3-phenyl-1-oxa-2,3-diazol-5-one, is very frequently used. This nomenclature, though not correct, is simple and leads unequivocally to only one structure. Consequently, it may be regarded as acceptable.

Use of the adjective mesoionic and of a special symbol and nomenclature for these compounds was severely criticized by Katritzky.[5,15] He advanced

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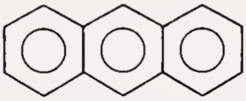
[329] The prefix oxo appears more adequate than keto for a ring C=O group of a heterocyclic ring. In an analogous manner, a C=S group may be named as thioxo or thio rather than thioketo, but such usage is found only occasionally in the literature. Thus we had to adopt the suffix thione to represent this group in a heterocyclic ring.

the view that these compounds can be represented satisfactorily by the usual betaine structures, and that the presence of resonance is obvious by inspection of the structural formulas. However, when sydnone, for example, is named as the anhydro compound of the hypothetical quaternary hydroxide **10**, and accordingly is represented by betaine structure **7**, it is not unequivocally clear that other canonical forms such as those shown in Eq. (23) contribute importantly to the resonance (and, moreover, that there will be a relatively unimportant contribution from structure **7**). At least when it is desirable to emphasize the contribution from various zwitterionic structures, structural formula **7** may not be regarded as satisfactory, and it appears of value to adopt a special symbol such as ±.

Such a symbol, however, probably should not be regarded as one to be universally used for these compounds. Rather, it should be used when one feels that a structure cannot be satisfactorily represented by other conventional structural formulas, or when it is necessary to emphasize the mesoionic nature of a compound. Such a situation is widely encountered with other conjugated ring systems. Anthracene, for example, is frequently represented by formula **510** to emphasize its aromatic nature. Formula **511** and even formula **512** have been utilized to indicate the localization of double bonds in anthracene.



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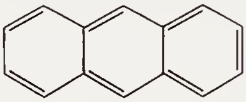

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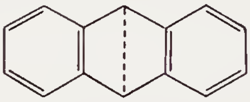

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These representations cannot be regarded as precise without the implicit understanding inherent in every structural formula. This is equally true for representations of the so-called mesoionic substrates. It appears acceptable and even desirable to use a special symbol which is fairly widely used and understood when trying to emphasize the special structural features of these compounds (or even to emphasize that the structures of these compounds are not fully characterized).

One may conclude that visualization of electron distribution for these compounds depends partly on the point of emphasis from which they are discussed, and it appears impossible or even meaningless to try to draw a distinct boundary line between mesoionic and other compounds.

The presentation in this section is based solely on the authors' personal views. The acceptability of such views will be judged by further study in the years to come. The authors would like to end this review by expressing their strong desire to see the unfortunately chaotic present state of "mesoionic" chemistry promptly rectified.

Addendum

SYDNONES

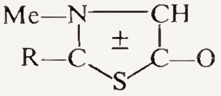
A series of detailed reports by Huisgen *et al.* on the 1,3-dipolar cycloaddition of sydnones (Section II,B,3,*d*) with alkenes, alkynes, benzyne, and aldehydes is now available.[330, 331]

The results of the ω-Hückel LCAO–MO calculations on 3-alkylsydnones predict for protonation of the nitrogen atom at the 2-position, nucleophilic attack at the carbon atom of the 5-position, and electrophilic and free-radical attack at the carbon atom of the 4-position. The mechanism of both acid- and base-catalyzed hydrolysis of sydnones as proposed by Kier and Roche (Section II,B,3,*h*) was advocated on the basis of these calculations.[332]

OTHER MESOIONIC COMPOUNDS

Section III,A,1,*d*: The ring closure of *N*-acylaminoacetonitrile derivatives to 5-imino-3,5-dihydro-1,3-oxazole derivatives has been reported independently by Ohta *et al.*[333] and by Roesler and Fleury.[334]

Section III,A,4,*b*: 5-Oxo-3,5-dihydro-1,3-thiazoles **513** undergo 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate to give the corresponding pyrrole-3,4-dicarboxylates,[335] and with phenyl isothiocyanate to give mesoionic 3,4-dihydro-1*H*-imidazole-4-thiones **514**.[336]



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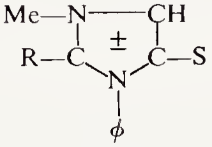

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Section III,A,5,*a*: The structure of 2-phenyl-4-oxo-4*H*-1,3-dithiole **364** has recently been questioned by Gotthardt and Christl.[337] The 2,5-diphenyl derivative was prepared by treating carboxybenzyl dithiobenzoate with a

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[330] R. Huisgen, H. Gotthardt, and R. Grashey, *Ber.* **101**, 536 (1968).

[331] H. Gotthardt and R. Huisgen, *Ber.* **101**, 552 (1968); R. Huisgen, R. Grashey, and H. Gotthardt, *ibid.* **101**, 829 (1968); R. Huisgen and H. Gotthardt, *ibid.* **101**, 839 (1968); H. Gotthardt, R. Huisgen, and R. Knorr, *ibid.* **101**, 1056 (1968); R. Huisgen and H. Gotthardt, *ibid.* **101**, 1059 (1968).

[332] E. B. Roche and L. B. Kier, *Tetrahedron* **24**, 1673 (1968).

[333] S. Sato, T. Mase, and M. Ohta, *Bull. Chem. Soc. Japan* **41**, 2218 (1968).

[334] P. Roesler and J. P. Fleury, *Bull. Soc. Chim. France* p. 631 (1968).

[335] K. T. Potts and D. N. Roy, *Chem. Commun.* p. 1061 (1968).

[336] K. T. Potts and D. N. Roy, *Chem. Commun.* p. 1062 (1968).

[337] H. Gotthardt and B. Christl, *Tetrahedron Letters* p. 4743 (1968).

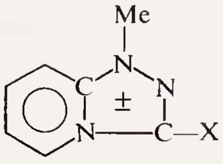
mixture of acetic anhydride and triethylamine. This product shows a polarized infrared carbonyl band at 1580 cm^{-1} and gives 1,3-dipolar adducts with alkenes and alkynes, the latter affording thiophene derivatives.[338]

Section III,B,1,*a*: 4,5-Diphenylisosydnone reacted with ethyl phenylacetylenecarboxylate, though more sluggishly than the corresponding sydnone, to give the corresponding pyrazole.[330]

Section III,B,1,*b*: 4-Methyl-5-phenyl-2,4-dihydro-1,3,4-oxadiazole-2-thione, when heated with ethanol or treated with ethyl mercaptan in benzene, is converted to mesoionic 4-methyl-5-phenyl-2-oxo-2,4-dihydro-1,3,4-thiadiazole (Section III,B,2,*c*).[339]

Section III,B,2,*d*: New methods of preparation of 2,4-dihydro-1,3,4-thiadiazole-2-thiones by the reactions of *N*-thioacyl-*N*-methylhydrazine and thiophosgene[340] or carbon disulfide[341] are reported.

Section III,B,3: A general method of preparation of fused ring mesoionic triazole derivatives, e.g., **515** (X = O, S, and NH) and **516** (X = O and S) is reported. It consists in treating *N*-methyl-*N*-(2-pyridyl)hydrazine and 1-amino-2-methylimino-1,2-dihydropyridine with phosgene, thiophosgene, and cyanogen bromide, respectively.[342]



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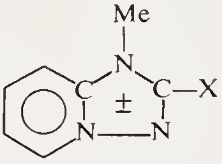

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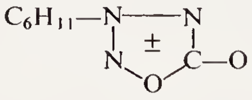
Section III,B,5,*a*: The thermal reaction of 3-cyclohexyl-5-oxo-3,5-dihydro-1,2,3,4-oxatriazole **517** and diphenylacetylene afforded 1-cyclohexyl-4,5-diphenyl-1*H*-1,2,3-triazole **518** instead of 2-cyclohexyl-3,4-diphenyl-2*H*-1,2,3-triazole, a normal 1,3-dipolar adduct.[330] This must mean that **517** was first pyrolyzed to cyclohexyl azide with rearrangement of the cyclohexyl group.



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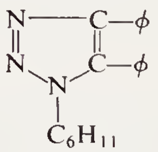

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[338] H. Gotthardt and B. Christl, *Tetrahedron Letters* p. 4751 (1968).

[339] A. R. McCarthy, W. D. Ollis, and C. A. Ramsden, *Chem. Commun.* p. 499 (1968).

[340] K. T. Potts and C. Sapino, Jr., *Chem. Commun.* p. 672 (1968).

[341] L. B. Kier and M. K. Scott, *J. Heterocycl. Chem.* 5, 277 (1968).

[342] K. T. Potts, S. K. Roy, S. W. Schneller, and R. M. Huseby, *J. Org. Chem.* **33**, 2559 (1968).

5

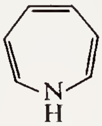
Azepines, Oxepins, and Thiepins

LEO A. PAQUETTE

I. Introduction

A. THE QUESTION OF ANTIAROMATICITY

The seven-membered unsaturated heterocycles, 1*H*-azepine (**1**), oxepin (**2**), and thiepin (**3**), are of substantial intrinsic interest. This group of compounds is characterized by a cyclic array of 8 π-electrons and therefore can be expected



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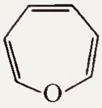

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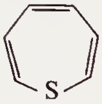

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to differ chemically from related monocyclic systems with $(4n + 2)$ π-electrons. These $4n$ π heterocycles are isoelectronic with the cycloheptatrienide anion[1a, b, c] and, if planar, may actually be antiaromatic.[2] Although planarity is feasible in

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[1a] H. J. Dauben, Jr., and M. R. Rifi, *J. Am. Chem. Soc.* **85**, 3041 (1963).

[1b] W. von E. Doering and P. P. Gaspar, *J. Am. Chem. Soc.* **85**, 3043 (1963).

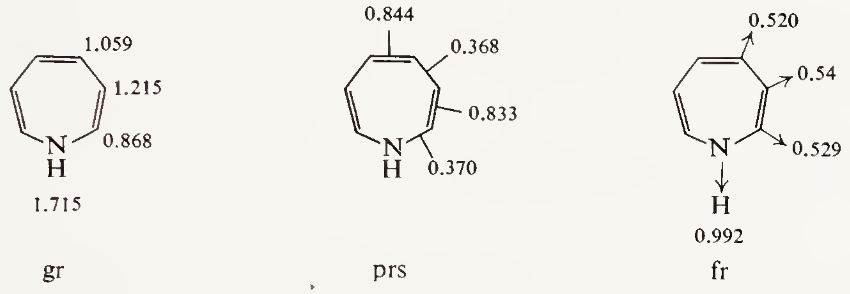
[1c] R. Breslow and H. W. Chang, *J. Am. Chem. Soc.* **84**, 1484 (1962).

[2] R. Breslow, J. Brown, and J. Gajewski, *J. Am. Chem. Soc.* **89**, 4383 (1967).

such molecules (with some small increase in strain energy), it would seem unlikely that maintenance of such a conformation would be energetically rewarding, since the resulting overlap of two heteroatomic electrons with the triene unit is predicted to lead to a total increase in the energy of the system.[3] Interestingly, the Hückel molecular orbital calculations of Schmid[4] for such a model (Table I) indicate that **1** has marked polyene character accompanied by strong localization of the π-electrons on nitrogen and the double bonds and little, if any, tendency for delocalization.

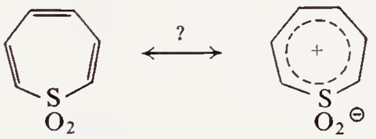
TABLE I

CALCULATED CHARGE DENSITY (gr), BOND ORDER (prs), AND FREE VALENCE (fr) OF 1*H*-AZEPINE (**1**)[a]



[a] R. W. Schmid, *Helv. Chim. Acta* **45**, 1982 (1962).

In the case of thiepin 1,1-dioxide (**4**), however, the sulfonyl group can conceivably assist in delocalizing the 6 π-electrons over the seven atoms by electron attraction and possible participation of its vacant *d* orbitals if the molecule is planar. These considerations parallel those advanced for tropone (**5**).



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Despite their simple structure, and perhaps because of such adverse theoretical considerations, no successful synthesis of **1**, **2**, and **3** or their derivatives appeared in the literature prior to 1963. Scattered reports concerning perhydro

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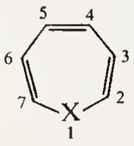
[3] A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," pp. 280–282. Wiley, New York, 1961.

[4] R. W. Schmid, *Helv. Chim. Acta* **45**, 1982 (1962).

counterparts and benzofused analogs of these heterocycles can be found at an earlier date, however. Attempts to prepare **1** and **3** remain unsuccessful to this time, and it is likely that these substances are highly reactive. However, synthetic entry to a large variety of substituted azepines and a sizeable number of oxepins can now be gained with little difficulty. A successful preparation of **4** has also recently been described.

B. NOMENCLATURE

Throughout this chapter, the numbering of the heterotropylidenes will follow the specifications indicated in **6**. Because the name azepine applies equally



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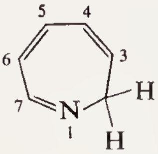

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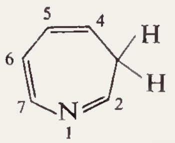

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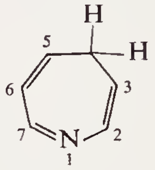

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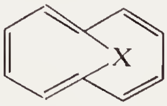
well to four isomeric parent ring systems (**1**, **7–9**), the structure in question is denoted by indicating the position of the odd hydrogen atom with a locant followed by an italicized capital *H*.[5] Thus, **7** is properly termed 2*H*-azepine, **8** becomes 3*H*-azepine, and **9** is 4*H*-azepine.

C. SCOPE

While the chemistry of azepines and oxepins has received considerable attention recently (with the exception of 2*H*-azepines, no example of which has yet been reported), thiepin chemistry remains relatively unexplored. Because of the limited data on thiepins, we have included discussion of their aryl-fused analogs with a view to outlining their unique chemical properties. Benzazepines and benzoxepins are not discussed, nor is the chemistry of [10]annulenes such as **10**, since it is apparent that the fused aromatic ring of the benzo derivatives



10, X = O, N—R

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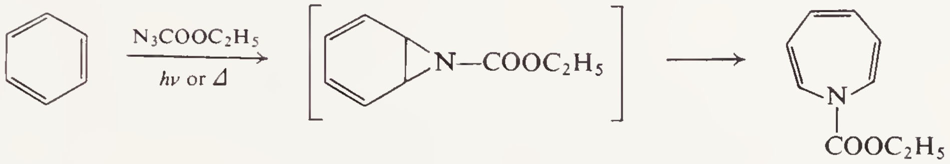
[5] *J. Am. Chem. Soc.* **82**, 5566 (1960).

and the 10 π-electrons of the annulene dominate their chemical properties.[6] Despite the fact that 3*H*- and 4*H*-azepines are not 8 π-electron systems, their chemistry is presented to complete the subject and to provide an overall contrast of reactivity within the series.

II. Synthesis of 1*H*-Azepines

A. NITRENE INSERTION INTO BENZENE AND DERIVATIVES

The first syntheses of a 1*H*-azepine derivative was accomplished by photolysis[7,8a,b] or pyrolysis[9] of ethyl azidoformate in benzene solution. This ring enlargement reaction seems to proceed via an aziridinobenzene intermediate. Decompositions of such electron-deficient azides in the presence of benzene appear to be reasonably general modes of preparation of unsubstituted 1*H*-azepines and have become well-traveled routes to this ring system (Table II). A notable exception is the decomposition of sulfonyl azides under these conditions, which leads only to products of C—H insertion in low yield.[10] Lwowski and Maricich[8b] have demonstrated that it is carbethoxynitrene and not its precursor, ethyl azidoformate, that leads to **11** from benzene. Lwowski and Johnson have provided evidence indicating that only the singlet form of carbethoxynitrene does so react.[11] ^{15}N-Labeling studies with cyanogen azide have likewise shown that *N*-cyanoazepine is formed from a symmetrical cyanonitrene intermediate.[12]



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Since singlet nitrenes appear to be involved in such cycloadditions, a concerted process (i.e., **12**) is expected to operate in preference to a stepwise mechanism involving a transition state species such as **13**. Small substituent

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[6] E. Vogel, *Chem. Soc. (London), Spec. Publ.* **21**, 113–147 (1967).

[7] K. Hafner and C. König, *Angew. Chem.* **75**, 89 (1963).

[8a] W. Lwowski, T. J. Maricich, and T. W. Mattingly, Jr., *J. Am. Chem. Soc.* **85**, 1200 (1963).

[8b] W. Lwowski and T. J. Maricich, *J. Am. Chem. Soc.* **87**, 3630 (1965).

[9] R. J. Cotter and W. F. Beach, *J. Org. Chem.* **29**, 751 (1964).

[10] R. A. Abramovitch and B. A. Davis, *Chem. Rev.* **64**, 149 (1964); R. A. Abramovitch, J. Roy, and V. Uma, *Can. J. Chem.* **43**, 3407 (1965).

[11] W. Lwowski and R. L. Johnson, *Tetrahedron Letters* p. 891 (1967).

[12] F. D. Marsh and H. E. Simmons, *J. Am. Chem. Soc.* **87**, 3529 (1965).

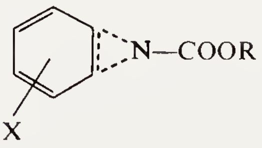
TABLE II

N-Substituted 1*H*-Azepines Prepared by Azide Decomposition

Substituent on nitrogen	Method of preparation	Yield (%)	BP or MP, (°C)	Reference
$—COOC_2H_5$	$h\nu$	70	130 (20 mm)	*a*
	Δ	41	55–56 (0.10 mm)	*b*
$—COOC_6H_5$	Δ	—	66–67	*b*
$—COOCH_3$	Δ	33	62–63 (0.05 mm)	*c*
$—COOC(CH_3)_3$	Δ	15	85 (0.5 mm)	*d*
$—COOC_6H_4—NO_2(p)$	$h\nu$	—	105–106	*e*
$—CON_3$	Δ	—	—	*f*
—CN	Δ	70	48 (0.2 μ)	*g*

[a] K. Hafner and C. König, *Angew. Chem.* **75**, 89 (1963).
[b] R. J. Cotter and W. F. Beach, *J. Org. Chem.* **29**, 751 (1964).
[c] L. A. Paquette and J. H. Barrett, unpublished results.
[d] L. A. Paquette and T. Dawson, unpublished results.
[e] K. Hafner, D. Zinser, and K.-L. Moritz, *Tetrahedron Letters*, p. 1733 (1964).
[f] L. E. Chapman and R. F. Robbins, *Chem. Ind.* (*London*), p. 1266 (1966).
[g] F. D. Marsh and H. E. Simmons, *J. Am. Chem. Soc.* **87**, 3529 (1965).

effects should be noted, since the former reaction profile exhibits little, if any, charge separation. Baldwin and Smith have measured the relative rates of reaction of carbethoxynitrene with various benzene derivatives (Table III).[13] From the observed substituent effect ($\rho = -1.32$), they concluded that the electrophilic cycloaddition is not subject to pronounced direct resonance interaction with the attached substituents and is quite likely concerted.[13]



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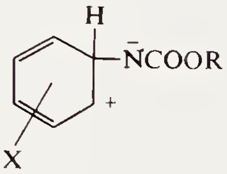

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The major drawback of the nitrene insertion route to 1*H*-azepine derivatives is the relative lack of selectivity of the nitrene in its reaction with monosubstituted benzenes. Usually, a mixture of isomeric 2-, 3-, and 4-substituted 1*H*-azepines is produced which, in general, defies preparative scale gas

[13] J. E. Baldwin and R. A. Smith, *J. Am. Chem. Soc.* **89**, 1886 (1967).

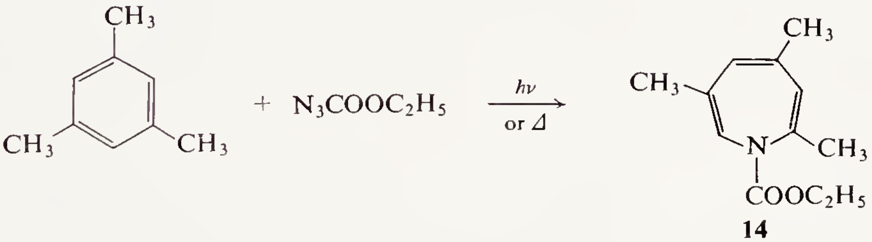
TABLE III

RELATIVE RATE RATIOS FOR THE REACTION OF CARBETHOXYNITRENE WITH BENZENE AND MONOSUBSTITUTED BENZENES AT 129.6°C[a]

Aromatic	$k_{C_6H_5X}/k_{C_6H_6}$
Anisole	2.88
Toluene	2.06
Benzene	1.00
Fluorobenzene	0.62
Chlorobenzene	0.77
Trifluoromethylbenzene	0.22

[a] J. E. Baldwin and R. A. Smith, *J. Am. Chem. Soc.* **89**, 1886 (1967).

chromatographic separation.[12,14–16a,b,c] Due to such circumstances, this synthesis has not allowed for the specific introduction of one or more substituents at the three different ring positions of **1** except in examples such as **14**[15] and **15**[12] where symmetry considerations simplify matters.



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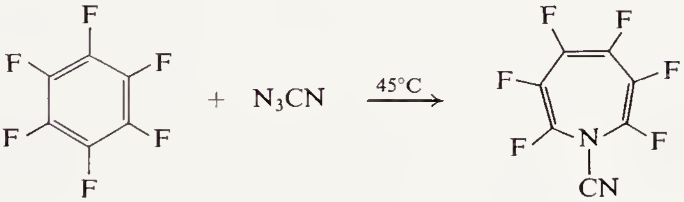

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[14] L. A. Paquette and J. H. Barrett, unpublished observations.

[15] K. Hafner, D. Zinser, and K.-L. Moritz, *Tetrahedron Letters* p. 1733 (1964).

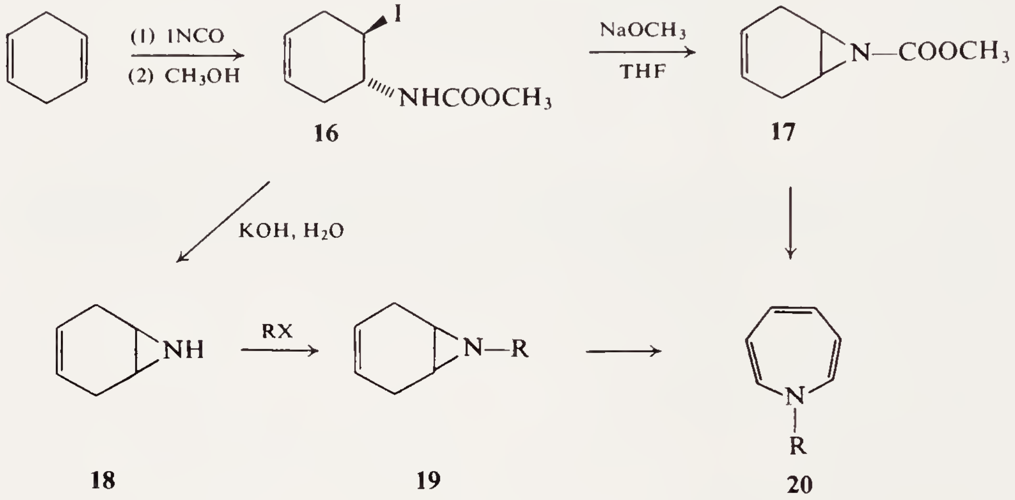
[16a] J. E. Baldwin and R. A. Smith, *J. Am. Chem. Soc.* **87**, 4819 (1965).

[16b] See also I. C. Paul, J. E. Baldwin, and R. A. Smith, *J. Am. Chem. Soc.* **88**, 3653 (1966).

[16c] R. A. Smith, J. E. Baldwin, and I. C. Paul, *J. Chem. Soc.* (*B*) p. 112 (1967).

B. VALENCE BOND ISOMERIZATION APPROACH

With a view to bypassing the early difficulties in obtaining 1*H*-azepines with specifically positioned ring substituents or with functional groups other than carbalkoxy and cyano on nitrogen via nitrene chemistry, a new synthetic approach based on reacting 1,4-dihydrobenzenes with iodine isocyanate was developed.[14,17,18] Treating 1,4-cyclohexadiene with silver cyanate and iodine in ether, and finally with methanol, produces crystalline iodocarbamate **16**. Cyclization of **16** with powdered sodium methoxide in dry tetrahydrofuran affords carbomethoxyaziridine **17**. Alternatively, reacting **16** with aqueous potassium hydroxide leads to aziridine **18** which has been converted to a variety of functionalized derivatives (**19**).[18] Bromination and dehydrobromination of **17** leads to 1-carbomethoxy-1*H*-azepine in good overall yield. Similar treatment of compounds of type **19** provides access to a wide variety of 1-substituted 1*H*-azepines (**20**).



The isomeric 2-, 3-, and 4-methyl-1-carbomethoxy-1*H*-azepines were likewise obtained in good yield by an identical sequence of reactions commencing with the appropriate 1,4-dihydrobenzene derivatives.

Additional studies in this laboratory have shown that the dehydrohalogenation of 1,2-aziridino-4,5-dibromocyclohexanes provides a simple scheme for synthesizing many 1*H*-azepines (see Table IV for selected examples).

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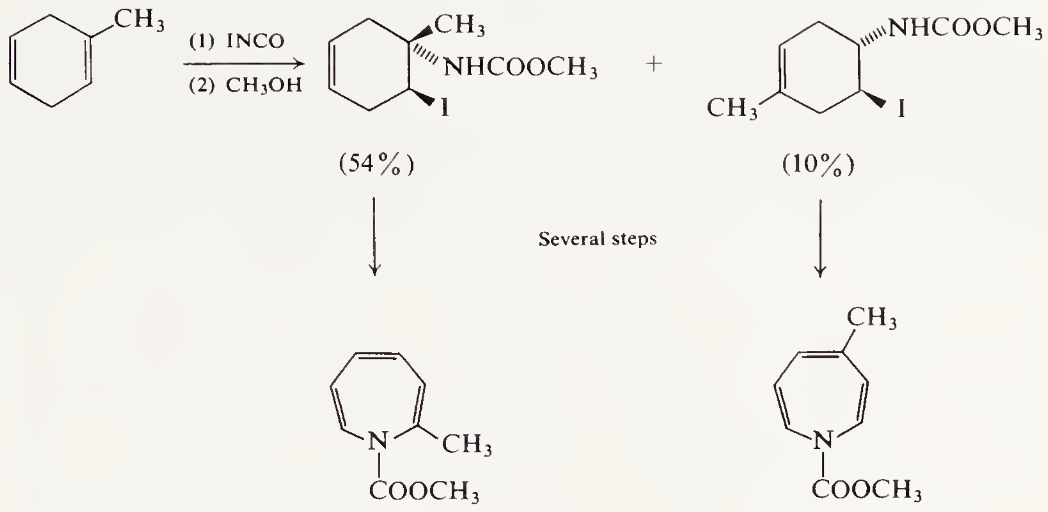
[17] L. A. Paquette and D. E. Kuhla, *Tetrahedron Letters* p. 4517 (1967).

[18] L. A. Paquette and R. J. Haluska, unpublished work.



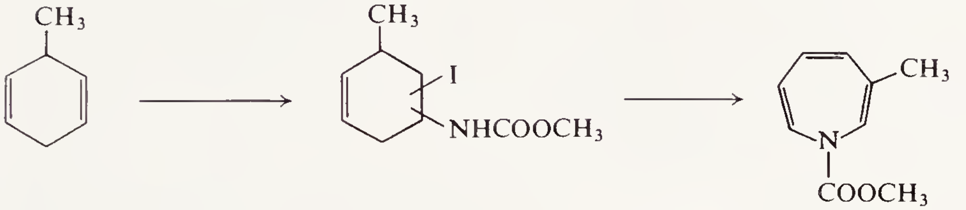


TABLE IV

1*H*-AZEPINES PREPARED BY THE IODINE ISOCYANATE ROUTE

Nitrogen substituent	Ring substituent(s)	BP or MP (°C)	Reference
$—COOCH_3$	—	59–61 (0.2 mm)	*a*
$—SO_2CH_3$	—	91.5–92.5	*b*
$—SO_2C_6H_5$	—	132–133	*b*
$—SO_2C_6H_4—Br(p)$	—	132.5–134	*b*
$—P(O)(C_6H_5)_2$	—	151.5–153	*b*
$—COOCH_3$	$2\text{-}CH_3$	62–64 (0.1 mm)	*c*
$—COOCH_3$	$3\text{-}CH_3$	62–65 (0.2 mm)	*c*
$—COOCH_3$	$4\text{-}CH_3$	62–65 (0.2 mm)	*c*
$—SO_2C_6H_4—Br(p)$	$2\text{-}CH_3$	94.5–95.5	*b*
$—COOCH_3$	$2,7\text{-}(CH_3)_2$	54–55	*d*
$—COOCH_3$	$3,6\text{-}(CH_3)_2$	30–32	*a*
$—COOCH_3$	$4,5\text{-}(CH_3)_2$	60–61	*d*
$—COOCH_3$	$4,5\text{-}(CH_2)_4$	120 (0.05 mm)	*a*
$—SO_2C_6H_5$	$4,5\text{-}(CH_2)_4$	105–107	*a*

[a] L. A. Paquette and D. E. Kuhla, unpublished results.

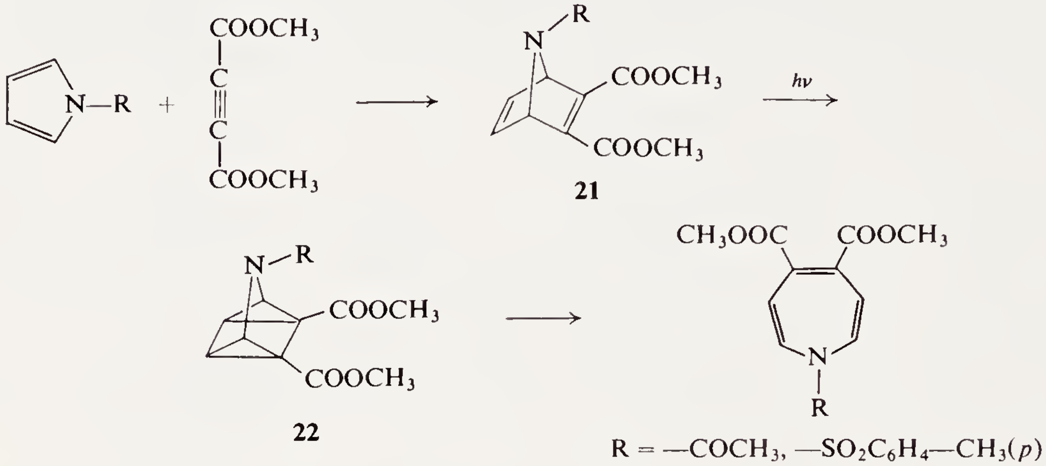
[b] L. A. Paquette and R. J. Haluska, unpublished results.

[c] L. A. Paquette and D. E. Kuhla, *Tetrahedron Letters* p. 4517 (1967).

[d] L. A. Paquette and J. H. Barrett, unpublished results.

C. THERMAL REARRANGEMENT OF AZAQUADRICYCLANES

Synthesis of 1*H*-azepines has also been accomplished by Diels-Alder addition of dimethyl acetylenedicarboxylate to pyrrole derivatives substituted with a powerful electron withdrawing group on nitrogen, followed by irradiation of the (4 + 2) π adduct. Such excitation induces almost quantitative conversion of **21** to the thermally labile 3-azaquadricyclane (**22**). Thermal rearrangement of **22** at approximately 20°–40°C leads to 4,5-disubstituted azepines.[19] Particularly relevant is the fact that the photocyclization of **21** to **22** is not reversed thermally, presumably because the process is disallowed.[20]



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R = —$COCH_3$, —$SO_2C_6H_4$—CH_3(*p*)

D. RING EXPANSION OF SUBSTITUTED 1,4-DIHYDROPYRIDINES

When 4-chloromethyl-1,4-dihydro-1-methylpyridine (**23**) is treated with potassium *t*-butoxide in 1,2-dimethoxyethane, ring expansion occurs and two isomeric products are formed.[21a,b] The first of these was shown to be the *N*-methylazepine **26**, while the second compound has been tentatively formulated as the bicyclic derivative **27**. The latter substance is unstable and is readily converted to azepine **26** even in solution at room temperature. The illustrated polar mechanism, which implicates cations **24** and **25** as intermediates, appears to be favored, although the possible intervention of a carbene has not yet been excluded.

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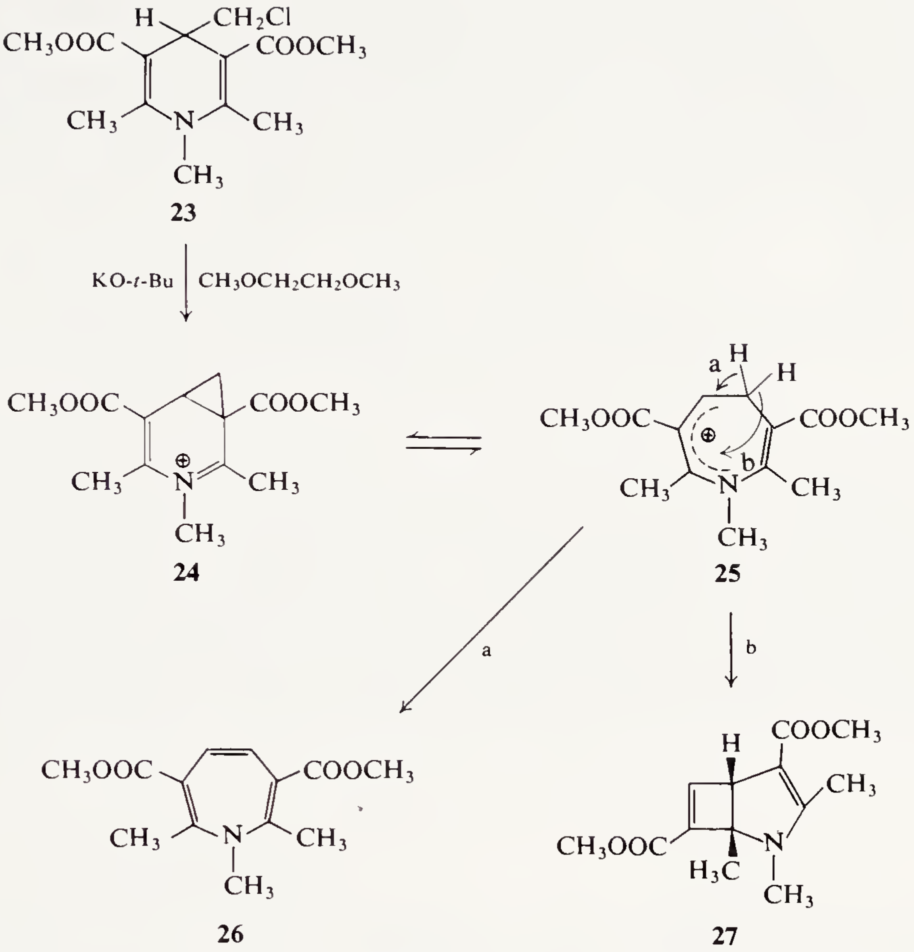
[19] H. Prinzbach, R. Fuchs, and R. Kitzing, *Angew. Chem.* **80**, 78 (1968); *Angew. Chem. Intern. Ed.* **7**, 67 (1968).

[20] R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 395 (1965).

[21a] R. F. Childs and A. W. Johnson, *Chem. Commun.* p. 95 (1965).

[21b] R. F. Childs and A. W. Johnson, *J. Chem. Soc.* (*C*) p. 1950 (1966).

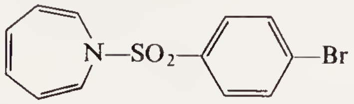


Ring expansion of analogs of **23** lacking a substituent on nitrogen leads to the formation of 3*H*- and 4*H*-azepines and, therefore, discussion of these reactions is deferred to the appropriate sections of this review.

III. Structural Parameters and Spectral Characteristics of 1*H*-Azepine Derivatives

A. X-RAY STUDIES

One of the more provocative questions in heterotropylidene chemistry concerns the relationship of chemical reactivity to their molecular geometry. As mentioned earlier, should the preferred conformation approach planarity, the impact of the destabilizing influence of the cyclic 8 π-electrons upon the molecule would be at a maximum. From an examination of molecular models, it is seen that planarity can be readily attained in this class of compounds with relatively small increases in strain energy. (In 1*H*-azepines, for example, the absolute magnitude of nonbonded interactions increases somewhat as the bulk of the 1-substituent is made larger.) A solution to this fascinating structural problem has recently been made possible for 1*H*-azepines with the advent of a new synthetic approach (Section II, B) by which derivatives of 1*H*-azepines bearing a heavy atom, e.g., **28**, can be prepared. Three-dimensional X-ray studies promise to provide the most revealing information.



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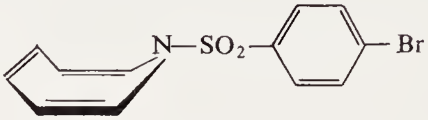

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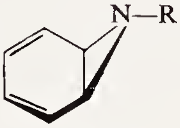
The structure of **28** has been determined by the heavy atom method.[22] The molecule clearly exists in a boat conformation; the double bonds are localized at C-2–C-3, C-4–C-5, and C-6–C-7 and the four atoms comprising each double bond and its immediate neighbors are coplanar (see **29**). Additional molecular dimensions denote substantial sp^2 character for the nitrogen atom. It should also be mentioned that **28** and presumably all closely related 1*H*-azepines exhibit little propensity to exist in the tautomeric azanorcaradiene form (**30**)



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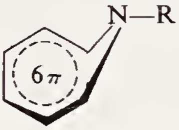

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or as azahomoaromatic entities such as **31**. These azepines are true polyenes. It follows that 1*H*-azepines are nonplanar in the crystalline state and, very likely, when in solution.

B. NUCLEAR MAGNETIC RESONANCE SPECTRA

The NMR spectrum of 1-carboethoxy-1*H*-azepine (**11**) displays a multiplet at δ 5.3–6.1 due to the six ring protons. The presence of more powerful electron-withdrawing substituents on nitrogen generally results in the appearance of the vinyl protons at lower field.[18] Günther and Hinrichs[23] have reported a detailed analysis of the spectrum of **11**. In Table V, the spectral parameters

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[22] I. C. Paul, S. M. Johnson, L. A. Paquette, J. H. Barrett, and R. J. Haluska, *J. Am. Chem. Soc.* **90**, 5023 (1968).

[23] H. Günther and H. H. Hinrichs, *Tetrahedron Letters* p. 787 (1966).

TABLE V

NMR SPECTRAL PARAMETERS FOR 1-CARBOETHOXY-1*H*-AZEPINE (**11**) AND CYCLOHEPTATRIENE (**32**)[a]

Compound[b]	$\nu_0\delta$[c]	J_{45}	$J_{34} = J_{56}$	$J_{46} = J_{35}$	J_{36}
11	35.74	11.44	5.43	0.65	−0.03
32	24.42	11.04	5.58	0.68	−0.12

[a] H. Günther and H. H. Hinrichs, *Tetrahedron Letters* p. 787 (1966).

[b] 20 vol% in CCl_4.

[c] Relative chemical difference (in Hz) between protons H-4,H-5 and H-3,H-6; J = coupling constant (in Hz).

for **11** are contrasted with those for cycloheptatriene (**32**). The remarkably close correspondence serves to further emphasize the gross structural similarities of the two molecules. Especially noteworthy is the observation that the NMR spectra of a number of 1*H*-azepines remain invariant over a substantial temperature range (−90° to +130°C).[24] This constancy points to the absence of valence tautomerism of the 1*H*-azepine–aziridinobenzene type.

C. ULTRAVIOLET SPECTRA

The ultraviolet spectra of 1*H*-azepine derivatives generally consist of three major bands comprising a low intensity maximum of variable position in the 285–330 mμ region, a medium intensity band (frequently seen only as a shoulder) at 240–247 mμ, and strong end absorption (Table VI). The location of the first band is notably dependent upon ring substitution, particularly at the 2- and 7-positions, and is probably associated with interaction of the nitrogen electron pair and the carbocyclic π system. The greater the steric hindrance about the nitrogen atom, the more the particular 1*H*-azepine derivative is constrained in the boat conformation. When this long wavelength band reaches a maximum at 320–330 mμ, the absorption extends to about 430 mμ, accounting for the yellow to orange color of such azepines. In contrast, no tailing into the visible region is seen when this band is blue-shifted to below 300 mμ and such azepines, e.g., 1-carbomethoxy-2,7-dimethyl-1*H*-azepine, are colorless. It may be concluded, therefore, that the electronic transition energy of this azepine chromophore is quite sensitive to distortions in molecular geometry.

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[24] L. A. Paquette and D. E. Kuhla, unpublished results.

TABLE VI

ULTRAVIOLET SPECTRA OF SOME 1*H*-AZEPINE DERIVATIVES

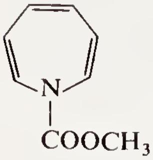
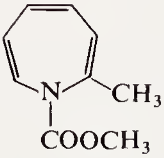
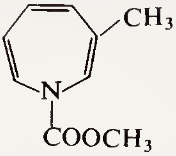
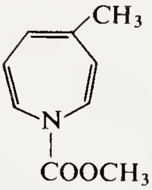
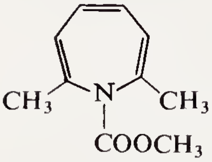
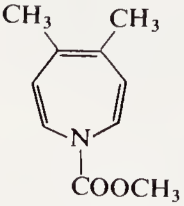
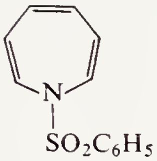
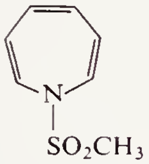
		n-Hexane		95% Ethanol		
Compound	Color	$\lambda_{\max}$[a] (mμ)	ϵ	$\lambda_{\max}$[a] (mμ)	ϵ	Reference
	Dark orange	210.5 238 sh 330	23,075 3,145 570			*b*
	Very pale yellow	211.5 302	21,870 1,015	209.5 291	23,900 1,615	*c*, *d*
	Yellow-orange	212 238 sh 321	23,560 3,030 640	212 238 sh 309	23,780 2,425 745	*c*, *d*
	Dark orange	210.5 239 sh 323	22,740 3,210 675	207 241 sh 309	24,980 4,720 975	*c*, *d*
	White	215 230 sh 285	19,600 3,830 2,110	208.5 275.5	21,000 2,510	*b*
	Very pale yellow	 247 313	 5,480 1,120	208 251 306	22,600 4,980 1,180	*b*

TABLE VI, *Continued*

Compound	Color	*n*-Hexane		95% Ethanol		Reference
		λ_{max}[a] (mμ)	ϵ	λ_{max}[a] (mμ)	ϵ	
	Pale yellow	Insoluble		205 266	22,200 3,000	*e*
	Yellow	Insoluble		205 307	17,200 760	*e*

[a] Sh = shoulder.

[b] L. A. Paquette and J. H. Barrett, unpublished observations.

[c] L. A. Paquette and D. E. Kuhla, *Tetrahedron Letters* p. 4517 (1967).

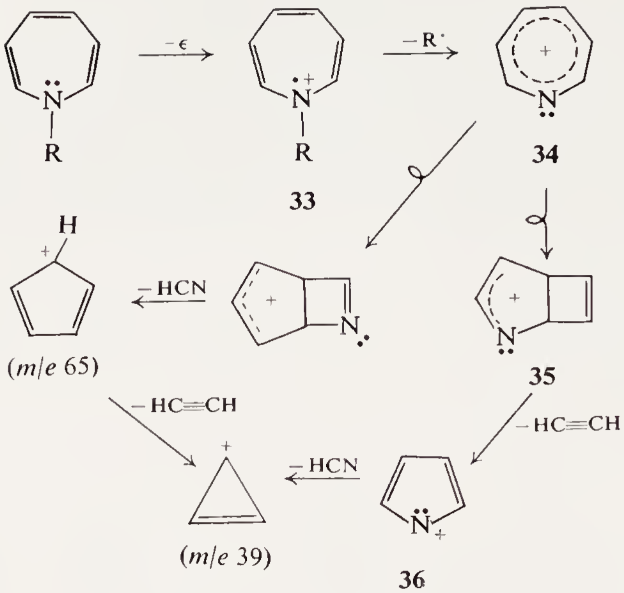
[d] L. A. Paquette and D. E. Kuhla, unpublished observations.

[e] L. A. Paquette and R. J. Haluska, unpublished observations.

D. MASS SPECTRA

The overwhelmingly favored electron impact fragmentation of ring unsubstituted 1*H*-azepines occurs between the ring nitrogen atom and the 1-substituent, giving the corresponding azatropylium cation **34** [base peak, mass/energy (*m*/*e*) 92]. Although the azepinium molecular ion **33** is always seen, its intensity is variable within the series, presumably because it tends to convert to cation **34** in certain derivatives. The second most pronounced feature of the spectra is due mainly to loss of the elements of HCN from **34**. The particle thus formed, which is presumably the cyclopentadienyl cation, decomposes further by the loss of acetylene to yield the cyclopropenium cation. Alternate bond reorganization in **34** can lead to **35** from which the elements of acetylene can be expelled producing **36**. However, this mode of cleavage does not seem to be important. In fact, the mass spectral fragmentation of 1*H*-azepines parallels the behavior of anilines under such conditions; the latter compounds fragment by way of intermediate azepinium ions.[25]

[25] K. L. Rinehart, Jr., A. C. Buchholz, and G. E. Van Lear, *J. Am. Chem. Soc.* **90**, 1073 (1968).



The mass spectra of 1-carbomethoxy-1*H*-azepines bearing methyl groups at the 2-, 3-, or 4-positions show that loss of methanol and formation of a base peak at *m/e* 133 are the most significant processes. Although of considerable mechanistic interest, these observations have not been studied to an extent warranting mechanistic speculation.

IV. Thermal Reactions of 1*H*-Azepines

A. DIMERIZATION

When 1-carboalkoxy-1*H*-azepines are heated at 200°C for 5–10 minutes, crystalline dimers of structure **37** are produced in high yield.[14,26] 1-Cyano-1*H*-azepine is similarly dimerized when heated at 210°–215°C for 15–30 minutes,[27] whereas 1-methyl-1*H*-azepine is reported to dimerize readily in ether solution above 0°C.[28] The gross structure of the various dimers has been elucidated from a large amount of spectroscopic data, chemical intercorrelation, and an X-ray analysis of **39**.[29]

The mechanism of this dimerization is of particular interest since it involves a $(6 + 6)\ \pi$ thermal cycloaddition, a concerted process which is disallowed on

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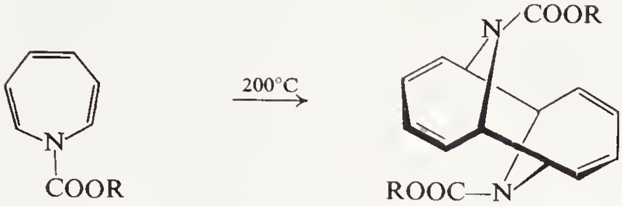
[26] L. A. Paquette and J. H. Barrett, *J. Am. Chem. Soc.* **88**, 2590 (1966).

[27] A. L. Johnson and H. E. Simmons, *J. Am. Chem. Soc.* **88**, 2591 (1966); **89**, 3191 (1967).

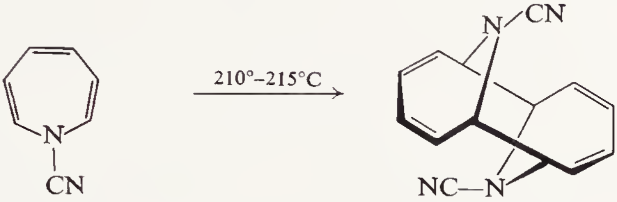
[28] K. Hafner and J. Mondt, *Angew. Chem.* **78**, 822 (1966); *Angew. Chem. Intern. Ed.* **5**, 839 (1966).

[29] G. Habermehl and S. Göttlicher, *Angew. Chem.* **79**, 820 (1967); *Angew. Chem. Intern. Ed.* **6**, 805 (1967).



R = CH_3, $—C_2H_5$, $—C(CH_3)_3$, etc.

37



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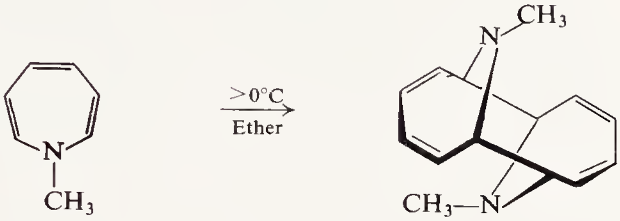
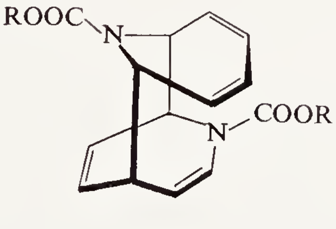


39

the basis of orbital symmetry.[30] Evidence for a multistep pathway has been obtained in each instance. At lower temperatures, the parent azepines dimerize to kinetically controlled products lacking an element of symmetry; at higher temperatures, the unsymmetrical dimers are smoothly converted to the thermally more stable dimers **37**–**39**.[26–28] Although the structures of unsymmetrical dimers derived from 1-cyano- and 1-methyl-1*H*-azepines remain unknown, the dimers derived from 1-carbalkoxy-1*H*-azepines appear to possess structure **40**.[14,26] Proof that these dimers are in fact products of (6 + 4) π *exo* addition comes from their NMR spectra, three-dimensional X-ray analysis of derived methiodide **41**,[31] and chemical degradation to ethylcyclodecane (**42**) (Scheme



40

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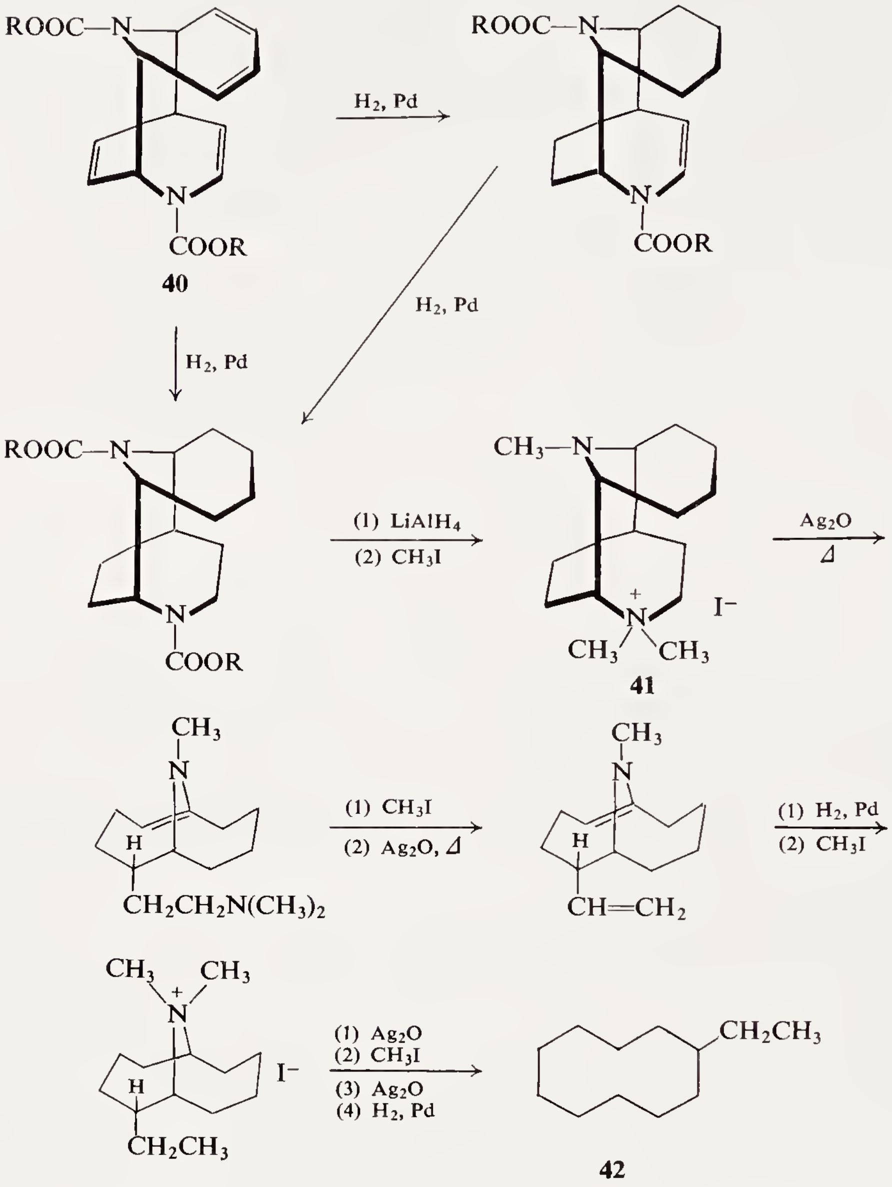
[30] R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.* **87**, 4388 (1965).

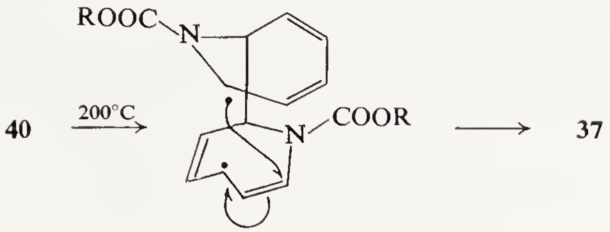
[31] I. C. Paul, S. M. Johnson, J. H. Barrett, and L. A. Paquette, *Chem. Commun.* p. 6 (1969).



SCHEME I. Chemical degradation of (6 + 4) π dimers of 1-carboalkoxy-1*H*-azepines.

I).[14] The dimerization of such 1*H*-azepines at moderate temperatures is obviously the result of a symmetry-allowed (6 + 4) π cycloaddition. This structurally unique dimer (**40**) undergoes rearrangement to **37** only at higher temperatures, perhaps by way of stabilized diradical **43**.

The thermal behavior of 1-methanesulfonyl-1*H*-azepine parallels that of the carbalkoxy series, at least at moderate temperatures.[18] Decomposition has been found to occur when the azepine or dimer **44** are heated to temperatures necessary for further rearrangement.



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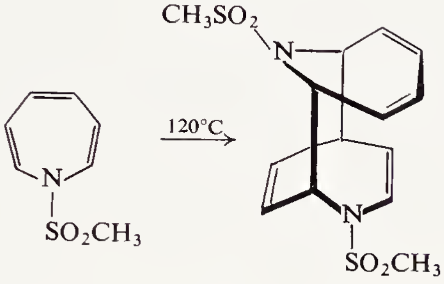
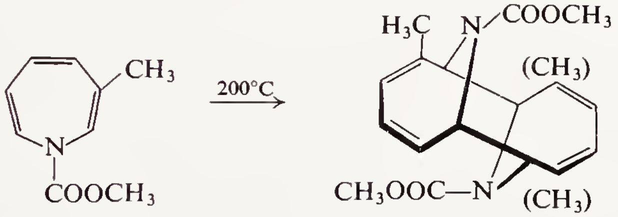


44

Finally, heating of **45** and **46** at 200°C for 10 minutes results in the formation of 13,14-diazatricyclo[6.4.1.$1^{2,7}$]tetradeca-3,5,9,11-tetraenes, but the relative position of attachment of the methyl groups is not known with certainty.[24] 1*H*-Azepines containing carbomethoxy substituents at the 4,5-positions have been reported to dimerize slowly in solution at 20°C; however, no further data are yet available concerning their structure.[19]



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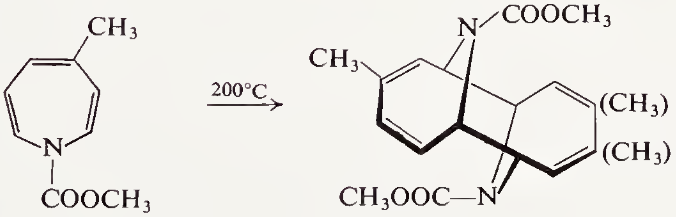
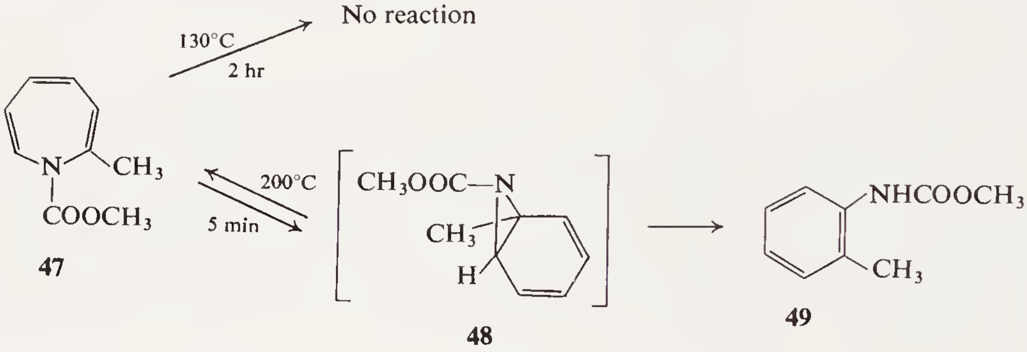
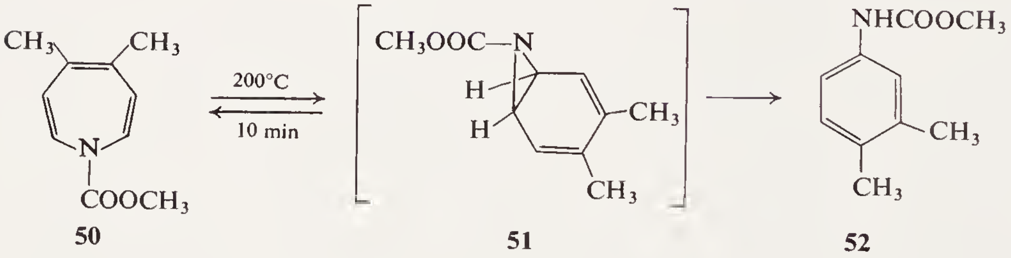


46

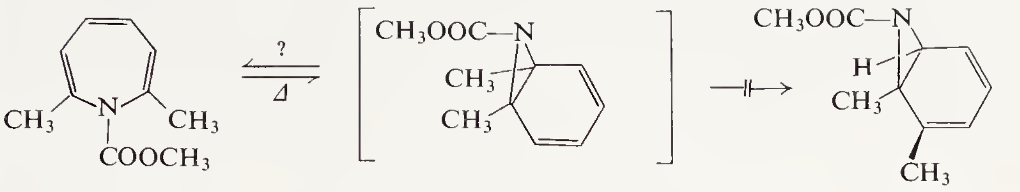
B. AROMATIZATION

The observation that thermal dimerization of 1-carboalkoxy-1*H*-azepines proceeds by way of initial (6 + 4) π cycloaddition prompted an examination of the effect of alkyl substitution at the 2, 4, and 7 ring positions involved in the intermolecular bonding process. Interestingly, heating of the 2-methyl derivative (**47**) at 130°C for periods ranging up to 2 hours leads to no reaction. At 200°C, **47** shows no tendency to dimerize; instead, this azepine is converted quantitatively to the aromatic urethan **49**.[24] In similar fashion, the 4,5-dimethyl congener **50** is transformed in this temperature range to **52**; again, no evidence of dimerization was found.[14] Obviously, therefore, the dimerization of this group of 1*H*-azepines is subject to pronounced steric inhibition. The reaction path leading from such azepines to their aromatic isomers very probably involves aziridinobenzene valence tautomers such as **48** and **51**. Homolytic rupture of the more highly substituted C—N bond with synchronous hydrogen atom transfer permits ultimate benzenoid stabilization.





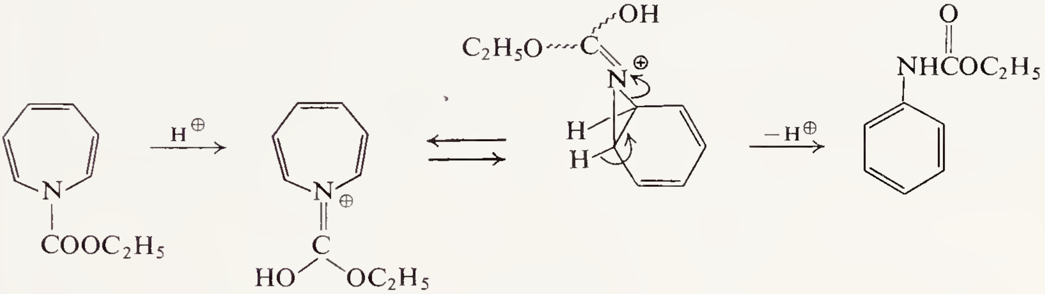
In the case of 1-carbomethoxy-2,7-dimethyl-1*H*-azepine (**53**), the corresponding valence tautomer **54** cannot undergo hydrogen atom migration. Although in a formal sense this molecule (**53**) contains three conjugated double bonds and is entirely azepine-like in its spectral characteristics, it shows no tendency to dimerize and is not converted to a benzenoid isomer at elevated temperatures. Remarkably, azepine **53** withstands prolonged heating (24 hours) at 200°C without noticeable dire effects.[14] The marked difference in reactivity



53 **54** **55**

between **53**, on the one hand, and **47** and **50**, on the other, is very likely due to the absence of a proton in **54** which would migrate. Perhaps most striking is the fact that thermally induced, suprafacial sigmatropic shifts of order [1,5][32] (e.g., **54** → **55**) such as those observed in tropylidene skeletal rearrangements[33a, b, c] do not occur in these heterocyclic examples under the stated conditions.

The reaction of 1-carboalkoxy-1*H*-azepines with acids also leads rapidly to *N*-phenylurethans which presumably result from protonation on oxygen, valence bond isomerization, and irreversible rupture of the aziridinium ring.[34]



C. Additional Rearrangements

When dimethyl 1,2,7-trimethyl-1*H*-azepine-3,6-dicarboxylate (**26**) is heated under reflux in benzene, it undergoes almost quantitative rearrangement to the 6-aminofulvene **56**.[21a, b] The same thermal reorganization also occurs when **26** is passed through a tube containing fine sand at 130°C. A possible mechanism for this complex rearrangement is depicted above. The driving force for the various electronic shifts is perhaps derived from the aromatic stabilization associated with the aminofulvene.

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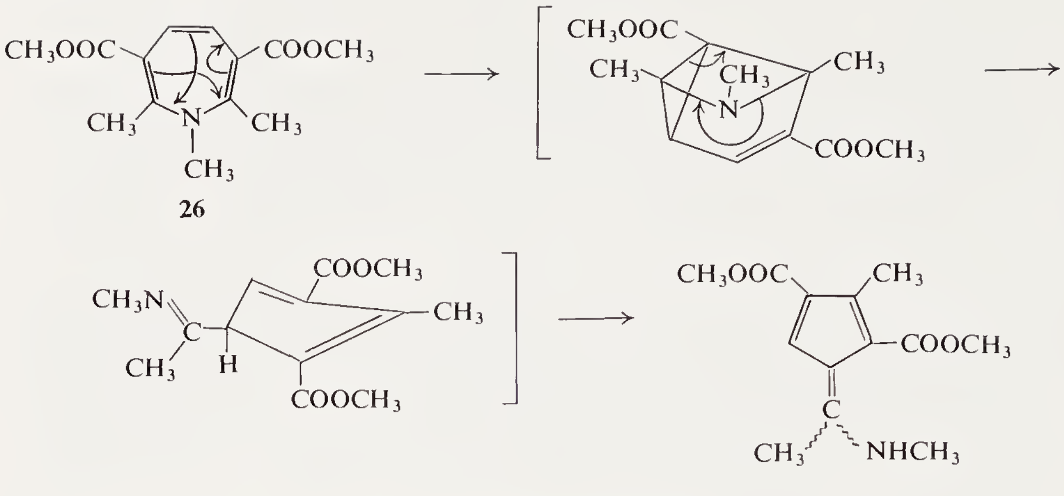
[32] R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 2511 (1965).

[33a] J. A. Berson and M. R. Wilcott, III, *J. Am. Chem. Soc.* **88**, 2494 (1966).

[33b] J. A. Berson and M. R. Wilcott, III, *Record Chem. Progr.* **27**, 139 (1966).

[33c] J. A. Berson, *Accounts Chem. Res.* **1**, 152 (1968).

[34] K. Hafner, *Angew. Chem.* **75**, 1041 (1963); *Angew. Chem. Intern. Ed.* **3**, 165 (1964).



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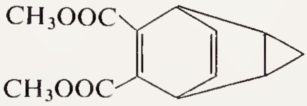
V. Cycloaddition Reactions of 1*H*-Azepines

Because of the relative ease with which medium-ring conjugated polyenes undergo valence bond tautomerization and because the diene unit in the bicyclic isomer is quite planar and therefore somewhat more reactive as a 4 π-electron donor, additions of dienophiles to such polyenes frequently give rise to abnormal products. For example, reaction of cycloheptatriene with dimethyl acetylenedicarboxylate leads to the tricyclic adduct **57** formally derived from norcaradiene,[35] and oxepin and maleic anhydride afford the epoxide **58** (see Section XVII,C) by reaction through the benzene oxide form.[36] Similarly, the production of **59** from cyclooctatetraene and tetracyanoethylene is known to involve a rapid preequilibrium between the tetraene and bicyclo[4.2.0]octatriene, with the latter giving rise to **59** in the rate-determining step.[37] 1,3,5-Cyclooctatriene behaves analogously.[38] The more



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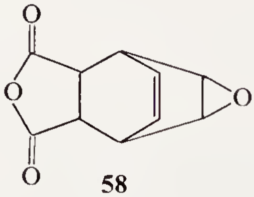

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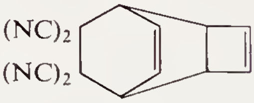

59

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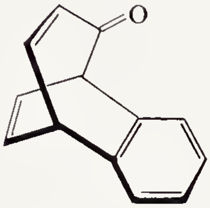
[35] K. Alder and G. Jacobs, *Ber.* **86**, 1528 (1953).

[36] E. Vogel, W. A. Böll, and H. Günther, *Tetrahedron Letters* p. 609 (1965).

[37] R. Huisgen and F. Mietzsch, *Angew. Chem.* **76**, 36 (1964).

[38] A. C. Cope, A. C. Haven, Jr., F. L. Ramp, and E. R. Trumbull, *J. Am. Chem. Soc.* **74**, 4867 (1952).

highly polarized tropones and tropolones give (4 + 2) π cycloadducts such as **60** (from reaction with benzyne) directly.[39a–g]



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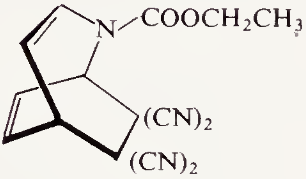
1-Carboethoxy-1*H*-azepine (**11**) is surprisingly inert to dienophiles such as maleic anhydride and dimethyl acetylenedicarboxylate without solvent even at temperatures above 100°C.[40] The azepine reacts readily, however, with tetracyanoethylene in benzene at room temperature[40] and with *N*-phenylmaleimide in refluxing toluene[14] to give the crystalline adducts **61** and **62**, respectively. Proton spin decoupling data have provided ample evidence for



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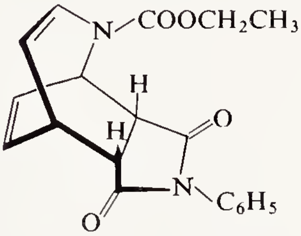

62

these structural assignments and have permitted deduction of the *endo* configuration for the succinimide residue in **62**.[14] In addition, methoxybromination

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[39a] T. Nozoe, T. Mukai, K. Takase, and T. Nagase, *Proc. Japan Acad.* **28**, 477 (1962); *Chem. Abstr.* **48**, 2678 (1954).

[39b] J. Meinwald, S. L. Emerson, N. C. Yang, and G. Buchi, *J. Am. Chem. Soc.* **77**, 4400 (1955).

[39c] O. L. Chapman and D. J. Pasto, *J. Am. Chem. Soc.* **81**, 3696 (1959).

[39d] T. Nozoe, T. Mukai, T. Nagase, and Y. Toyooka, *Bull. Chem. Soc. Japan* **33**, 1147 (1960).

[39e] J. Ciabattoni, J. E. Crowley, and A. S. Kende, *J. Am. Chem. Soc.* **89**, 2778 (1967).

[39f] Y. Kitahara, I. Murata, and T. Nitta, *Tetrahedron Letters* p. 3003 (1967).

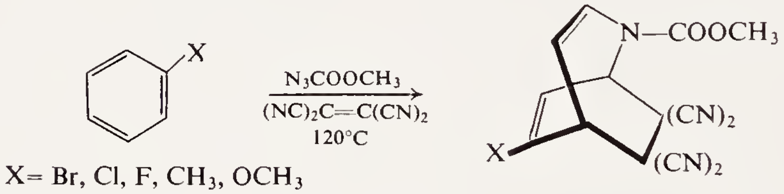
[39g] S. Ito, H. Takeshita, Y. Shoji, Y. Toyooka, and T. Nozoe, *Tetrahedron Letters* p. 3215 (1968).

[40] A. S. Kende, P. T. Izzo, and J. E. Lancaster, *J. Am. Chem. Soc.* **87**, 5044 (1965).

of **61** provides a crystalline methoxybromide, X-ray analysis of which provides unequivocal evidence for the structure of this cycloaddition product.[41]

As with cycloheptatriene, oxepin, cyclooctatetraene, and related molecules, two modes of (4 + 2) π cycloaddition to **11** are theoretically possible: (*1*) direct 1,4 Diels-Alder addition to two of the three double bonds of the ring, or (*2*) preequilibrium valence tautomerization of **11** to the aziridinobenzene form followed by kinetically controlled cycloaddition. In contrast to these closely related analogs, **11** does not react via its bicyclic tautomeric form (path *2*). Such results suggest that whereas the transition state energies involved in the cycloheptatriene–norcaradiene, oxepin–benzene oxide, and cyclooctatetraene–bicyclo[4.2.0]octatriene bond reorganizations are not large, the energy of activation relating **11** to the aziridinobenzene tautomer must be appreciable. Apparently, this barrier can be surmounted at temperatures in the vicinity of 200°C, but only when the rate of dimerization is sufficiently retarded by steric influences (Section IV,B). Also relevant to this question is the fact that the NMR spectra of various 1*H*-azepines down to −90°C show no evidence for the presence of the bicyclic aziridinobenzene tautomer (Section III,B).

Decomposition of methyl azidoformate at 120°C in monohalobenzenes, toluene, or anisole containing tetracyanoethylene gave rise to a crystalline 1:1 adduct (15–38% yields) shown to have structure **63**.[16a] Structural assignment for these adducts was made by considering their spectral characteristics (Table VII). Compounds of type **63** obviously result from (4 + 2) π cycloaddition of tetracyanoethylene exclusively to the derived 4-substituted 1*H*-azepines. These results are somewhat surprising since nitrene insertions into monosubstituted benzenes are known to give mixtures of all possible positional isomers (Section II,A) and three cycloaddition products are therefore expected. Actually subsequent X-ray single crystal structure analysis of the adduct derived from bromobenzene demonstrated that the substance was a mixture of cocrystallized isomers **63** (X = Br) and **64** in the approximate ratio of 5:1.[16b,c]



63

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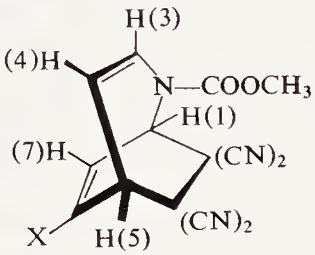
[41] J. H. van den Hende and A. S. Kende, *Chem. Commun.* p. 384 (1965).

TABLE VII

COUPLING CONSTANTS AND CHEMICAL SHIFTS IN TETRACYANOETHYLENE-1*H*-AZEPINE ADDUCTS[a]

Formula		Coupling constants (Hz)					Chemical shifts (τ)				
		$J_{4,5}$	$J_{3,4}$	$J_{1,7}$	$J_{5,7}$	$J_{1,3}$	H-1	H-3	H-4	H-5	H-7
	X = Br	9.0	8.9	7.7	1.8	1.5	3.96	2.93	4.68	5.70	3.07
	X = Cl	9.1	9.2	8.0	1.9	1.5	3.87	2.93	4.65	5.75	3.26
	X = F	9.2	9.2	—	1.6	—	3.80	2.92	4.66	5.70	3.80
	X = H	8.8	8.8	7.5	1.3	1.4	4.05	2.9	4.78	6.08	3.0
	X = CH$_3$	9.0	9.2	7.5	1.4	1.5	4.11	3.07	4.78	6.20	3.72
	X = OCH$_3$	9.2	9.3	8.4	2.0	1.3	3.91	3.01	4.75	6.07	4.55

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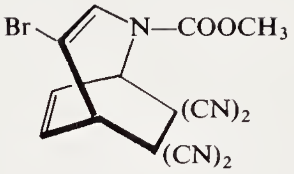
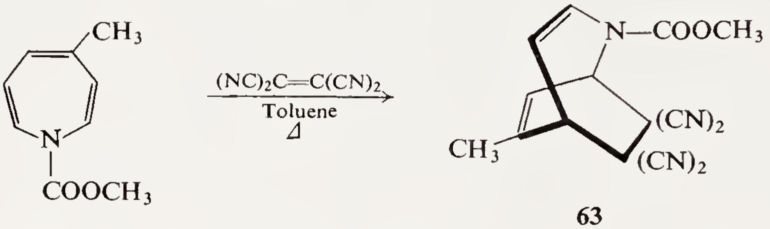
[a] J. E. Baldwin and R. A. Smith, *J. Am. Chem. Soc.* **87**, 4819 (1965).

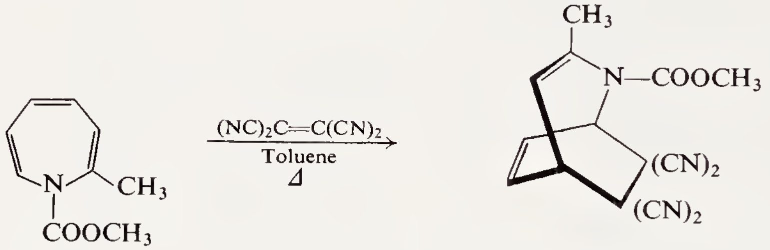


64

Because of the uncertainties introduced in working with such mixtures of unknown composition, we have extended our cycloaddition studies to include the three isomerically pure methyl-1-carbomethoxy-1*H*-azepines.[24] It was found that **46** reacts readily with tetracyanoethylene in refluxing toluene to produce the previously characterized 1:1 adduct **63** ($X = CH_3$) in 65% yield. In marked contrast, the 2-methyl isomer **47** under identical conditions led to **65**, but only in 2.5% yield. The urethan **49** can also be isolated (5% yield);



46 **63**



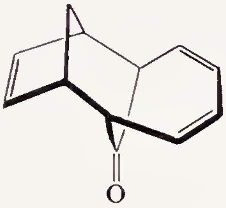
47 **65**

the major portion of the reaction mixture is an intractable black tar. The 3-methyl isomer **45** also produces much dark resin; the small proportion of tractable material is a mixture of both possible isomeric adducts.

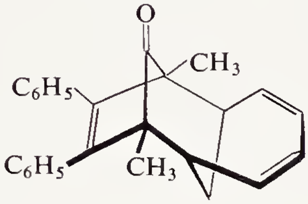
This scale of reactivity clearly indicates that the adducts derived from 4-substituted 1-carbomethoxy-1*H*-azepines were isolated by Baldwin and Smith because of the intrinsic ease with which they condense with tetracyanoethylene. More important, it should be noted that all the examples of $(4 + 2)\ \pi$ cycloaddition which have been examined to date have proceeded with a high degree of positional selectivity, the isomer less influenced by steric effects in the set of transition states of the two competing reactions being produced.

Earlier, the kinetically controlled dimerization of 1-carbalkoxy-1*H*-azepines was shown to be the result of a (6 + 4) π cycloaddition with *exo* orientation. In this cycloaddition, the azepine molecules are required to play the rather unique bifunctional role of 6 π- and 4 π-electron donor. Because of this unprecedented capability of the 1*H*-azepines, a more detailed investigation of the behavior of these 8 π heterocycles in a variety of cycloaddition reactions seemed warranted.

It should be mentioned here that other examples of (6 + 4) π cycloaddition are of the intermolecular variety and are very few in number. To the present time, the reactions of tropone with cyclopentadiene to give **66**,[42,43] of dimethyldiphenylcyclopentadienone with cycloheptatriene to afford **67**,[44] and of dimethyldiphenylcyclopentadienone with tropone to give **68**,[44] represent the other known illustrations of this interesting and novel bonding process.



66



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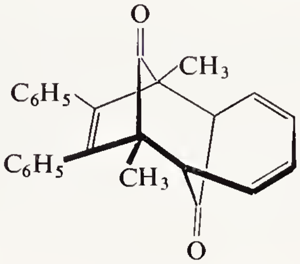
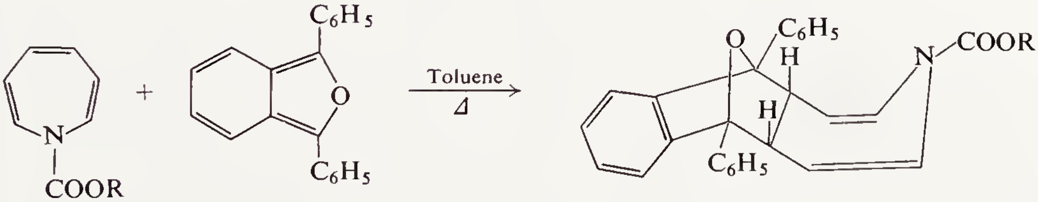


68

We have observed that 1-carboalkoxy-1*H*-azepines, when heated with 1,3-diphenylisobenzofuran in refluxing toluene, are converted in good yield to 1:1 adducts of structure **69**.[14,45] The gross structure of these heteroatomic poly-



69

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[42] R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Commun.* p. 15 (1966).

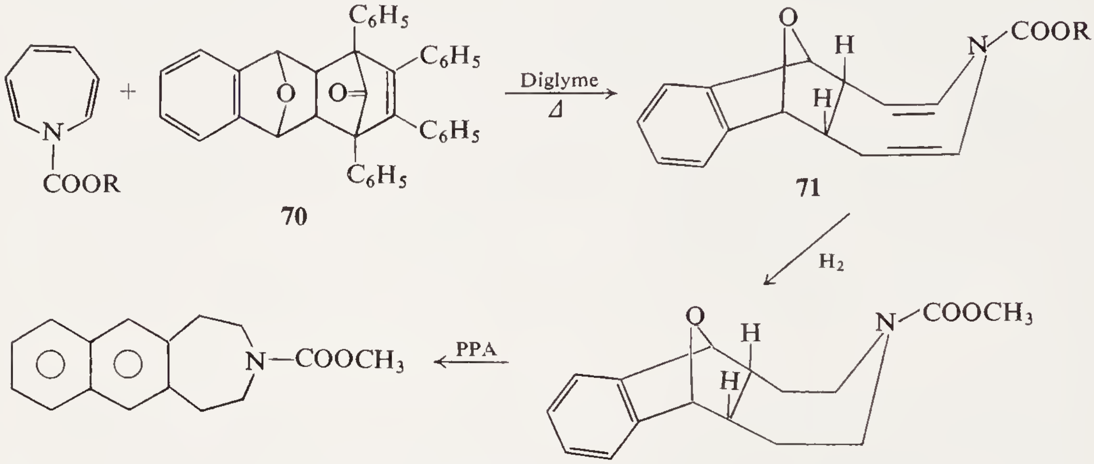
[43] S. Ito, Y. Fujise, T. Okuda, and Y. Inoue, *Bull. Chem. Soc. Japan* **39**, 1951 (1966).

[44] R. B. Woodward and K. Houk, unpublished work cited by R. B. Woodward, *Chem. Soc.* (*London*), *Spec. Publ.* **21**, 242–246 (1967).

[45] L. A. Paquette and L. Leichter, unpublished results.

cycles was derived principally on spectroscopic grounds except for their stereochemistry which was assigned by analogy to **71** (see below).

These same azepines were found to condense smoothly with isobenzofuran (generated *in situ* from **70**) to give *endo* adducts of type **71**.[14,45] In these derivatives, the stereochemical course of the addition could be established as *endo* from the coupling constant exhibited by the equivalent pairs of bridgehead protons. The magnitude of this coupling is known to be a function of the internal dihedral angle between the planes of the C—H bonds. Additionally, **71** was catalytically hydrogenated and dehydrated in polyphosphoric acid to give a 2,3-disubstituted naphthalene.



Thus, the adducts from *N*-substituted azepines and isobenzofurans result from (4 + 2) π cycloaddition to the 4,5 bond rather than from (6 + 4) π cycloaddition.

VI. Photorearrangement of 1*H*-Azepines

Heretofore, discussion has centered on the ground-state properties of 1*H*-azepines. The excited-state reactivity of these 8 π heterocycles can be conveniently examined under ultraviolet irradiation. In particular, it was deemed interesting to determine if 1*H*-azepines would undergo transformations from their electronically excited states either paralleling or differing from those observed with related 6 π-electron systems such as the cycloheptatrienes.[46] Irradiation of a 2% tetrahydrofuran solution of **11** under nitrogen for 2–3 days with a 450 W mercury arc led to the total disappearance of the azepine and the

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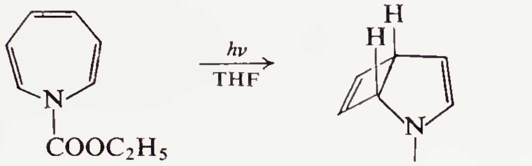
[46] O. L. Chapman, *Advan. Photochem.* **1**, 323 (1963).

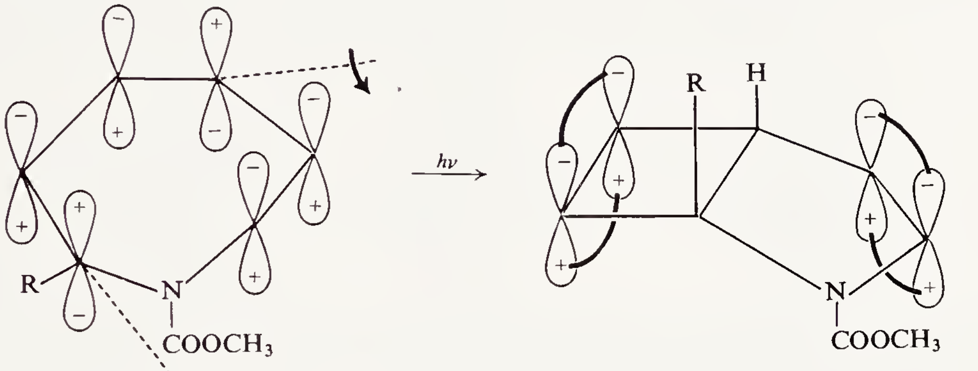
concomitant formation of a single photoproduct identified as **72**.[47] The isomeric nature of **72** was deduced from its spectral characteristics and its facile



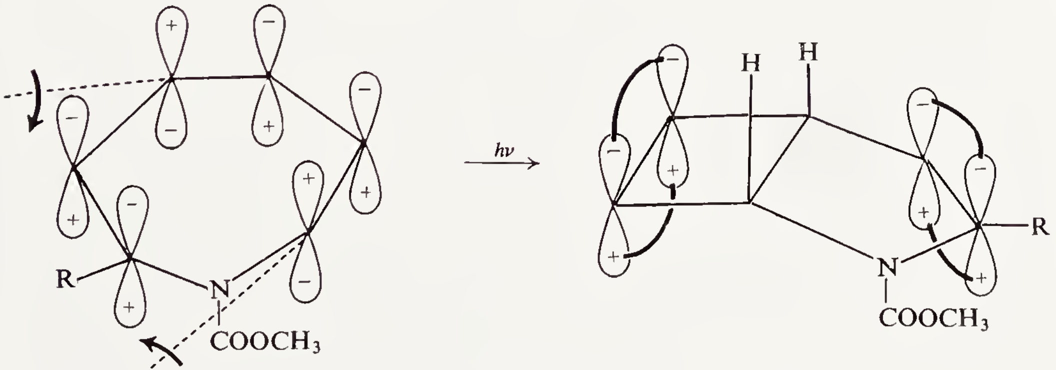
11 **72**

thermal reversal to **11** at about 100°C. Clearly, therefore, the photochemical behavior of 1*H*-azepines such as **11** parallels the general photoisomerization pathway of cycloheptatrienes and cycloheptadienes.

Woodward-Hoffmann orbital symmetry arguments for electrocyclic reactions[20] indicate that the formation of bicyclic photoproduct **72** proceeds by disrotatory motion of π orbital envelopes in the lowest lying excited state. In monosubstituted derivatives of **11**, however, two different disrotatory cyclizations are possible, as illustrated for a 2-substituted isomer in formulas **73** and **74**. By merely analyzing the primary photoproducts resulting from the ir-



73



74

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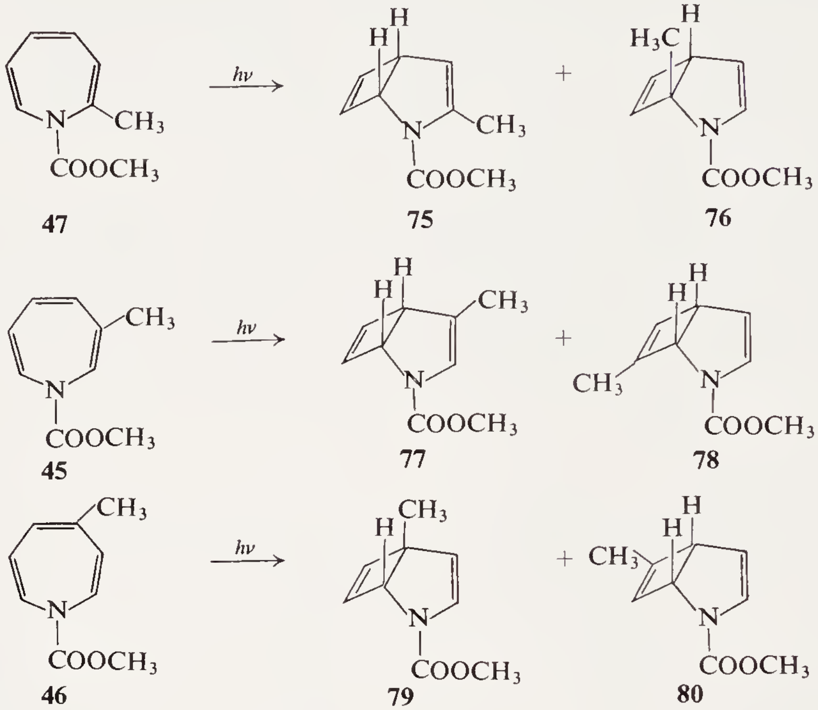
[47] L. A. Paquette and J. H. Barrett, *J. Am. Chem. Soc.* **88**, 1718 (1966).

radiation of such substituted 1*H*-azepines, the influence exerted by the R group upon the two electrocyclic processes can be evaluated. Irradiation of **47** was observed to give rise to **75** and **76** in a ratio of 14:1. Photorearrangement of the 3-methyl isomer **45** led to the formation of **77** and **78** in equimolar quantities. Last, photolysis of **46** under the same conditions afforded **79** and **80** in a ratio of 1.5:1.[24] The structures of photoproducts **75**–**80** were deduced on the



47 **75** **76**

45 **77** **78**

46 **79** **80**

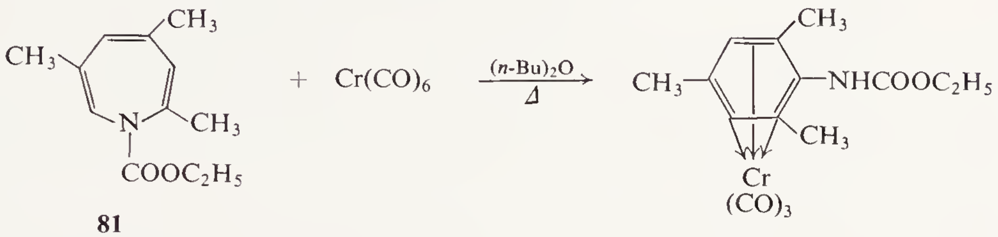
basis of their NMR spectra, analysis of which was particularly easy because of the extensively analyzed spectrum of 72.[47]

The photoreaction observed for **47** is quite selective; of the two possible products, that in which the ring methyl substituent occupies the more congested angular position (**76**) is produced only in low yield. This would appear to indicate that steric effects are dominant in this reaction. On this basis, the observation that **45** produces both possible valence tautomers (**77** and **78**) in equal amounts is anticipated since the photoisomers are not expected to differ measurably in strain energy. Surprisingly, however, the 4-methyl function in **46** does not exert an overwhelming directive influence on the course of the photoreaction. It has been concluded that the presence of a methyl group alone at an angular position is not a strong enough deterrent to product formation. Rather, the proximity of such a substituent to a bulky group on nitrogen effectively retards the rate of that disrotatory motion which gives rise to the more strained bicyclic isomer.

VII. Transition Metal Complexes of 1*H*-Azepines

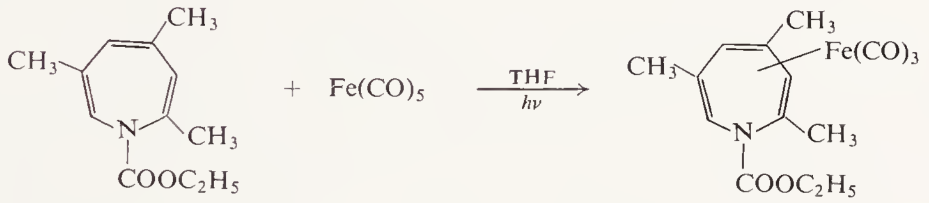
A. SYNTHESIS

On reaction of **11** with chromium hexacarbonyl in di-*n*-butyl ether at 110°–120°C, benzene chromium tricarbonyl is formed through elimination of the urethan function. Under analogous conditions, the 2,4,6-trimethyl congener **81** is converted to mesitylurethan chromium tricarbonyl (**82**).[48]

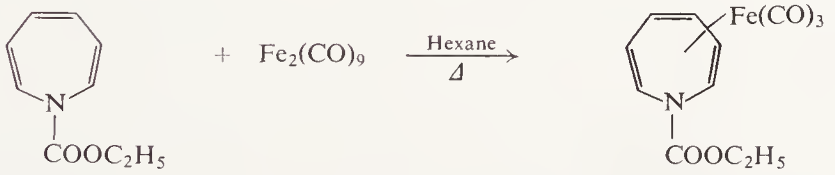


81 **82**

In contrast, irradiation of **11** or **81** with iron pentacarbonyl in tetrahydrofuran solution yields air-stable iron tricarbonyl complexes.[48] The same transition metal complexes can be more conveniently prepared by warming the azepine briefly with iron enneacarbonyl in hexane solution.[49]



81 **83**



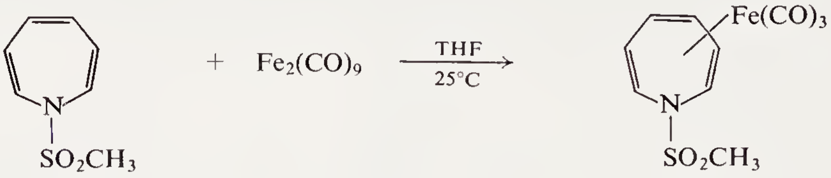
11 **84**

Careful alkaline hydrolysis of **83** and **84** leads to the corresponding air-sensitive azepine iron tricarbonyl complexes with a free N—H group.[48] It should be mentioned that alkaline hydrolysis of uncomplexed azepine **11** has been reported to yield the potassium salt of the derived carbamic acid which

[48] E. O. Fischer and H. Rühle, *Z. Anorg. Allgem. Chem.* **341**, 137 (1965).
[49] L. A. Paquette, unpublished results.

decarboxylated readily under the influence of acids. The expected 1*H*-azepine apparently exhibited only transitory existence[34]; unfortunately, the details of this work have not been published.

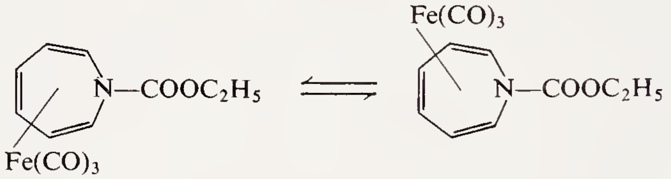
Complex formation is not restricted to 1-carboalkoxy-1*H*-azepines, but appears to be generally applicable, as indicated by the preparation of **85**.[18]



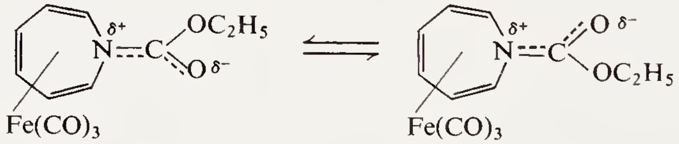
85

B. Nuclear Magnetic Resonance Spectra

Metal carbonyl complexes of olefinic ligands possessing additional noncomplexed π bonds in conjugation are known to be capable of rapid and reversible valence tautomerism.[50a–g] Iron tricarbonyl complexes of 1*H*-azepines do not deviate from this general behavior. Variable-temperature NMR studies of various 1-substituted-1*H*-azepine iron tricarbonyls have confirmed the existence not only of equilibria of type **84a** ⇆ **84b**, but also of restricted rotation



84a **84b**



84a (cis) **84a** (trans)

[50a] J. E. Mahler, D. A. K. Jones, and R. Pettit, *J. Am. Chem. Soc.* **86**, 3589 (1964).

[50b] G. F. Emerson, J. E. Mahler, R. Pettit, and R. Collins, *J. Am. Chem. Soc.* **86**, 3590 (1964).

[50c] C. E. Keller, G. F. Emerson, and R. Pettit, *J. Am. Chem. Soc.* **87**, 1388 (1965).

[50d] C. G. Kreiter, A. Maasbol, F. A. L. Anet, H. D. Kaesz, and S. Winstein, *J. Am. Chem. Soc.* **88**, 3444 (1966).

[50e] F. A. L. Anet, H. D. Kaesz, A. Maasbol, and S. Winstein, *J. Am. Chem. Soc.* **89**, 2489 (1967).

[50f] F. A. L. Anet, *J. Am. Chem. Soc.* **89**, 2491 (1967).

[50g] R. B. King, *J. Organometal. Chem.* **8**, 129 (1967).

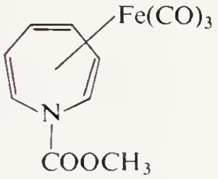
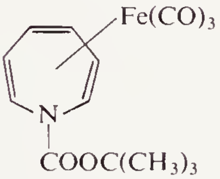
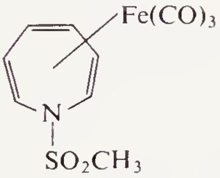
of the *N*-substituent, e.g., **84a** (cis) ⇆ **84a** (trans).[51,52] From the several coalescence temperatures in the spectra of **84**, Günther and Wenzl[51] have obtained for the valence tautomerism at 34°C the values k ~60 sec^{-1} and $\Delta G^\ddagger$ ~15.5 kcal/mole. Further, rotation of the carboethoxy group at −28°C proceeds at a rate ($\overrightarrow{k}$) of approximately 10 sec^{-1} and with an energy of activation ($\overrightarrow{\Delta G^\ddagger}$) approaching 13.1 kcal/mole.

C. ULTRAVIOLET AND INFRARED SPECTRA

The ultraviolet spectra of 1*H*-azepine iron tricarbonyl derivatives (Table VIII) indicate, as expected, that the electronic transition energies of the 1*H*-azepine chromophore are appreciably altered in the complexed state. Thus,

TABLE VIII

ULTRAVIOLET SPECTRA OF SOME 1*H*-AZEPINE-$Fe(CO)_3$ DERIVATIVES

	95% EtOH		
Compound	λ_{max} (mμ)	ϵ	Reference
	250 297 sh	17,670 5,390	*a*
	249.5 298 sh	18,770 5,825	*a*
	ca. 232 (plateau)	14,600	*b*

[a] L. A. Paquette and D. E. Kuhla, unpublished observations.
[b] L. A. Paquette and R. J. Haluska, unpublished observations.

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[51] H. Günther and R. Wenzl, *Tetrahedron Letters* p. 4155 (1967).

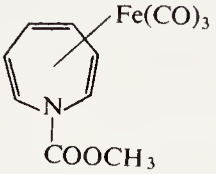
[52] L. A. Paquette and J. R. Malpass, unpublished observations.

the spectra of these complexes are usually structureless with a single peak or plateau generally apparent on the tail of high intensity end absorption.

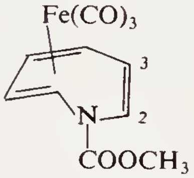
Two infrared vibration types are of utility for spectral correlations. The first type comprises the stretching vibrations of the metal carbonyl groups; these appear as a group of two bands occurring at 2050–2070 cm^{-1} and at 1970–2000 cm^{-1}. The first of the two absorptions is sharp while the latter is frequently structured and may actually appear as a split band. The second group of vibrations are peculiar to the characteristics of the substituent on nitrogen. For example, the amide I band of **84** occurs at 1712 cm^{-1} (in **11**, this particular vibration is seen at 1709 cm^{-1}) and the sulfonamide absorption of **85** is associated with intense absorption at 1350 and 1170 cm^{-1}.

D. X-Ray Studies

In order to elucidate the molecular geometry of the π-bonded iron complexes of 1*H*-azepines, an X-ray analysis of **86** was performed.[22] In **86**, the iron tricarbonyl moiety complexes to a four carbon atom residue cis to the carbonyl function. Because the Fe· · ·N-1 and Fe· · ·C-3 distances are almost equal, it does not appear that the nitrogen atom participates in complex formation. The measured bond distances are consistent with a localized double bond at C-2–C-3 and delocalization in the remaining carbocyclic portion of the seven-membered ring. The geometry of the complex **87** bears a general resemblance to the $Fe(CO)_3$ complexes of tropone[53] and its 2,4,6-triphenyl congener,[54] the most significant difference being a greater tendency toward planarity at N-1 in **86**.



86



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VIII. Homo-1*H*-azepines

Treatment of excess cycloheptatriene with methyl azidoformate at 125°C produces a mixture of 1:1 adducts from which a 35% yield of homoazepines

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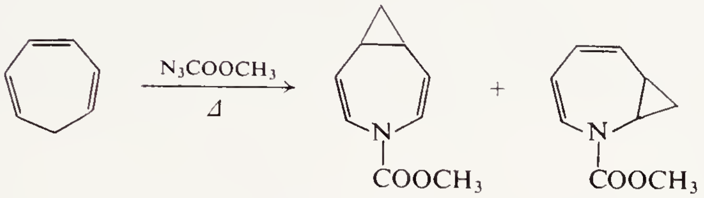
[53] R. P. Dodge, *J. Am. Chem. Soc.* **86**, 5429 (1964).
[54] D. L. Smith and L. F. Dahl, *J. Am. Chem. Soc.* **84**, 1743 (1962).

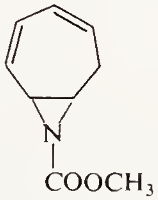
88 and **89** can be isolated.[55a] Similar results have been reported for the analogous ethyl azidoformate reaction.[55b] The ratio of **89** to **88** was approximately 2.2:1; in the carboethoxy series the ratio was somewhat higher (2.7:1). The minor products are apparently isomeric cycloheptatrienyl urethans. Homoazepine **88** exhibits ultraviolet absorption in ethanol at 231 mμ (ϵ 11,430) while isomer **89** displays a maximum at 262 mμ (ϵ 8430). The spectra of the analogous carboethoxy derivatives, measured in hexane, exhibited maxima at 265 mμ (ϵ 10,200) and 232 mμ (ϵ 13,000), respectively.



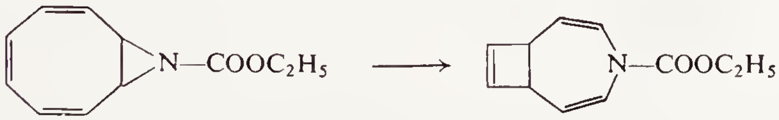
88 **89**

The homoazepines **88** and **89** are presumably formed by valence tautomerization of the initially produced aziridines **90** and **91**, respectively. The instabilities of the aziridine isomers relative to their homoazepine counterparts parallels the behavior of aziridinobenzenes and the carboethoxynitrene adduct of cyclooctatetraene (**92**).[56]

90



91



92

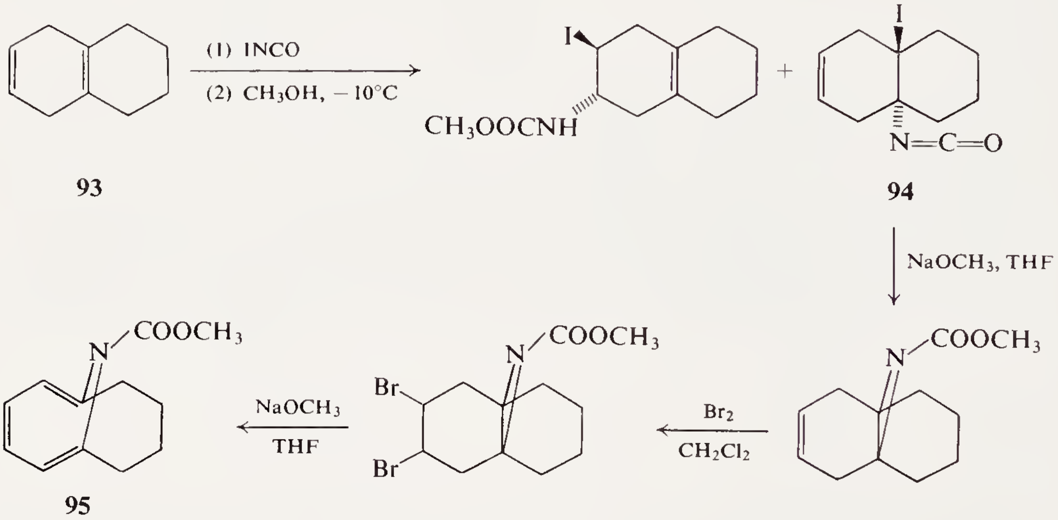
[55a] L. A. Paquette and R. J. Haluska, *Chem. Commun.*, p. 1370 (1968).

[55b] W. H. Okamura, W. H. Snider, and T. J. Katz, *Tetrahedron Letters* p. 3367 (1968).

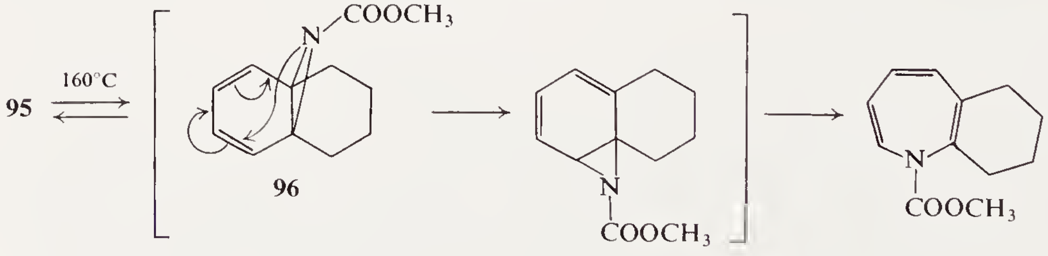
[56] S. Masamune and N. T. Castelluci, *Angew. Chem.* **76**, 569 (1964); *Angew. Chem. Intern. Ed.* **3**, 582 (1964).

IX. Annelated 1*H*-Azepines

The 1*H*-azepine–aziridinobenzene equilibrium is weighted so heavily in the direction of the 8 π-electron seven-membered ring that the bicyclic valence tautomeric form has never been detected [in significant contrast to the oxepin-benzene oxide system (see Sections XIV–XVI)]. Therefore, attempts were made to bridge the 2,7-positions of the 1*H*-azepine system with a methylene chain sufficiently short that steric factors would force complete displacement in favor of the aziridinobenzene.[24] From the product mixture obtained upon sequential reaction of dihydrotetralin **93** with iodine isocyanate and methanol, iodo isocyanate **94** could be readily converted to **95**. This tetramethylene-annelated substance was found to be uniform (colorless crystalline solid, MP 57.5°–59°C) and to exist in the 1*H*-azepine form [λ_{max} 213 (ϵ 18,950) and 258 mμ (ϵ 2700)]. This azepine does not appear to enter readily into (4 + 2) or (6 + 4) π cycloaddition reactions. In the vicinity of 160°C, it is rearranged cleanly to an isomeric 1*H*-azepine (**97**). This transformation is most readily interpreted via valence tautomer **96** which is subject to 1,5-sigmatropic shift of the nitrogen atom and Cope rearrangement as shown.

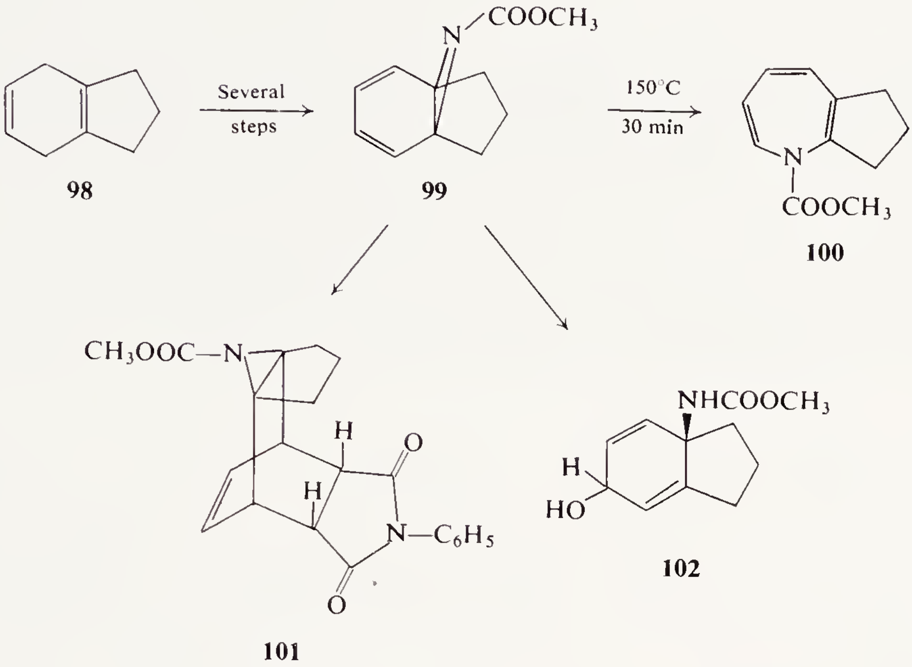


93 **94** **95**



96 **97**

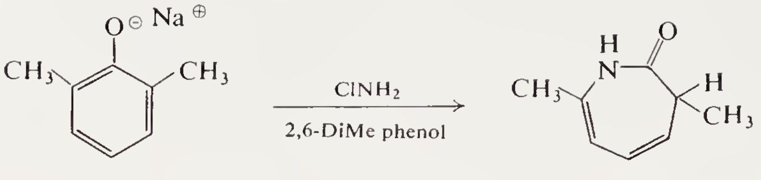
Complete reversal of the equilibrium is seen when the bridge consists of only three methylene groups. Thus, the reaction product obtained from tetrahydroindane **98** exhibits spectral and chemical properties, indicating that aziridinobenzene form **99** is locked in by the bracket. No evidence for the presence of a measurable concentration of the related 1*H*-azepine has been found.[24] When heated neat at 150°C, **99** is quantitatively converted to the stable isomeric 1*H*-azepine **100**. Although reaction of **99** with tetracyanoethylene affords only tarlike material, adduct **101** can be isolated in near quantitative yield when **99** is treated with *N*-phenylmaleimide. Especially worthy of note is the fact that **101** represents the only known example of a Diels-Alder addition to the aziridinobenzene tautomer of a 1*H*-azepine. Chromatography of **99** on Florisil with "wet" ether leads to the formation of **102** in 80% yield,[24] a transformation which expresses the high reactivity of aziridinobenzenes.



X. Synthesis of 3*H*-Azepine Derivatives

A. REACTION OF PHENOXIDE IONS WITH CHLORAMINE

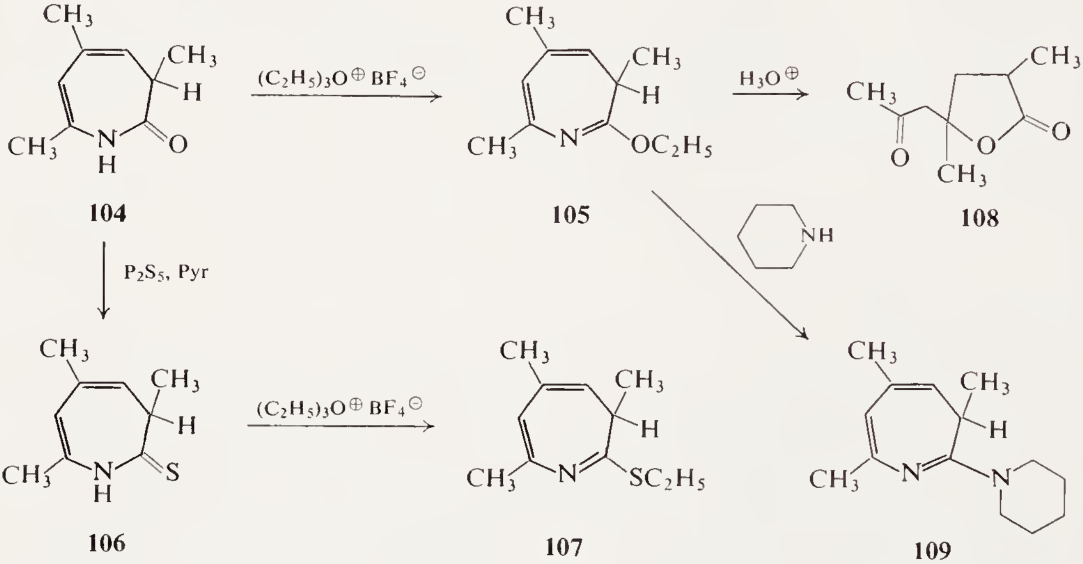
When hot (125°–150°C) solutions of sodio 2,6-dialkyl- and 2,4,6-trialkylphenoxides in excess of the corresponding phenols are treated with cold (–70°C) ethereal chloramine, 1,3-dihydro-2*H*-azepin-2-ones (e.g., **103**) are



103

obtained in good yield.[57a,b,c] The mechanism of this reaction is founded on the ambident nature of phenoxide ions and very likely involves initial C-amination of an α-carbon followed by thermal rearrangement of the resulting 2-aminocyclohexadienones.[57a,b,c] The *o*-alkyl substituents are necessary to prevent a simple prototropic shift from occurring at the 2-aminocyclohexadienone stage, a process which would eventuate merely in the production of *o*-aminophenols.

Reaction of the dihydroazepinones with triethyloxonium fluoroborate proceeds readily to afford 2-ethoxy-3*H*-azepines (e.g., **105**) in excellent yield.[58a,b]



The dihydroazepinones can also be converted to their thio analogs **106** with phosphorus pentasulfide in pyridine; the resulting thioamides are likewise capable of smooth conversion to 3*H*-azepine derivatives (**107**).[58a,b]

The 3*H*-azepines **105** and **107** are stable substances which can be stored indefinitely at room temperature with only slight coloration. Acid treatment of

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[57a] L. A. Paquette, *J. Am. Chem. Soc.* **84**, 4987 (1962).

[57b] L. A. Paquette, *J. Am. Chem. Soc.* **85**, 3288 (1963).

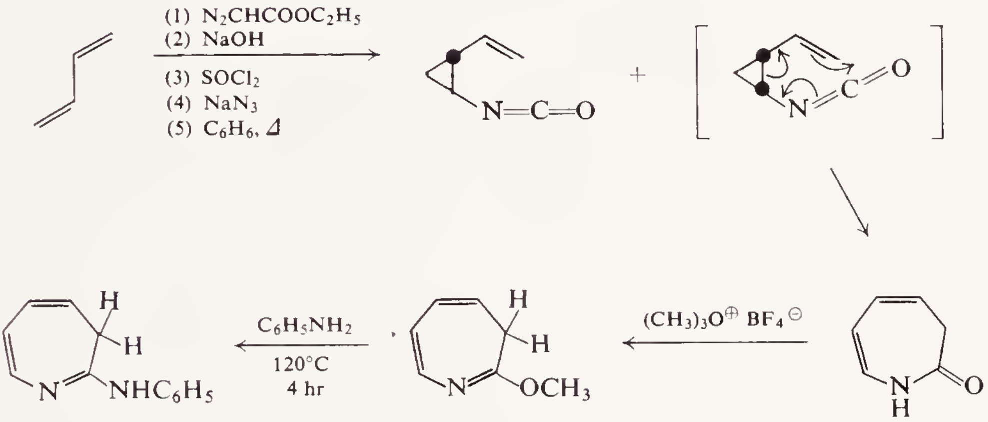
[57c] L. A. Paquette and W. C. Farley, *J. Am. Chem. Soc.* **89**, 3595 (1967).

[58a] L. A. Paquette, *J. Am. Chem. Soc.* **85**, 4053 (1963).

[58b] L. A. Paquette, *J. Am. Chem. Soc.* **86**, 4096 (1964).

105 yields ketolactone **108**, presumably by initial hydrolysis to the derived dihydroazepinone **104** and subsequent rearrangement.[58b] 3*H*-Azepine **105** reacts sluggishly with secondary amines. In refluxing piperidine, for 5 days, for example, 58% of **105** may be recovered; however, a 72% yield (based on recovered **105**) of 2-piperidino-3,5,7-trimethyl-3*H*-azepine (**109**) is obtainable.[58a, b]

Vogel and co-workers have reported a novel five-step synthesis of the parent 1,3-dihydro-2*H*-azepin-2-one (**110**).[59a, b] In view of the fact that the chloramine-phenoxide ion ring expansion of necessity leads only to alkylated derivatives of this ring system, Vogel's scheme nicely complements this synthetic approach.



110

B. GENERATION OF ARYLNITRENES IN PRIMARY AND SECONDARY AMINES

Thermal[60a–d] or photochemical[61] decomposition of aryl azides in the presence of amines bearing an active hydrogen results in the formation of 2-amino-3*H*-azepines (e.g., **111–113**). This reaction, which provides facile one-step access to such azepines, appears to be quite general. The overall transformation is best accommodated by a mechanism in which initially produced phenyl nitrene closes to azirine **114**. The latter intermediate then reacts with the amine component to form the observed seven-membered ring.

[59a] E. Vogel and R. Erb, *Angew. Chem.* **74**, 76 (1962).

[59b] E. Vogel, R. Erb, G. Lenz, and A. A. Bothner-By, *Ann.* **682**, 1 (1965).

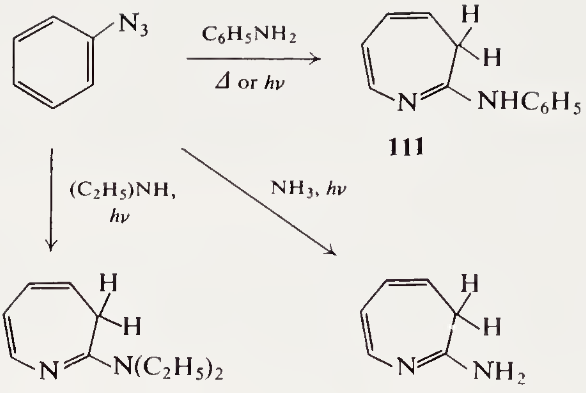
[60a] R. Huisgen, D. Vossius, and M. Appl, *Angew. Chem.* **67**, 756 (1955).

[60b] R. Huisgen, D. Vossius, and M. Appl, *Ber.* **91**, 1 (1958).

[60c] R. Huisgen and M. Appl, *Ber.* **91**, 12 (1958).

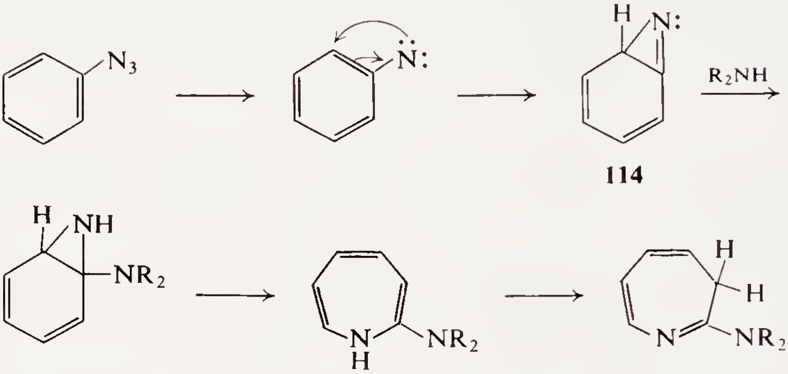
[60d] M. Appl and R. Huisgen, *Ber.* **92**, 2961 (1959).

[61] W. von E. Doering and R. A. Odum, *Tetrahedron* **22**, 81 (1966).



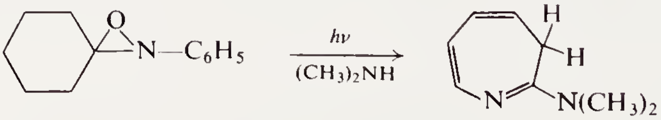
111

112 **113**



114

When phenyl nitrene is generated by alternative routes in the same medium, 2-amino-3*H*-azepines again result. For example, irradiation of spirooxazirane **115** in freshly distilled dimethylamine affords **116** through initial photofragmentation of **115** to phenyl nitrene.[62] Similarly, deoxygenation of nitrosobenzene with either triphenylphosphine or tributylphosphine in amine solvents eventuates in 2-amino-3*H*-azepine formation.[63]



115 **116**

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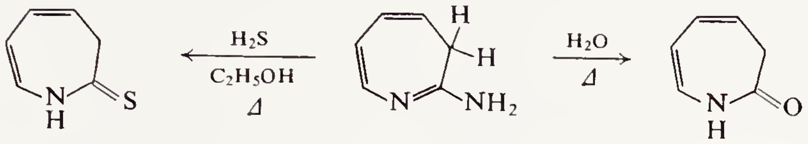
[62] E. Meyer and G. Griffin, *Angew. Chem.* 79, 648 (1967); *Angew. Chem. Intern. Ed.* **6**, 634 (1967).

[63] R. A. Odum and M. Brenner, *J. Am. Chem. Soc.* **88**, 2074 (1966).

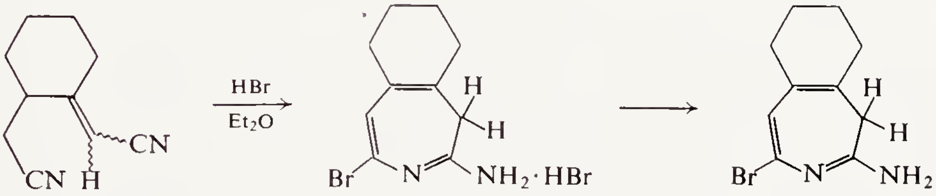
3*H*-Azepines such as **111**–**113** react with water or hydrogen sulfide in ethanol solution with hydrolysis of the amidine function producing the derived cyclic amide or thioamide, respectively.[61]



113 **110**

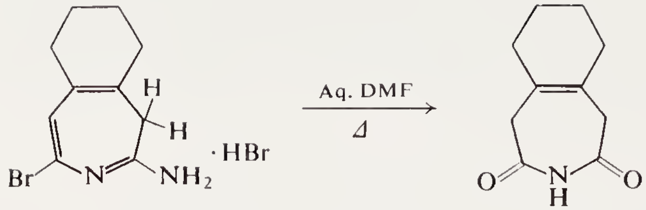
C. Cyclization of Dinitriles

The action of hydrogen halides on a dinitrile such as **117**, in which the cyano functions are held in sufficiently close proximity to permit interaction, leads to cyclization and formation of 3*H*-azepine derivatives.[64a,b,c] The transformation appears reasonably general for 1,2- and 1,3-dicyanoalkanes, but 1,4-dicyano compounds lead to highly unstable substances.[64a,b,c] Despite the fact that attempts to dehalogenate the bromine in **118** and its congeners by reductive methods have so far failed, these halo 3*H*-azepines are subject to other chemical changes. For instance, heating hydrobromide **120** in aqueous dimethylformamide at 90°C for several hours yields imide **121**. Also, reaction of **119** with sodium thiocyanate in hot dimethylformamide gives thiocyanate **122** whereas the action of sodium borohydride in methanol replaces the bromine by methoxy to give **123**.[64c]

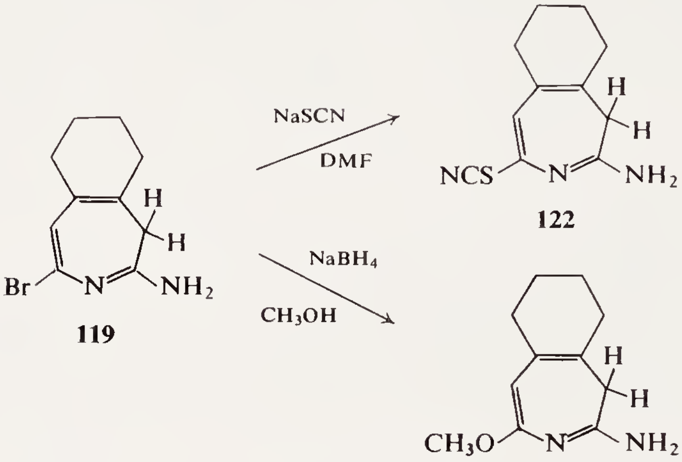


117 **118** **119**

[64a] F. Johnson and W. A. Nasutavicus, *J. Heterocyclic Chem.* **2**, 26 (1965).
[64b] W. A. Nasutavicus and F. Johnson, *J. Org. Chem.* **32**, 2367 (1967).
[64c] W. A. Nasutavicus, S. W. Tobey, and F. Johnson, *J. Org. Chem.* **32**, 3325 (1967).



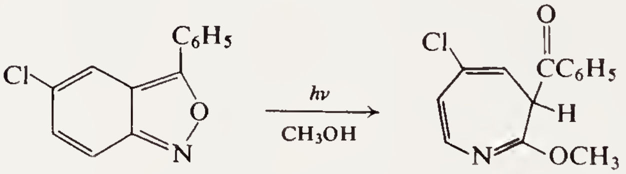
120 **121**

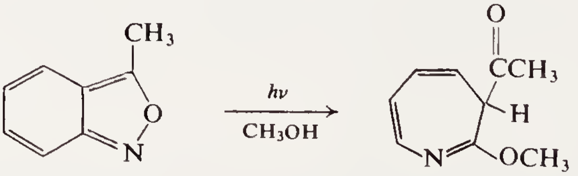


119 **122** **123**

D. PHOTOREARRANGEMENT OF ANTHRANILS

Irradiation of anthranils in methanol solution through Pyrex optics leads to 2-methoxy-3*H*-azepines.[65] A reasonable mechanism for such photorearrangements involves initial N—O bond cleavage to give an aryl nitrene. This is followed by ring closure to a stabilized azirine which undergoes addition of methanol and ring expansion to the azepine.





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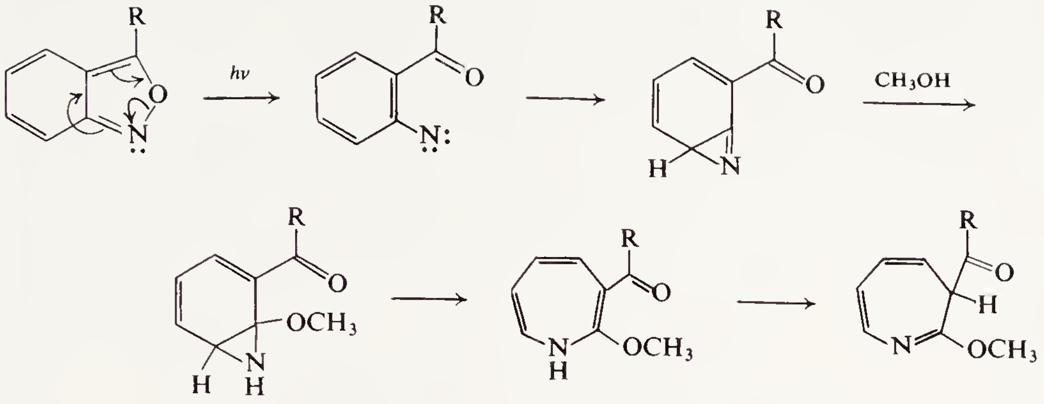
[65] M. Ogata, H. Kano, and H. Matsumoto, *Chem. Commun.* p. 397 (1968).



It is noteworthy that the product of such photorearrangements, as well as those of the nitrene reactions discussed in Section X, B, are not 1*H*-azepines but the presumably more stable 3*H*-tautomers.

XI. Nuclear Magnetic Resonance Spectra of 3*H*-Azepines

The published NMR spectra of **105** and **107** demonstrate that such systems display long-range coupling.[58b] Thus, normal allylic coupling exists between the 7-methyl and H-6 on the one hand ($J = \approx 1$ Hz), and between the 5-methyl and H-4 on the other hand ($J = 1.5$ Hz). The differing electronic environments of H-6 and H-4 are probably responsible for the difference in the allylic coupling constants. Particularly revealing, however, is the fact that the 5-methyl group is actually a triplet ($J = 1.5$ Hz) because of superimposed homoallylic coupling to H-3. Because only axial protons are ideally positioned to transmit spin information via the π-electron system, these spectra substantiate the greater population of conformers **105a** and **107a**.[58b]

A further intriguing aspect of the spectrum of **105** is the appearance of the methylene portion of the ethoxy group as an AB system, presumably due to its proximity to the asymmetric C-3 carbon. The sulfur analog displays this methylene group as a normal quartet as a result of the increased van der Waals radius of the sulfur atom.

The NMR spectrum of 2-anilino-3*H*-azepine (**111**) has been carefully analyzed.[66] At 34°C, the methylene protons appear as a doublet ($J = 7$ Hz) at τ 7.2; on cooling to −75°C, this signal separates into two doublets centered at τ 8.26 and τ 6.36. These results have been interpreted on the basis of a rapid equilibration of tub conformations **111a** and **111b** at the higher temperature, the rate of interconversion being greatly slowed at the lower temperature. From coalescence data, an energy of activation ($\Delta G^{\ddagger}$) for the flipping process was calculated to be 10.2 ± 0.4 kcal/mole at −55°C in acetone-d_6.[66]

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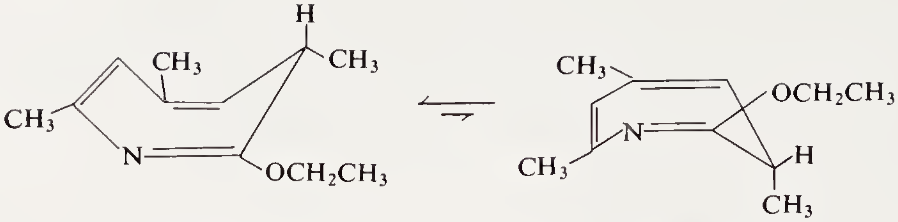
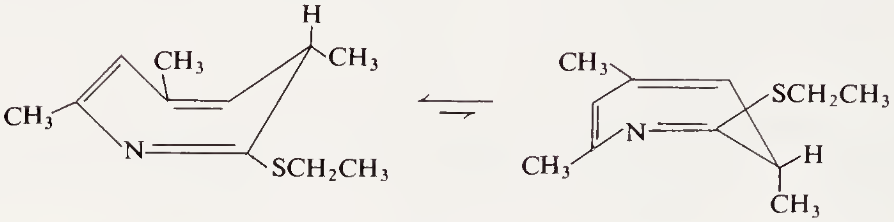
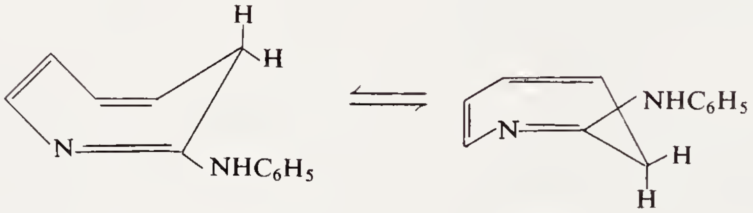
[66] A. Mannschreck, G. Rissmann, F. Vögtle, and D. Wild, *Ber.* **100**, 335 (1967).



105a **105b**



107a **107b**



111a **111b**

XII. Rearrangement Reactions of 3*H*-Azepines

The reaction of 2-amino-3*H*-azepines with acid chlorides and anhydrides leads to ring contraction and formation of *o*-amido aniline derivatives.[60a, b, 61] The overall transformation may be triggered by acylation of the azepine at N-1, after which valence bond isomerization provides an opportunity for aromatization, as illustrated.

When the 3*H*-azepine ester **124** is treated with warm concentrated sulfuric acid or with hot methanolic sodium methoxide, rearrangement to pyridine derivative **125** occurs.[67] The formation of this pyridylacetic ester from the 3*H*-azepine can be formulated as resulting from attack of acidic or basic reagents on the valence tautomer **126**, as depicted.

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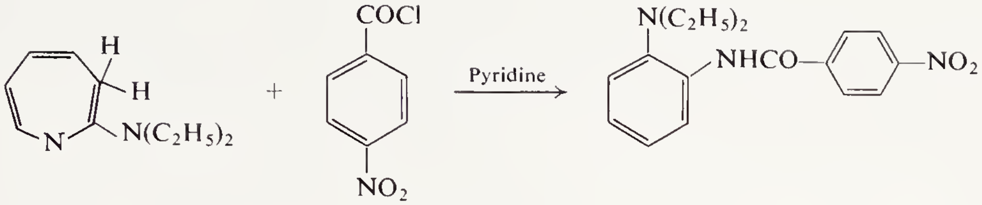
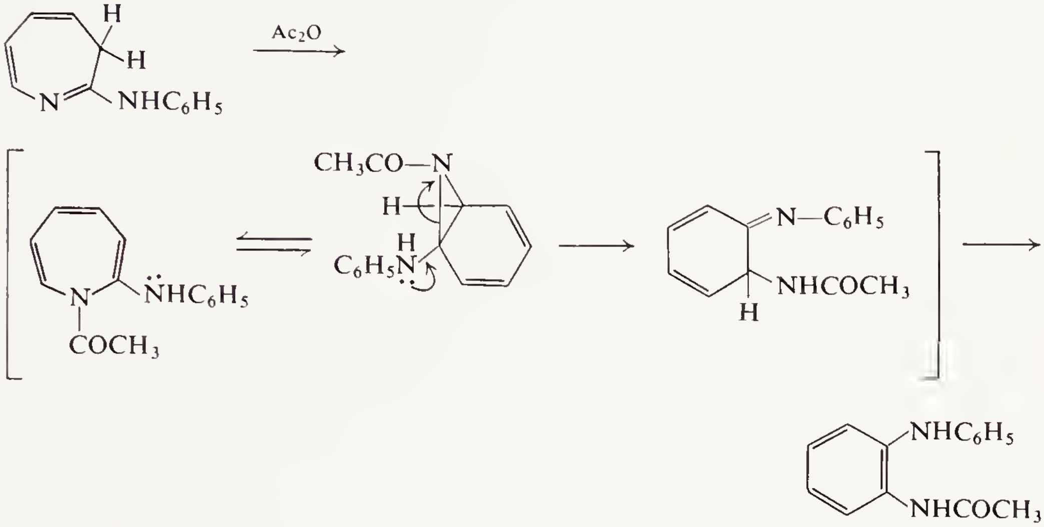
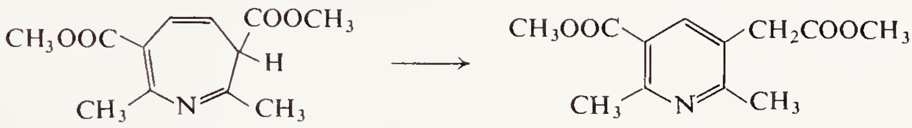
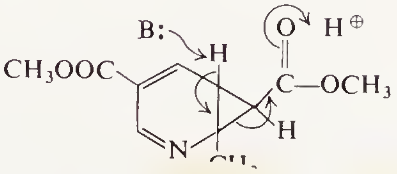
[67] M. Anderson and A. W. Johnson, *J. Chem. Soc.* (*C*) p. 1075 (1966).







124 **125**



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XIII. Preparation and Reactions of 4*H*-Azepines

The action of sodium methoxide in refluxing ether on dihydropyridines such as **127** (R = CH_3 or C_2H_5) serves to give rise to 4*H*-azepines **128**.[68a, b] This ring

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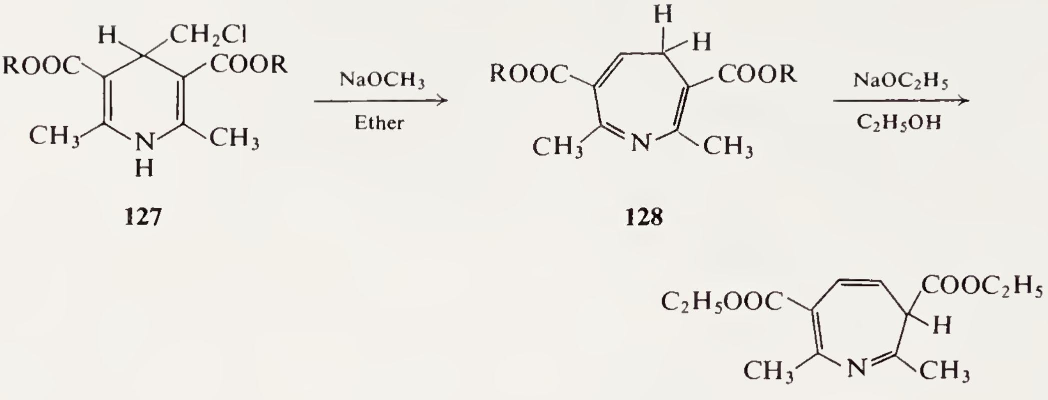
[68a] M. Anderson and A. W. Johnson, *Proc. Chem. Soc.* 263 (1964).

[68b] M. Anderson and A. W. Johnson, *J. Chem. Soc.* p. 2411 (1965).

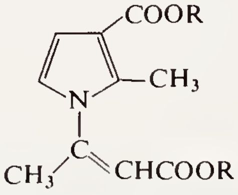


127 **128** **129**

expansion may, in actuality, be brought about by a variety of nucleophilic reagents. Also, the process may be reversed, the dihydropyridines being formed when the 4*H*-azepine esters are treated with hydrohalogen acids.[68a, b]

When the 4*H*-azepine (**128**, R = C_2H_5) is treated with sodium ethoxide in hot ethanol, the corresponding 3*H*-azepine ester **129** is obtained. Such evidence again suggests that the 3*H*-azepine ring contains the most stable arrangement of bonds within the azatropilidene system.

The pyrrole derivative **130** has been found as the product of rearrangement of the 4*H*-azepines **128** in the presence of ammonium hydroxide.[68a, b]



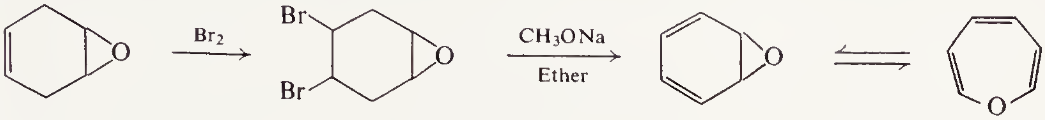
130

XIV. Synthesis of Oxepins

A. VALENCE BOND ISOMERIZATION APPROACH

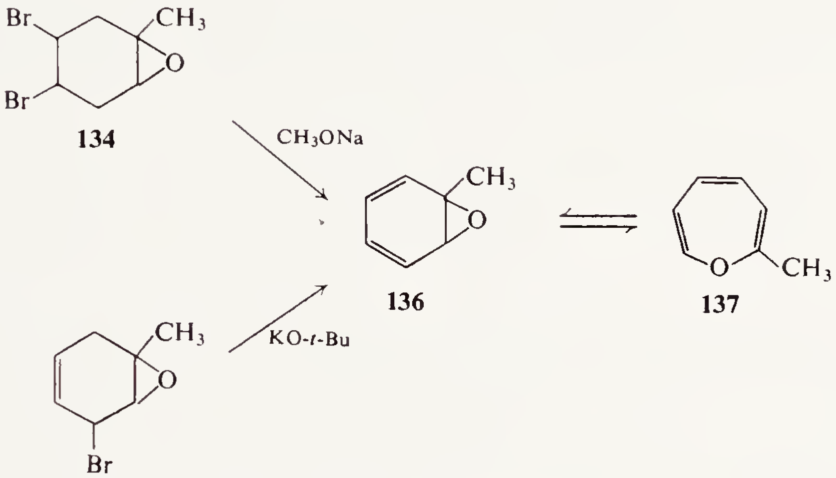
The elegant work of Vogel and his co-workers has demonstrated that a variety of oxepins can be readily prepared by a synthetic procedure based upon the concept of valence bond isomerization. For example, bromination of monoepoxide **131**, followed by double dehydrohalogenation of the resulting dibromide with sodium methoxide in refluxing ether, gives an orange liquid in high yield.[36] On the basis of spectral data (Section XVI) and chemical evidence

(Section XVII), this substance has been identified as a valence tautomeric mixture of benzene oxide (**132**) and oxepin (**133**).[36,69]



131 **132** **133**

2-Methyloxepin (**137**) can be prepared both from the related dibromide **134** and from monobromide **135** by dehydrobromination with sodium methoxide and potassium *t*-butoxide, respectively.[70] As with the parent oxepin (**133**), the 2-methyl derivative exists in rapid equilibrium with a relatively high proportion of 1-methylbenzene oxide (**136**).[71]



134 **136** **137** **135**

In the case of 2,7-dimethyloxepin (**140**), obtainable in high yield by dehydrobromination of **138**, the oxepin form is overwhelmingly preferred.[72] The equilibrium proportion of the arene oxide form is below the spectroscopic

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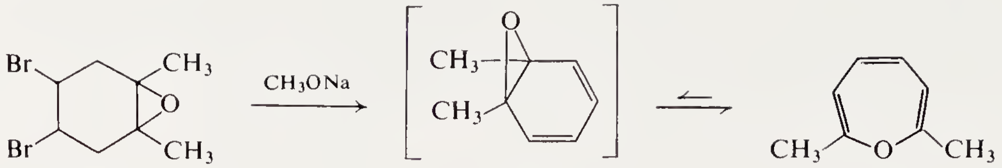
[69] H. Günther, *Tetrahedron Letters* p. 4085 (1965).

[70] E. Vogel and H. Günther, *Angew. Chem.* **79**, 429 (1967); *Angew. Chem. Intern. Ed.* **6**, 385 (1967).

[71] H. Günther, R. Schubart, and E. Vogel, *Z. Naturforsch.* **22b**, 25 (1967).

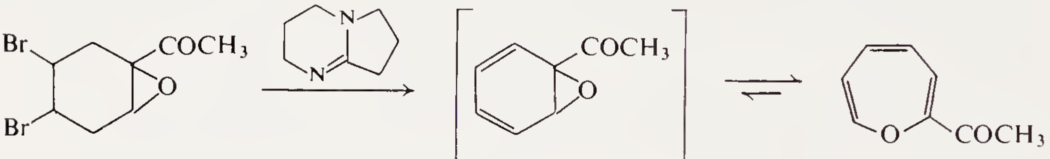
[72] E. Vogel, R. Schubart, and W. A. Böll, *Angew. Chem.* **76**, 535 (1964); *Angew. Chem. Intern. Ed.* **3**, 510 (1964).



138 **139** **140**

detection limit ($<5\%$). The strong displacement of the equilibrium to the oxepin side in the present instance can be attributed to the stabilizing influence of the two methyl groups upon the triene unit and to the unfavorable conformation in **139** where the methyl substituents are eclipsed. Because **140** undergoes cycloaddition reactions through the epoxide tautomer **139** (Section XVII,C), the presence of the latter in the equilibrium, albeit in low concentration, can be surmised.

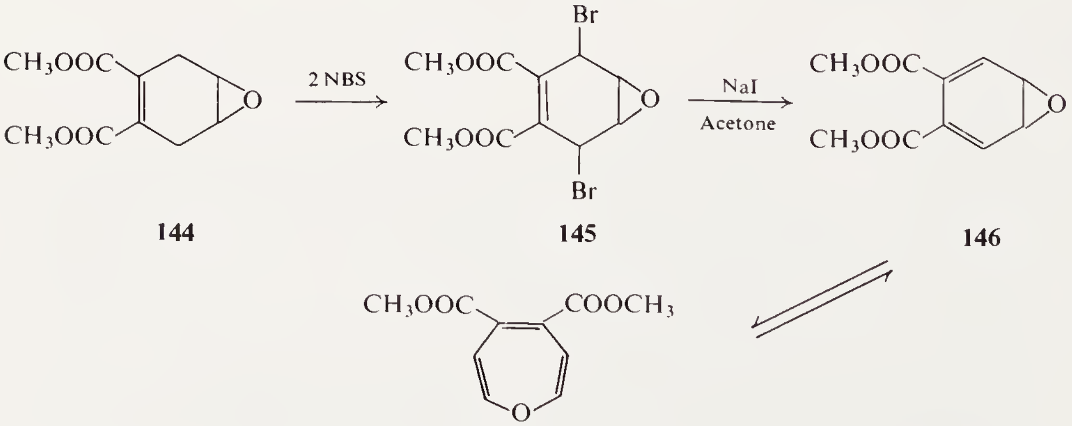
A 2-acetyl substituent is equally effective at stabilizing the oxepin form, presumably by conjugative interactions. With dibromide **141**, dehydrobromination was effected uniquely with 1,5-diazabicyclo[4.3.0]non-5-ene; all other bases apparently yield polymeric products.[70] Although the oxide component



141 **142** **143**

(**142**) cannot be detected, this tautomer appears to determine the chemical reactivity of the system as in the case of the 2,7-dimethyl derivative.

An interesting modification of this oxepin synthesis has been realized by allylic bromination of **144** with two equivalents of *N*-bromosuccinimide and debromination of dibromide **145** with sodium iodide in acetone.[70]. Because

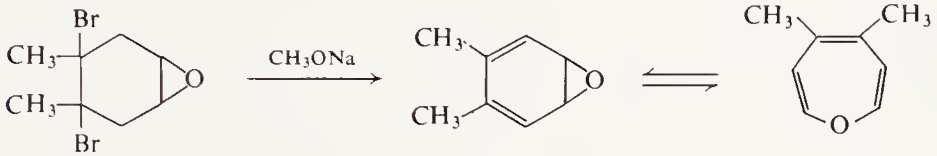


144 **145** **146**

147

the NMR spectrum of **147** is highly temperature dependent (Section XVI,A), a considerable proportion of oxide tautomer **146** has been assumed to be present in solution.

4,5-Dimethyloxepin (**149**) behaves quite similarly. Unfortunately, because of its instability, this substance has been obtained only in solution.[70,73]



148 **149**

At this point, it becomes very important to single out a significant difference in the chemical properties of oxepins and 1*H*-azepines. Whereas oxepins appear capable of ready disrotatory cyclization to the corresponding arene oxides, especially in the course of chemical reactions (see Section XVII), 1*H*-azepine derivatives are particularly reluctant to form their related aziridinobenzene counterparts and will do so apparently only as a last resort. For example, cycloaddition reactions and thermal dimerization of 1*H*-azepines all proceed by way of the seven-membered ring structure except in those where steric inhibition precludes normal reaction. In contrast, most, if not all, reactions of oxepins kinetically favor the arene oxide tautomer. The exact reason for this divergence in chemical reactivity remains unclear.

B. PYROLYSIS OF OXAQUADRICYCLANES

Prinzbach and co-workers have devised a new route to oxepins which consists in the Diels-Alder addition of furans to electron-deficient acetylenes and irradiation of the adduct to provide a tetracyclic isomer which on pyrolysis undergoes cleavage of two cyclopropane bonds.[74a,b] The overall scheme is exemplified below and the oxepins which have been prepared to date by this method are collected in Table IX.

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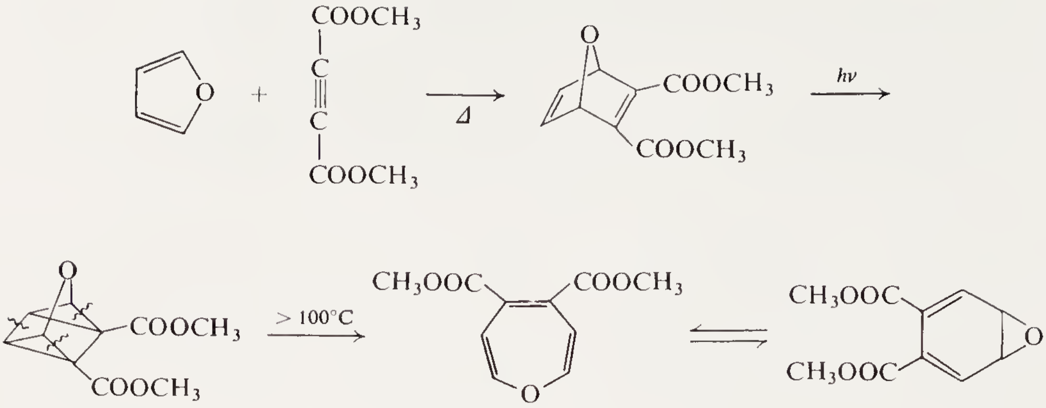
[73] For a synthesis of 1,2-naphthalene oxide see E. Vogel and F.-G. Klärner, *Angew. Chem.* **80**, 402 (1968); *Angew. Chem. Intern. Ed.* 7, 374 (1968).

[74a] H. Prinzbach, M. Arguëlles, and E. Druckrey, *Angew. Chem.* **78**, 1057 (1966); *Angew. Chem. Intern. Ed.* 5, 1039 (1966).

[74b] H. Prinzbach, P. Vogel, and W. Auge, *Chimia (Aarau)* **21**, 469 (1967).



150 **151**

TABLE IX

OXEPINS PREPARED BY THE PYROLYSIS OF OXAQUADRICYCLANES[a]

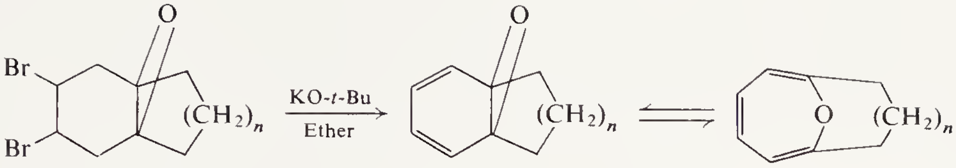
R_2	R_3	R_4	R_5	R_6	R_7
H	H	$—COOCH_3$	$—COOCH_3$	H	H
$—CH_3$	H	$—COOCH_3$	$—COOCH_3$	H	$—CH_3$
$—CH_3$	H	$—COOCH_3$	$—COOCH_3$	H	H
$—CH_3$	$—CH_3$	$—COOCH_3$	$—COOCH_3$	$—CH_3$	$—CH_3$
H	$—COOCH_3$	$—COOCH_3$	$—COOCH_3$	$—COOCH_3$	H
H	H	$—CONH_2$	$—CONH_2$	H	H

[a] H. Prinzbach, P. Vogel, and W. Auge, *Chimia* (*Aarau*) **21**, 469 (1967).

XV. Annelated Oxepins

In view of the marked fundamental differences in the equilibrium positions of the 1*H*-azepine–aziridinobenzene and oxepin–benzene oxide tautomer pairs it was to be expected that annelated oxepins would display concentrations of tricyclic isomers which would vary substantially from those found for the annelated 1*H*-azepines (Section IX). The earlier work of Vogel has shown this to be the case.[70]

The bridged oxepins were prepared by dehydrobromination of dibromides **152** with potassium *t*-butoxide in ether. In the case of **152** with $n = 1$, arene oxide **153a** is obtained; evidently, the oxepin tautomer in this example (**154a**)



$n = 1, 2, 3$
152

153a, $n = 1$
153b, $n = 2$
153c, $n = 3$

154a, $n = 1$
154b, $n = 2$
154c, $n = 3$

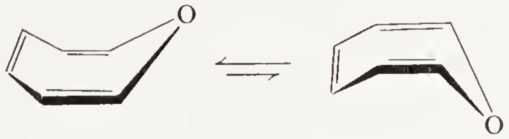
is quite strained and is not observed. The product obtained from **152** with $n = 2$ was also the arene oxide tautomer (**153b**), without **154b** in observable concentration. Treatment of **152** with $n = 3$ gave an orange product which was not uniform. Its spectral characteristics indicated the presence of an arene oxide–oxepin mixture with approximately equal concentrations of **153c** and **154c**.[70]

Comparison of the closely related bridged *N*-carbomethoxy and oxygen molecules indicates further the marked propensity of 1*H*-azepine derivatives to exist in the seven-membered ring form, steric factors permitting. On the other hand, the oxepin system prefers to exist predominantly in the oxide form in the tetramethylene-bridged structure **153b** and remains in the oxide form at a concentration level approaching 50%, even in the pentamethylene-bridged example **153c**.

XVI. Spectral Characteristics of Oxepins

A. NUCLEAR MAGNETIC RESONANCE SPECTRA

The NMR spectrum of benzene oxide–oxepin (**132** ⇋ **133**) at 37°C shows three multiplets between 3.8–4.9 τ (intensity ratio 1:1:1)[36] with $\nu_0\delta = 27.62$ Hz, $J_{45} = 9.68$ Hz, $J_{34} = J_{56} = 6.80$ Hz, $J_{46} = J_{35} = 0.73$ Hz, and $J_{36} = -0.16$ Hz (see Table V).[23] At −113°C in a CF_3Br–C_5H_{12} (2:1) solvent system, a broadening of the entire spectrum is seen with splitting of the α-proton signal and superposition of a second spectrum with signals at 3.7, 4.3, and 6.0 τ (relative intensities 2.67:0.89:1.00). Calculations of the kinetic data gave $\Delta H^\circ_{123} = 1.5 \pm 0.2$ kcal/mole, $\Delta H^\circ_{133} = 1.9 \pm 0.2$ kcal/mole, and $\Delta S^\circ = 10.5 \pm 8.3$ eu. The higher entropy content of oxepin (**133**) has been rationalized on the basis of conformational mobility (**133a** ⇋ **133b**).[69]



133a

133b

It is interesting that valence tautomerism **132–133** is 10^4 times more rapid at 0°C than that of bullvalene and 15 times as fast at −85°C as that of the norcaradiene–cycloheptatriene system.

The NMR spectrum of 2-methyloxepin (**137**) is likewise temperature dependent. At −119°C, the individual spectra of **136** and **137** appear. The reaction enthalpy of the 1-methylbenzene oxide → 2-methyloxepin isomerization has been calculated as 1.3 kcal/mole, slightly lower than that of the corresponding reaction of the parent system. ΔS° was calculated to be 5.0 eu.[70] In contrast, the NMR spectrum of **140** shows no line broadening, even at −110°C.

Similar considerations pertain to the spectra of the remaining known oxepin derivatives.

B. ULTRAVIOLET SPECTRA

The yellow 2,7-dimethyloxepin (**140**) displays a broad ultraviolet absorption band in isooctane with λ_{max} 297 mμ (ϵ 1800). 8,9-Indan oxide (**153a**) is colorless and in isooctane possesses an ultraviolet spectrum of a typical 1,3-cyclohexadiene with λ_{max} 258 mμ (ϵ 4900). Both spectra are practically solvent independent.

The ultraviolet spectrum of benzene oxide–oxepin is strongly dependent on solvent and exhibits an isosbestic point, a strong indication of a two-component equilibrium. On the basis of the above model spectra, it may be concluded that in isooctane the maximum at 271 mμ (ϵ 1430) is due to the benzene oxide tautomer and the shoulder at 305 mμ (ϵ 900) to the oxepin form and that the concentration of **132** is about 30%. In water–methanol (85:15), the concentration of **132** is seen to rise to about 90%, showing that the proportion of benzene oxide is favored by solvents of high dielectric constant.

2-Acetyloxepin in cyclohexane exhibits bands at 222 (ϵ 10,900), 315 (ϵ 2500), and 360 mμ (ϵ 1200); the spectrum is only weakly solvent dependent.

XVII. Reaction of Oxepins

A. PHOTOISOMERIZATIONS

Irradiation of a 2% ether solution of 2,7-dimethyloxepin with a 450 W mercury arc leads to the formation of photoisomer **155**.[47] Oxepin has also been reported to undergo photochemical isomerization in ether solution and to give 2-oxabicyclo[3.2.0]heptadiene (**156**) in quantitative yield.[70,75] In contrast, irradiation at −80°C with 2537 Å light gave **156** (11%), benzene (15%), and phenol (74%). Under the same conditions but with acetone as solvent, oxepin

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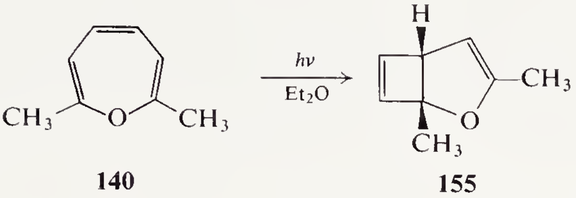
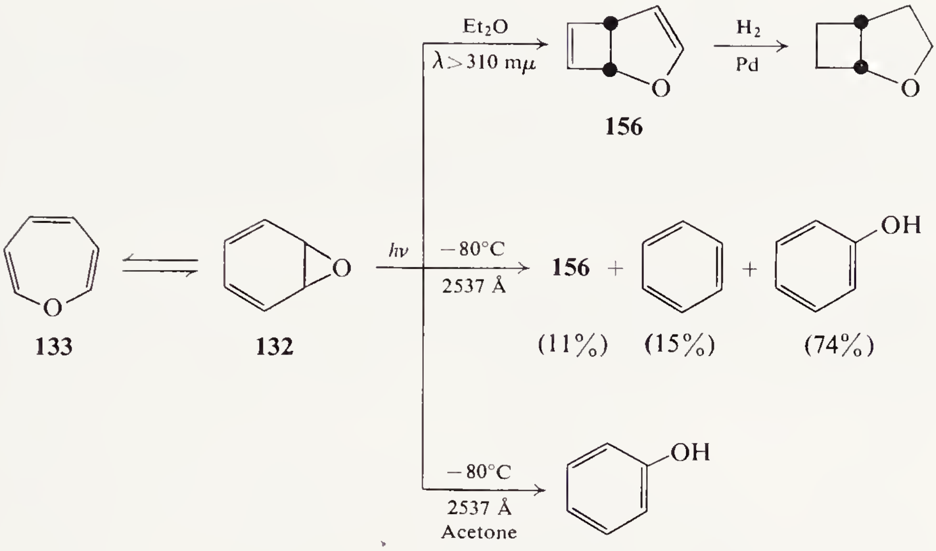
[75] J. M. Holovka and P. D. Gardner, *J. Am. Chem. Soc.* **89**, 6390 (1967).

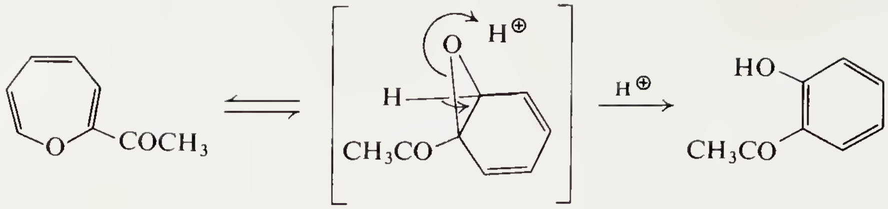




gave phenol as the sole product. These results suggest that **156** is formed from singlet **133**, that benzene is derived from singlet **132**, and that phenol is the product of a triplet process. The significant sensitizing effect of acetone has been construed as an indication that singlet **132** crosses to the triplet state with only fair efficiency.[75] Because irradiation of **132** ⇋ **133** with 2537 Å light in the presence of naphthalene gave only phenol and at a rate some 30 times faster than the unsensitized run and since the concentration of **133** under the conditions is 70%, phenol production very likely arises from both **132** and **133**. Finally, since direct irradiation affords only **156**, intersystem crossing of singlet **133** must be extremely inefficient.[75]

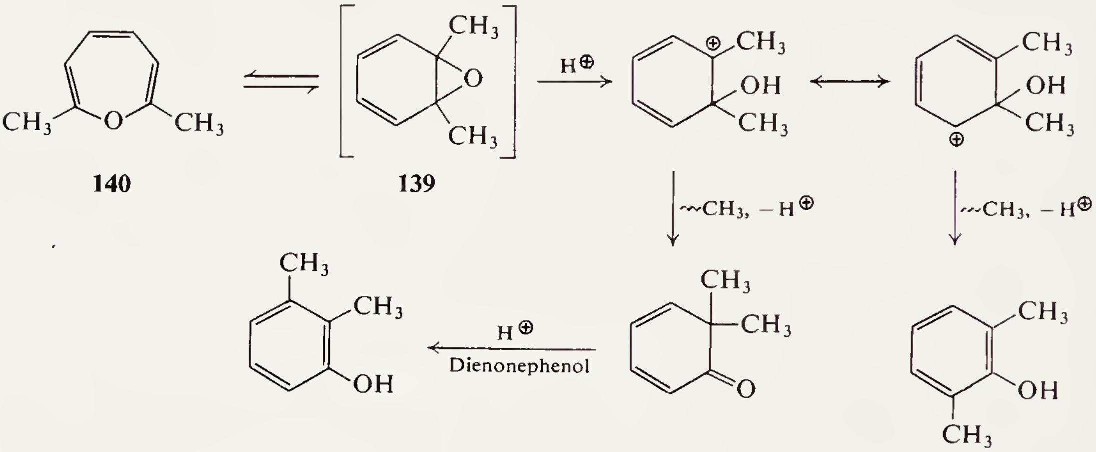
B. THERMAL AND ACID-CATALYZED REARRANGEMENTS

Distillation of oxepin–benzene oxide at normal pressure causes ready isomerization to phenol. It is also easily isomerized to phenol by Brönsted and Lewis acids. 2-Acetyloxepin is similarly aromatized in the presence of catalytic quantities of mineral acid to *o*-hydroxyacetophenone.



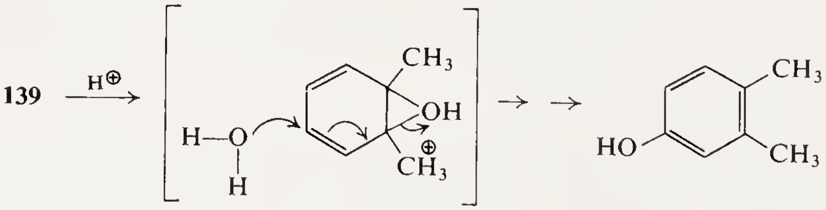
143 **142**

Dilute acids cause 2,7-dimethyloxepin (**140**) to be isomerized to 6,6-dimethylcyclohexadienone (**157**), and 2,3- (**158**), 3,4- (**159**), and 2,6-dimethylphenols (**160**). All of the products except **159** can be formed from the mesomeric carbonium ions produced by electrophilic ring opening of the epoxide ring in **139**. The production of **159** is believed to occur by attack of solvent water as shown in formula **161**.^{70}



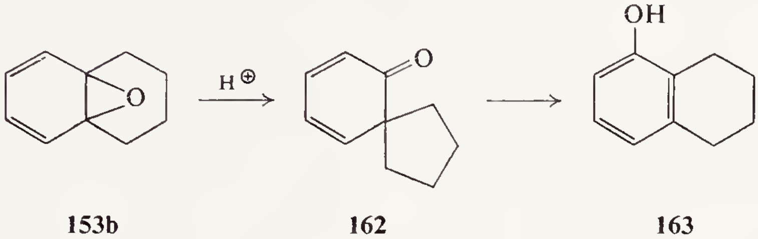
140 **139**

158 **157** **160**

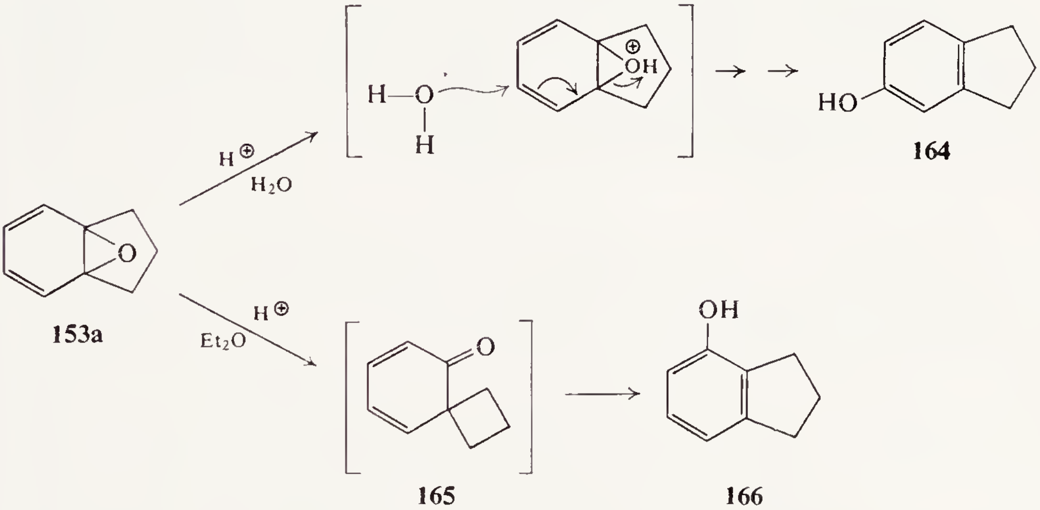


161 **159**

As expected, the annelated oxepins react with acids in a manner parallel to the 2,7-dimethyl derivative. In an aqueous acid–ethereal medium, 9,10-tetralin oxide (**153b**) is quantitatively converted into spiro[5.4]deca-7,9-dien-6-one (**162**). At higher concentrations of acids, or when Lewis acids are employed, 5-tetralol (**163**) is isolated because of further rearrangement of the dienone.



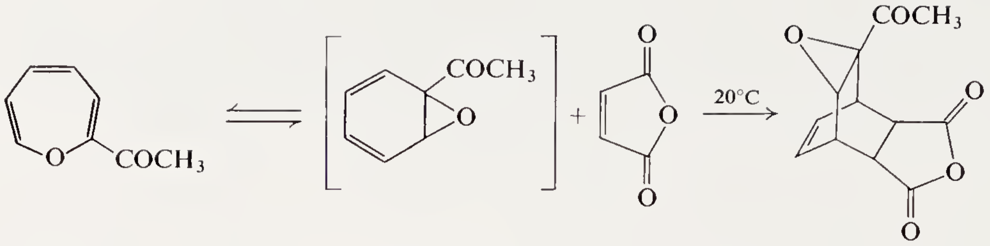
In aqueous acid, 8,9-indan oxide (**153a**) is aromatized to 5-indanol (**164**). Again in this instance, the –OH group appears to be derived from the solvent.

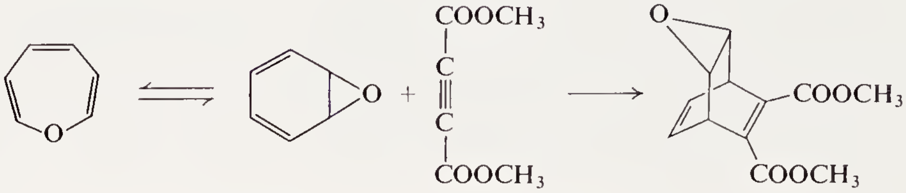


In aprotic media, 4-indanol (**166**) is produced presumably by way of dienone **165**.

C. Cycloaddition Reactions

All cycloaddition reactions of oxepins proceed via the arene oxide form; no example is yet known in which the seven-membered ring acts as either a

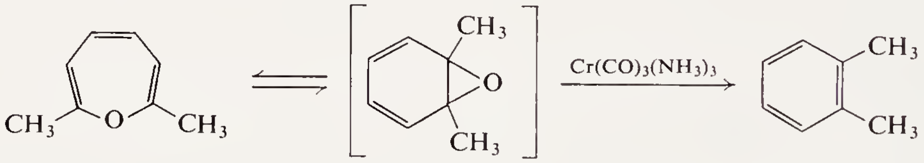


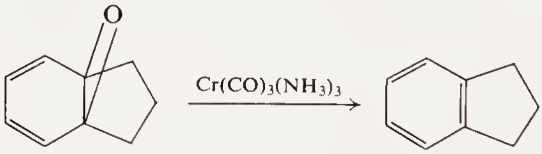


4 π or 6 π donor. The typical behavior of oxepins toward dienophiles is illustrated.

D. Deoxygenation

Oxepins which are 2,7-disubstituted have been found to suffer loss of oxygen and aromatization upon reaction with reagents such as triphenylphosphine and $Cr(CO)_3(NH_3)_3$.[70] Platinum-catalyzed hydrogenation in ether at 0°C also leads to the corresponding aromatic hydrocarbons. The arene oxide tautomers are evidently involved in these transformations.





E. Preparation of Transition Metal Complexes

When approximately equimolar amounts of 2,7-dimethyloxepin and iron pentacarbonyl in petroleum ether (40°–80°C) solution are irradiated for 1 day, low yields of 2,7-dimethyloxepiniron tricarbonyl and 2,7-dimethyloxepindiiron hexacarbonyl are produced.[76]

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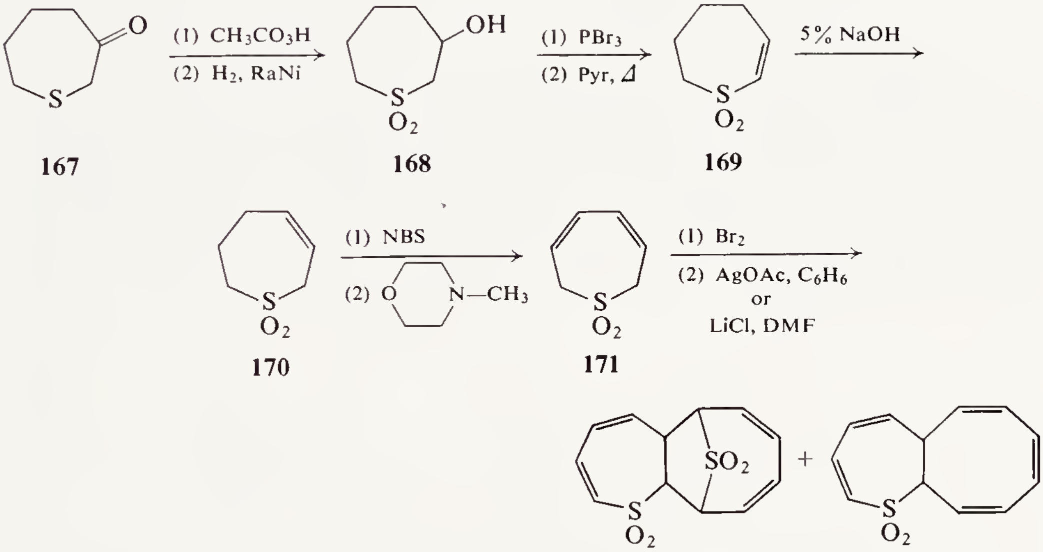
[76] E. O. Fischer, C. G. Kreiter, H. Rühle, and K. E. Schwarzhans, *Ber.* **100**, 1905 (1967).

XVIII. Synthesis and Properties of Thiepin 1,1-Dioxide

The possibility that thiepin 1,1-dioxide (**4**) may possess aromatic properties due to the occupancy by six π electrons of analogous cyclic molecular orbitals derived from six $2p_z$ carbon orbitals and one $3d$ sulfur orbital (either vacant or available on polarization of a π_{SO} bond) appears to have first attracted the attention of Dauben and Maerov.[77a,b] In their synthesis, 3-ketothiacycloheptane (**167**) was oxidized with 40% peracetic acid and hydrogenated over W-4 Raney nickel to give hydroxysulfone **168**. The action of phosphorus tribromide and then hot pyridine on **168** yielded $\Delta^{2(3)}$-thiacycloheptene 1,1-dioxide (**169**), which could be cleanly isomerized to the $\Delta^{3(4)}$ isomer **170**. This sulfone underwent NBS bromination only at C-5; dehydrobromination of the 5-bromo derivative with *N*-methylmorpholine furnished 2,7-dihydrothiepin 1,1-dioxide (**171**). Addition of bromine ($CHCl_3$, 25°–40°C) to **171** presumably yielded the very unstable 3,6-dibromo-$\Delta^{4(5)}$-thiacycloheptene 1,1-dioxide which, upon reaction with silver acetate in refluxing benzene or lithium chloride in dimethylformamide at 25°C, effected almost quantitative dehydrobromination giving a product with properties accordant with those for a dimer of **4** (**172**) admixed with its desulfonylation product **173** (and/or its bridgehead valence tautomer). Attempted sublimation of the mixture liberated



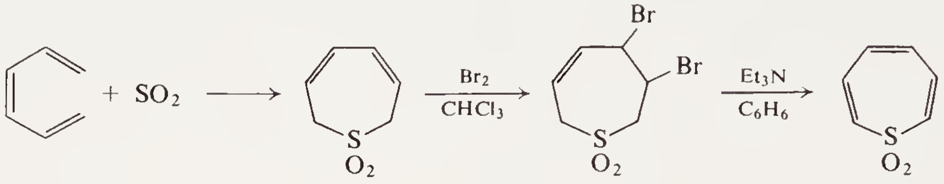
167 **168** **169** **170** **171** **172** **173**

[77a] H. J. Dauben, Jr., and S. B. Maerov, unpublished observations.

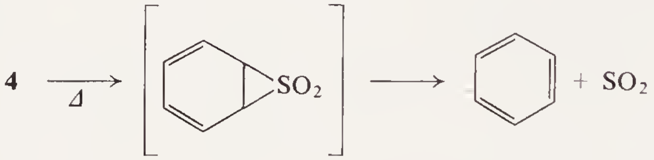
[77b] S. B. Maerov, Ph.D. Dissertation, Univ. of Washington, 1954.

benzene; no thiepin 1,1-dioxide (**4**) was found. In view of the ensuing information, it appears that certain aspects of this work are worthy of reexamination with the aid of modern instrumentation.

In any event, this problem remained dormant for an additional 13 years until Mock reported his remarkably simple synthesis of **4**.[78] Addition of sulfur dioxide to an ethereal solution of *cis*-hexatriene at room temperature affords 2,7-dihydrothiepin 1,1-dioxide (**171**) directly. Bromination of **171** formed a dibromide provisionally formulated as **174**. Treatment of **174** with two equivalents of triethylamine in benzene solution at 25°C leads readily to thiepin 1,1-dioxide (**4**), MP 117°–118°C. This sulfone may be catalytically hydrogenated to its hexahydro derivative. Thiepin 1,1-dioxide may be sublimed at 100°C (1 mm Hg) but decomposes above its melting point; at 100°C in deuteriochloroform, **4** has a half life of approximately 3 hours. The decomposition affords benzene and sulfur dioxide exclusively, probably by way of intermediate episulfone **175**.



171 **174** **4**



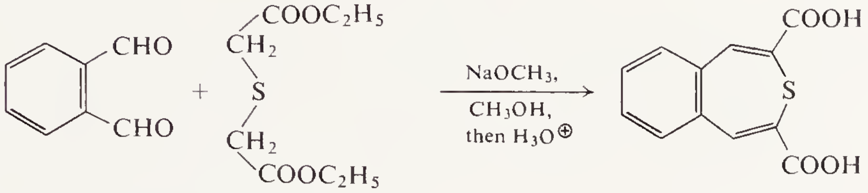
175

The ultraviolet spectrum of **4** [$\lambda_{\max}^{\mathrm{EtOH}}$ 215 (ϵ 13,000), 232 (ϵ 2070), and 262 mμ (ϵ 4610)] is similar to that of cycloheptatriene but unlike that of tropone.[78] The chemical shift of the olefinic protons in the NMR spectrum (2.8–3.5 τ) does not indicate a substantial diamagnetic shift current. Chemical properties as well as these, and other, spectral characteristics suggest a lack of aromatic character in the system, probably resulting from the fact that resonance energy (if any) acquirable from polarized forms is not important. Further, **4** appears not to be a planar conjugated molecule.

[78] W. L. Mock, *J. Am. Chem. Soc.* **89**, 1281 (1967).

XIX. Synthesis and Properties of Fused Aromatic Thiepin Derivatives

Condensation of *o*-phthalaldehyde with diethyl thiodiacetate with a sodium methoxide catalyst affords benzo[d]thiepin-2,4-dicarboxylic acid (**176**).[79] Upon mild heating of **176**, sulfur is eliminated with the formation of 2,3-naphthalenedicarboxylic acid. Upon reinvestigation and extension of this study, Dimroth noted that diester derivatives of **176** were remarkably more stable than the acid.[80]



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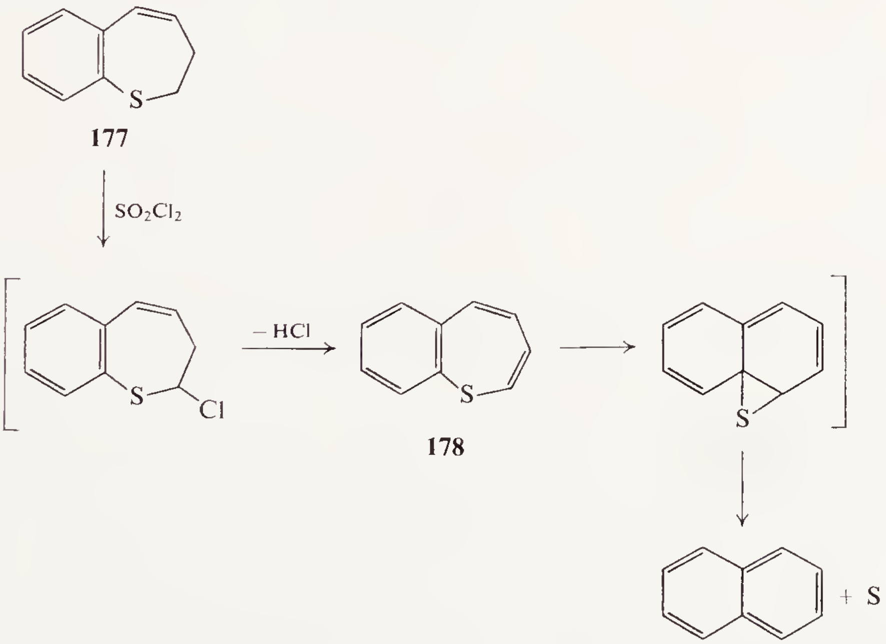
Traynelis and Livingston have attempted to prepare benzo[b]thiepin.[81] When **177** was subjected to sulfuryl chloride chlorination, sulfur and naphthalene were isolated. The appearance of these products in equal amounts led



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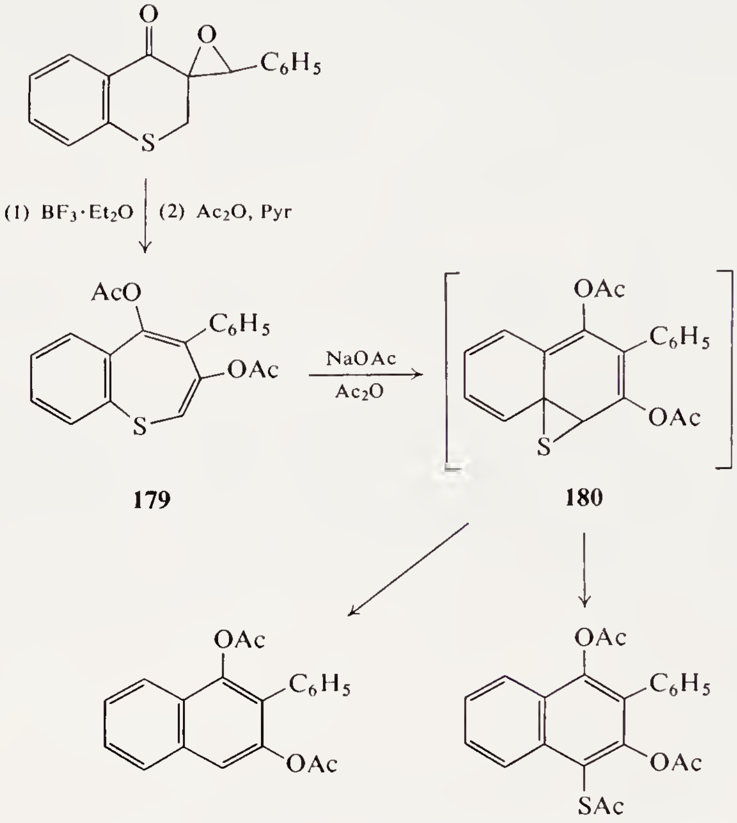
[79] G. P. Scott, *J. Am. Chem. Soc.* **75**, 6332 (1953).

[80] K. Dimroth and G. Lenke, *Ber.* **89**, 2608 (1956).

[81] V. J. Traynelis and J. R. Livingston, Jr., *J. Org. Chem.* **29**, 1092 (1964).

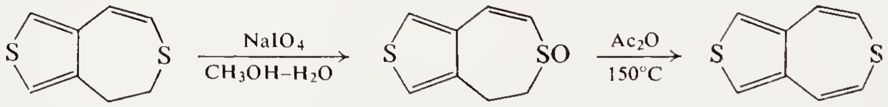
the authors to suspect the intervention of thermally unstable **178** which suffered sulfur extrusion.[81]

An additional example of sulfur extrusion was observed when 3,5-diacetoxy-4-phenylbenzo[b]thiepin (**179**) was heated under reflux with sodium acetate in acetic anhydride.[82,83] Again in this instance, the presumed episulfide intermediate was not isolated.



179 **180**

Periodate oxidation of 4,5-dihydrothieno[3,4-*d*]thiepin (**181**) in aqueous methanol afforded vinyl sulfoxide **182**, brief treatment of which with acetic anhydride at 150°C resulted in thieno[3,4-*d*]thiepin (**183**).[84] When heated



181 **182** **183**

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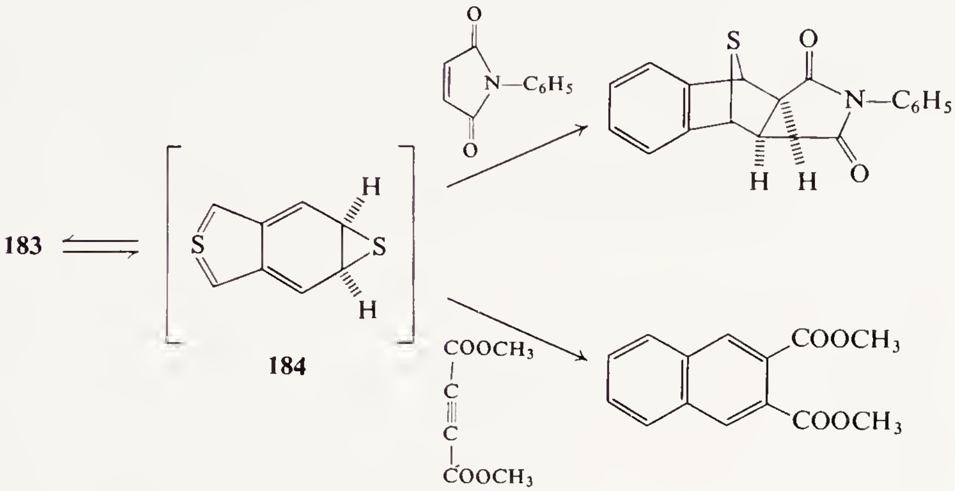
[82] H. Hofmann and H. Westernacher, *Angew. Chem.* **78**, 980 (1966); *Angew. Chem. Intern. Ed.* 5, 958 (1966).

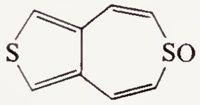
[83] H. Hofmann and H. Westernacher, *Angew. Chem.* **79**, 238 (1967); *Angew. Chem. Intern. Ed.* 6, 255 (1967).

[84] R. H. Schlessinger and G. S. Ponticello, *J. Am. Chem. Soc.* **89**, 7138 (1967).

above its melting point, **183** decomposes to a mixture of products. However, when **183** is heated in the presence of *N*-phenylmaleimide or dimethylacetylene dicarboxylate, adducts are produced which appear to result from reaction of the dienophile with the *o*-quinonoid intermediate **184** followed by sulfur expulsion.[84]



Thiepin **183** is sufficiently stable to be capable of oxidation with *m*-chloroperbenzoic acid to the derived thiepin sulfoxide **185** and sulfone **186**.[85]



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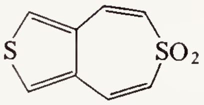

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XX. Concluding Remarks

Interest in the chemistry of seven-membered 8 π-electron heterocycles is at an all time high. Clearly, many questions remain to be answered. One of the most persistent points of inquiry is that which centers about the causative factor(s) behind the substantial differences in valence tautomeric equilibria which separate the 1*H*-azepines and the oxepin group. Interestingly, the sole chemical indication of the existence of oxepins is the formation of 2-oxabicyclo-[3.2.0]hepta-3,6-dienes on photolysis. In marked contrast, the only true aziridinobenzene chemistry studied to this date is associated with **99**. Many

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[85] R. H. Schlessinger and G. S. Ponticello, *Tetrahedron Letters* p. 3017 (1968).

more reactions remain to be discovered. In fact, it is quite certain that many of the results presented in this review will require amplification, supplementation, and perhaps reinterpretation before much time has elapsed. Should this review set the stage for an appreciative and analytical evaluation of future developments in this area, it will have fulfilled its intended purpose.

6

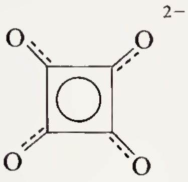
The Aromatic Oxocarbons

ROBERT WEST AND JOSEPH NIU

1. Introduction

What was the first aromatic compound ever isolated? Most chemists would probably answer "benzene," and the textbooks generally agree, crediting Michael Faraday's isolation of benzene from coal tar in 1825. Yet in the same year, dipotassium croconate, an aromatic compound of a totally different sort, was prepared by Gmelin.[1] The special properties of benzene and its derivatives were soon evident, and their examination led to the great flowering of aromatic chemistry in the latter half of the nineteenth century. The aromatic nature of croconate and related anions remained undetected for more than 130 years, however, and has come to light only quite recently.

Croconate ion is now known to be only one member of a series of aromatic anions, the aromatic oxocarbons. An oxocarbon is an organic species in which all or most of the carbon atoms are attached to carbonyl groups or their hydrated equivalents. This chapter will deal primarily with the monocyclic oxocarbons which have been studied closely during the last few years. Four members of this series are now known: the squarate (**1**), croconate (**2**), and rhodizonate (**3**) anions, and the tetraanion of tetrahydroxy-*p*-benzoquinone (**4**). Alkali metal salts of **1**, **2**, and **3** are stable, water-soluble materials, but the tetraanion **4** is rapidly oxidized in air.



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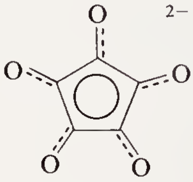

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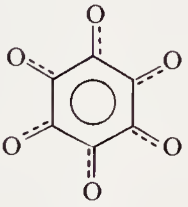

3, 2−
4, 4−

Two reviews on oxocarbons have appeared recently, one dealing with the synthesis and chemistry of the monocyclic oxocarbons[2] and their anions, and one with the chemistry of squaric acid and its derivatives.[3]

Oxocarbons were probably first prepared in the early 1820's, when Berzelius, Wöhler, and Kindt were studying the reaction of carbon with potassium hydroxide and observed the formation of a black powdery residue.[4] Gmelin then undertook the study of this reaction and isolated dipotassium croconate and croconic acid from the black material in 1825.[1] The six-membered ring oxocarbon, rhodizonic acid, was obtained from the same residue a few years later by Heller.[5] The names for these oxocarbons derive from the Greek words "krokos," yellow, and "rhodizein," rose-red, these being the colors of the

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[1] L. Gmelin, *Ann. Physik. Chem.* **4**, 31 (1825).

[2] R. West and H. Y. Niu, *In* "The Chemistry of the Carbonyl Group" (J. Zabicky, ed.). Wiley (Interscience), 1970.

[3] G. Maahs and P. Hegenberg, *Angew. Chem. Intern. Ed. Engl.* **5**, 888 (1966).

[4] C. Brunner, *Schweigger's J.* **38**, 517 (1823).

[5] J. F. Heller, *Ann.* **24**, 1 (1837).

alkaline earth derivatives of the two acids. After discovery of the rhodizonates, no new monocyclic oxocarbon anions were isolated for 122 years, until the discovery of squaric acid in 1959 by Cohen *et al.* at the University of Colorado.[6] The oxocarbon tetraanion **4** was prepared 3 years later.[7]

Although the chemistry of croconic and rhodizonic acids was studied repeatedly in the century between 1850 and 1950, the structures of the anions remained obscure. The first person to suggest a symmetrical delocalized structure for an oxocarbon anion was an undergraduate student at Nagoya University, K. Yamada, who, together with his teacher, Professor Y. Hirata, was studying croconates as part of his honors research.[8] In 1960, West *et al.*[9] suggested that the anions **1**, **2**, and **3** were aromatic and constituted a previously unrecognized aromatic series. Structural studies have confirmed this proposal and have led to the current interest in the unusual electronic structure of oxocarbon anions.

II. Synthesis of the Monocyclic Oxocarbons

A. RHODIZONATES AND CROCONATES

The treatment in this section is not intended to be exhaustive, but the most important methods for synthesis of the five- and six-membered ring oxocarbons will be outlined. Other synthetic methods are described in a recent review.[2]

1. *Cyclopolymerization of Carbon Monoxide*

The croconates and rhodizonates were first obtained from potassium hydroxide and carbon, but it was soon discovered that the cyclic oxocarbons could more easily be obtained by the reaction of carbon monoxide with potassium metal.[10] The reductive cyclopolymerization of carbon monoxide has provided an important route to oxocarbons for over 130 years, but only recently have details of the reaction begun to emerge.

In 1963 it was found that if the reaction of CO with potassium is carried out at low temperatures, a black compound of empirical formula $(KCO)_x$ can be isolated. This compound, which was thought to be $K_4C_4O_4$, is a precursor to the oxocarbons.[11]

The reaction of carbon monoxide with alkali metals in liquid ammonia solution to form yellow "alkali metal carbonyls," $(MCO)_x$, has been described

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[6] S. G. Cohen, J. R. Lacher, and J. D. Park, *J. Am. Chem. Soc.* **81**, 348 (1959).

[7] R. West and H. Y. Niu, *J. Am. Chem. Soc.* **84**, 1324 (1962).

[8] K. Yamada, M. Mizuno, and Y. Hirata, *Bull. Chem. Soc. Japan* **31**, 543 (1958).

[9] R. West, H. Y. Niu, D. L. Powell, and M. V. Evans, *J. Am. Chem. Soc.* **82**, 6204 (1960).

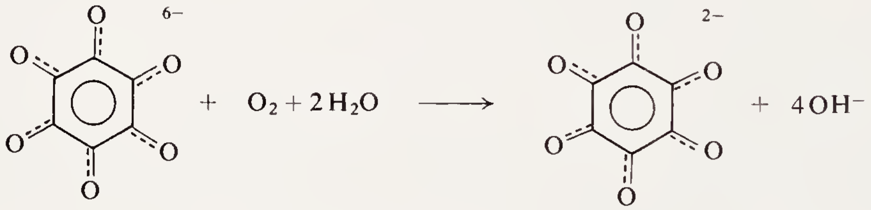
[10] J. Liebig, *Ann.* **11**, 182 (1834).

[11] W. F. Sager, A. Fatiadi, P. C. Parks, D. G. White, and T. P. Perros, *J. Inorg. Nucl. Chem.* **25**, 187 (1963).

by several workers.[12–14] Recently, Weiss and Büchner, in a series of X-ray crystallographic studies, have determined the structures of the sodium, potassium, rubidium, and cesium carbonyls.[15–17a] All are found to be dialkali metal derivatives of dihydroxyacetylene, $M^{\oplus}\,{}^{\ominus}O\text{—}C{\equiv}C\text{—}O^{\ominus}M^{\oplus}$.[17b] Moreover, the black product from the reaction of potassium with carbon monoxide is crystallographically identical with yellow $K_2C_2O_2$, and so must also have the dihydroxyacetylene salt structure.[15] Radical impurities are suggested to account for the black color.

The dianion of acetylenediol might be viewed as an acyclic oxocarbon anion. However, the bond lengths obtained from X-ray studies (C—O 1.27 Å, C—C 1.20 Å) are consistent with the formulation of the anion as ${}^{\ominus}O\text{—}C{\equiv}C\text{—}O^{\ominus}$, and indicate that, in contrast to the cyclic oxocarbons, little electron delocalization takes place in the $C_2O_2{}^{2-}$ anion.

If the potassium salt $K_2C_2O_2$ is heated, or if the reaction between potassium and carbon monoxide is allowed to proceed exothermically above the melting point of potassium, the product is $K_6C_6O_6$, the gray solid from which oxocarbons were first isolated.[11] $K_6C_6O_6$ is actually the hexapotassium salt of hexahydroxybenzene. This compound represents a point at which the benzenoid and aromatic oxocarbon series intersect, for it can be regarded either as an oxocarbon with 6– charge, or as a benzene derivative. Oxidation of $K_6C_6O_6$ produces **3**:



Recently, it has been found that sodium will also react with carbon monoxide, albeit at much higher temperatures (280°–340°C), to form the hexasodium salt of hexahydroxybenzene, $Na_6C_6O_6$. The latter is also easily oxidized to rhodizonate.[18]

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[12] A. Joannis, *Compt. Rend. Acad. Sci.* **116**, 1518 (1893); **158**, 874 (1914).

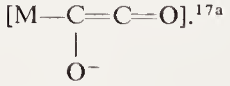
[13] T. G. Pearson, *Nature* **131**, 166 (1933).

[14] L. Hackspill and L. A. van Alten, *Compt. Rend. Acad. Sci.* **206**, 818 (1938).

[15] E. Weiss and W. Büchner, *Helv. Chim. Acta* **46**, 1121 (1963).

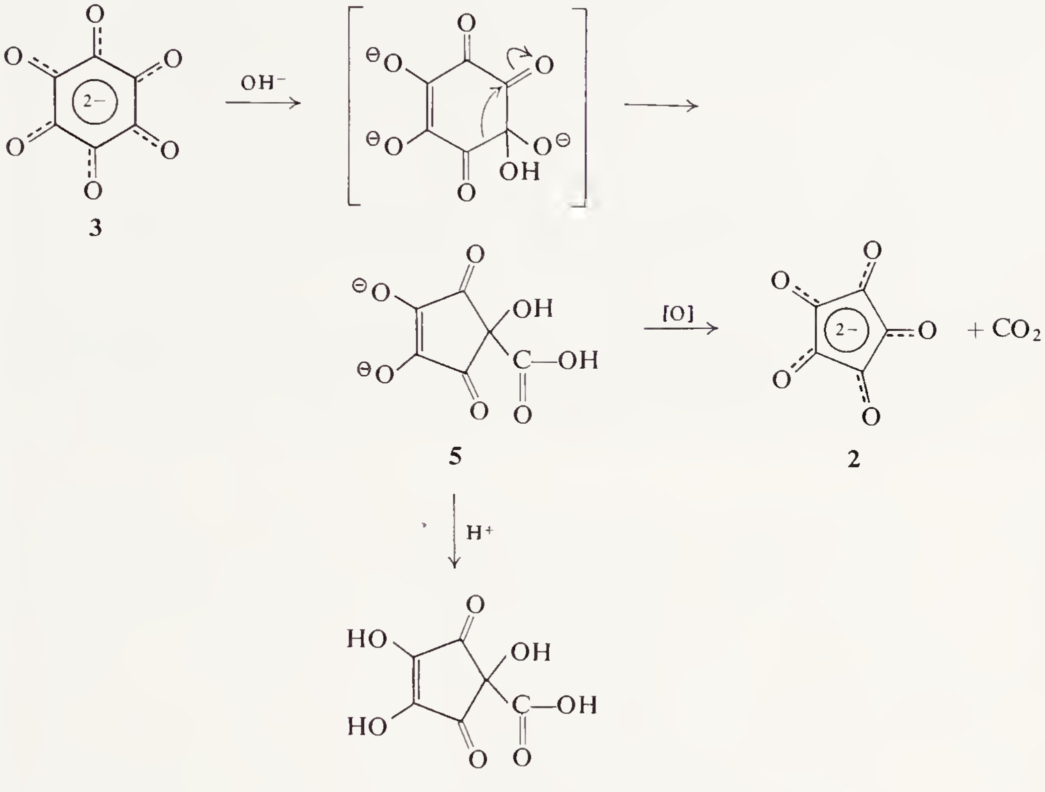
[16] E. Weiss and W. Büchner, *Z. Anorg. Allgem. Chem.* **330**, 251 (1964).

[17a] W. Büchner, *Helv. Chim. Acta* **46**, 2111 (1964).

[17b] From chemical evidence, Büchner suggests that the salts also contain small amounts of the tautomeric ketene derivatives,

$M^+\ [M\text{—}\underset{\underset{O^-}{|}}{C}{=}C{=}O]$.[17a]

[18] H. C. Miller, U.S. Patent 2,858,194 (1958).

As mentioned in the introduction, however, the oxocarbon first obtained from $K_6C_6O_6$ was not rhodizonate but the five-membered ring compound, croconic acid. As early as 1837, Heller was able to show that rhodizonate is the precursor of croconate ion.[5] How does this surprising ring contraction of **3** to **2** take place? This transformation has been studied repeatedly over the years, and it now seems certain that the reaction is an alpha-oxo alcohol rearrangement[19] whose course is as follows[20–22]:



3 **5** **2** **6**

This oxidative ring contraction provides an easy entry into the croconate series. So convenient is this method, in fact, that no other synthesis of croconic acid or the croconates has ever been developed.

2. *Cyclotrimerization of Glyoxal*

The oxidative trimerization of glyoxal to give the disodium salt of tetrahydroxyquinone was first discovered in 1921 by Homolka[23] and has been improved by later workers[2]:

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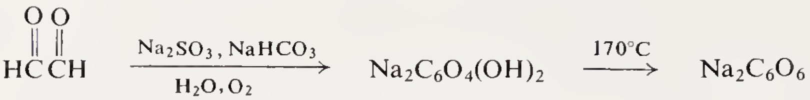
[19] S. Selman and J. F. Eastham, *Quart. Revs.* **14**, 221 (1960).

[20] R. Nietzki and T. Benckiser, *Ber.* **18**, 499, 1833 (1885); **19**, 301 (1886); **20**, 1618 (1887).

[21] R. Nietzki, *Ber.* **20**, 1617 (1887).

[22] F. Arcamone, C. Prevost, and P. Souchay, *Bull. Soc. Chim. France* p. 891 (1953).

[23] B. Homolka, *Ber.* **54**, 1393 (1921).

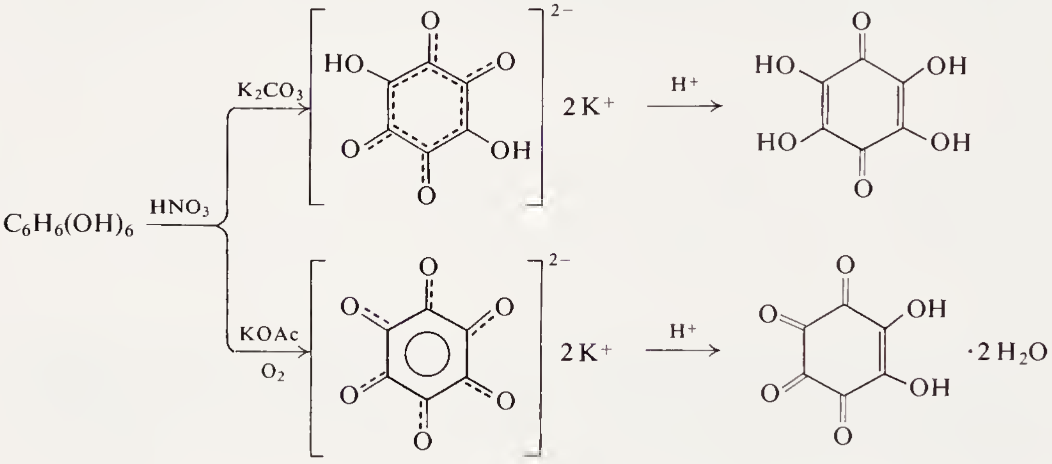


$$\overset{\overset{\mathrm{O}}{\|}}{\mathrm{HC}}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{CH}} \xrightarrow[H_2O,\,O_2]{Na_2SO_3,\,NaHCO_3} Na_2C_6O_4(OH)_2 \xrightarrow{170^\circ C} Na_2C_6O_6$$

Disodium rhodizonate can be obtained easily by heating the tetrahydroxyquinone salt, which is the initial product in air at 170°C. The yields in the cyclotrimerization are low, but this reaction employs cheap starting materials and can be conveniently carried out on a large scale, so it provides a useful method for obtaining the five- and six-membered ring oxocarbons. Good directions are given in a recent paper by Fatiadi and co-workers.[24]

3. *Oxidation of Inositol*

Existing fully substituted six-membered ring compounds can often be converted to salts of tetrahydroxyquinone or rhodizonic acid by oxidation. The most useful precursor is the readily available isomer of hexahydroxycyclohexane, *myo*-inositol. When inositol is oxidized with nitric acid and then treated with potassium carbonate, the dipotassium salt of tetrahydroxyquinone is produced. If, instead, potassium acetate is added to the oxidized solution and air is bubbled through, the product is dipotassium rhodizonate[25]:



B. SQUARIC ACID

All preparative methods for squaric acid to date depend on the solvolysis of halogen from polyhalogenated cyclobutenes. The syntheses of the required cyclobutenes fall into two classes, depending on whether olefins or butadienes are used as starting materials.

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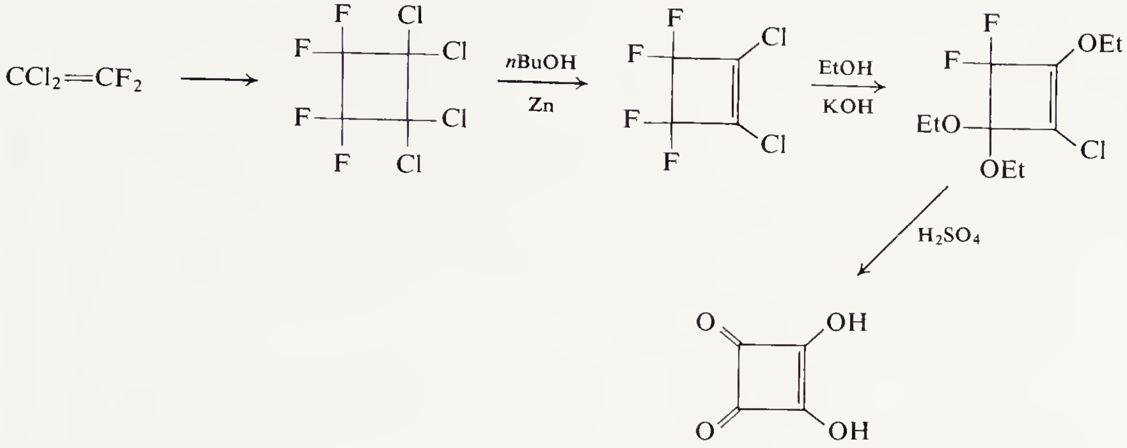
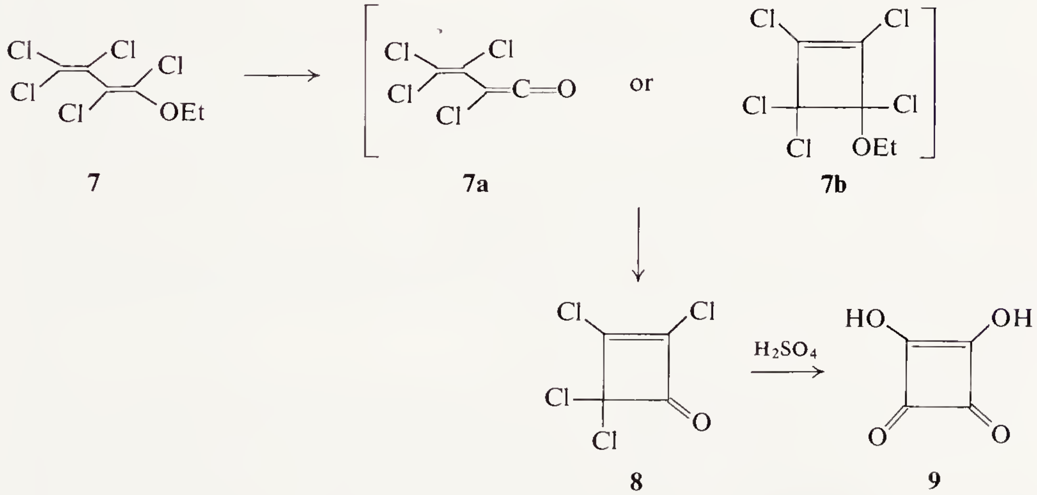
[24] A. J. Fatiadi, H. S. Isbell, and W. F. Sager, *J. Res. Natl. Bur. Std.* A67, 153 (1963).

[25] P. W. Preisler and L. Berger, *J. Am. Chem. Soc.* **64**, 67 (1942).

The method employed in the original synthesis by Cohen *et al.*[6] illustrates the route beginning with cycloaddition of polyhaloolefins:



An example of a synthesis starting from a butadiene is the method recently published by Maahs, beginning with 1-ethoxypentachloro-1,3-butadiene[26]:



When heated, **7** loses ethyl chloride, forming the tetrachlorocyclobutenone, **8**, which can be solvolysed to squaric acid. Maahs suggests that the ketene **7a** is an intermediate, but cycloaddition of **7** to **7b** seems at least equally likely. Other methods for the synthesis of squaric acid are related to these, and have been described in recent reviews.[2,3]

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[26] G. Maahs, *Ann.* **686**, 55 (1965).

III. Structure of the Oxocarbon Anions

A. VIBRATIONAL SPECTROSCOPIC STUDIES

Infrared and Raman spectroscopy have contributed much to knowledge of the structure of oxocarbon anions. Symmetrical structures were originally proposed for **1**[8] and **2**[6] largely on the basis that the infrared spectra of salts of these anions lacked normal C=O vibrational bands. After the recognition of the oxocarbons as an aromatic series,[7,27] complete vibrational analysis was used to show conclusively that squarate and croconate ions have planar, delocalized structures with D_{4h} and D_{5h} symmetry, respectively.[28] The oxocarbons thus provide an interesting example of the usefulness of vibrational analysis in structural investigations.

Vibrational assignment for the oxocarbon anions is aided greatly by the fact that exactly the same number of fundamental vibrations is predicted for all planar, symmetrical species $C_nO_n^{m-}$, where $n = 4, 5, 6 \ldots$. Aromatic, and hence planar and fully symmetrical, structures such as the anions **1**, **2**, **3**, and **4**, should each show just seven Raman lines, of which two (the totally symmetrical C—O stretching and ring breathing modes) should be strongly polarized. The infrared spectra for each anion should be even simpler, containing only *four* fundamental bands!

Figure 1 shows the infrared spectra of some typical oxocarbon salts, and a correlation diagram for the vibrational fundamentals is given in Fig. 2. The infrared spectra are dominated by the extremely strong and broad C=O stretching mode near 1500 cm^{-1}, but the three other fundamentals can easily be identified. For example, the infrared spectrum of $K_2C_4O_4$ contains just four bands of medium or strong intensity, along with two weaker bands assignable to overtones or combinations. Just two polarized Raman lines are found for the three oxocarbon salts, in accord with prediction. Especially important is the fact that there are no infrared–Raman coincidences, indicating that the anions have a centrosymmetrical structure.

Various structural models were selected for each of the oxocarbon anions, and the number of expected Raman and infrared bands was determined for each structure.[28] Figure 3 shows the structures tried for $C_4O_4^{2-}$, and Table I gives the predictions for each structure together with the observed vibrations. It is easily seen that the planar structure of point group D_{4h} is the only one in reasonable agreement with observation. Less symmetrical structures than those listed in Table I would give larger numbers of infrared and Raman bands, and so can be immediately excluded. Thus, the data show clearly that squarate ion must have the planar, fully symmetrical D_{4h} structure, consistent with complete

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[27] R. West and D. L. Powell, *J. Am. Chem. Soc.* **85**, 2577 (1963).

[28] M. Ito and R. West, *J. Am. Chem. Soc.* **85**, 2580 (1963).

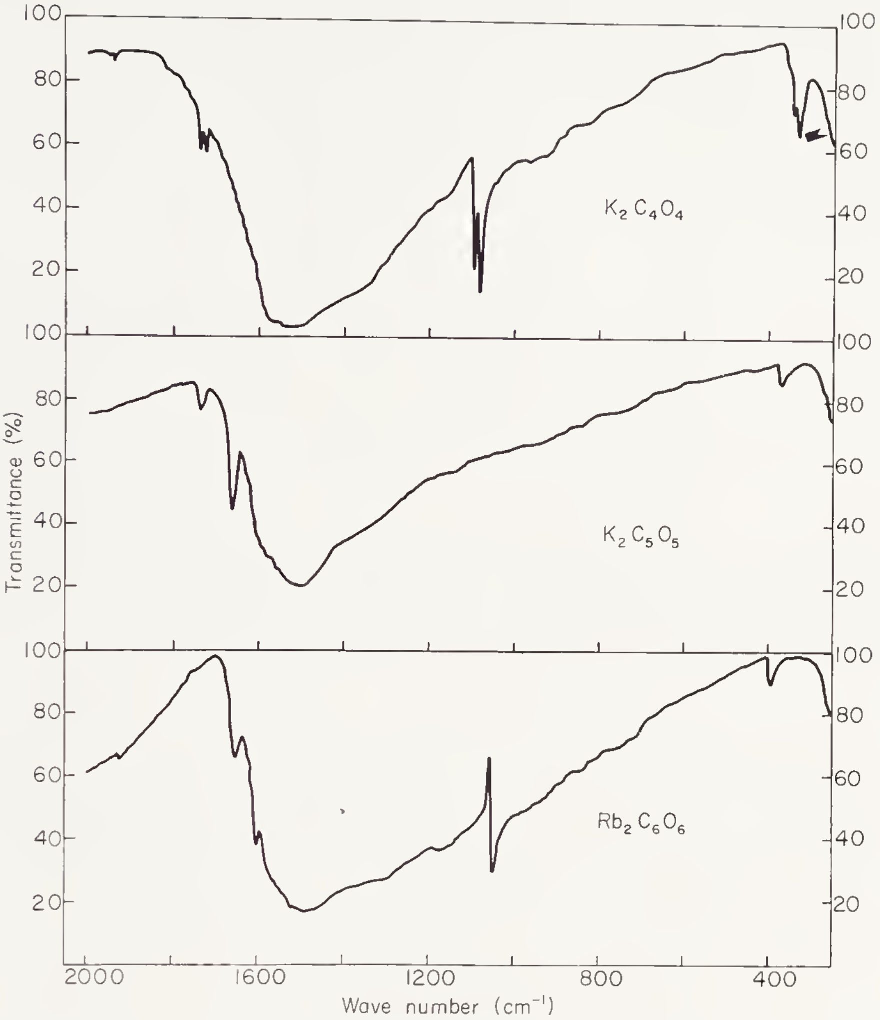

FIG. 1. Infrared spectra of $K_2C_4O_4$, $K_2C_5O_5$, and $Rb_2C_6O_6$ combined "Nujol"-fluorolube mulls.

electron delocalization and aromaticity. Similarly, vibrational studies established that croconate ion is also planar and symmetrical (D_{5h}).[28]

Vibrational spectra can also be used to gain information about bonding in oxocarbon anions. A normal coordinate analysis of the vibrations was carried out for **1** and **2**, using the Urey-Bradley force field. The resulting force constants, refined by a least-squares method, can be used to generate a calculated spectrum. The agreement between calculated and observed spectra is excellent for both **1** and **2**, showing that the force constants are internally consistent and the band assignments almost certainly correct.[28]

The Urey-Bradley force constants for **1**, **2**, and some comparison species are given in Table II. The C—O stretching force constant, K_{CO}, for $C_4O_4^{2-}$ is

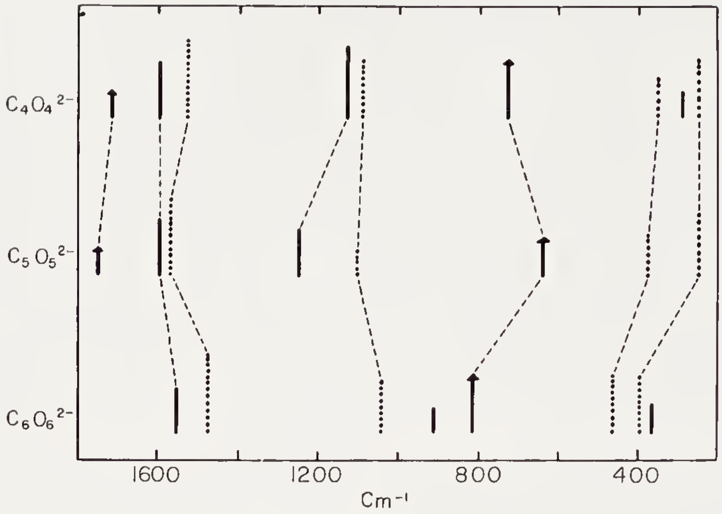

FIG. 2. Correlation diagram for the vibrational spectra of the oxocarbon anions.[28,29,30] (· · · ·) Infrared band; (——) Raman line; (->) polarized Raman line. The relative strengths of the absorptions are indicated qualitatively by the lengths of the lines.

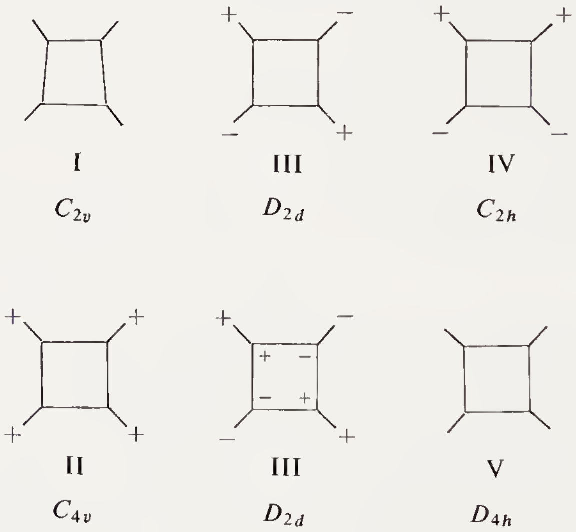

FIG. 3. Possible structures considered for the squarate ion, $C_4O_4^{2-}$.[28] See Table I.

[29] L. S. Whatley, private communication.

[30] R. West and M. Ito, unpublished studies.

TABLE I

COMPARISON OF PREDICTED AND OBSERVED BANDS FOR $C_4O_4^{2-}$ AND $C_5O_5^{2-}$

	$C_4O_4^{2-}$ predicted for model:					$C_4O_4^{2-}$ (obsd.)	$C_5O_5^{2-}$ (pred.)	$C_5O_5^{2-}$ (obsd.)
	I	II	III	IV	V			
Symmetry	C_{2v}	C_{4v}	D_{2d}	C_{2h}	D_{4h}	—	D_{5h}	—
Polarized Raman fundamentals	7	3	4	5	2	2	2	2
Total Raman fundamentals	18	13	13	9	7	7	7	5
Total infrared fundamentals	15	7	7	9	4	4	4	3 or 4
Raman–infrared coincidences	15	7	7	0	0	0	0	0

close to that for C—O single bonds (5–6 mdynes/Å). K_{CO} for croconate is somewhat larger, but still smaller than K_{CO} for carboxylate anions. Most important are the C—C stretching force constants, K_{CC}, which reflect bonding within the carbocyclic ring. The oxocarbon K_{CC} values are lower than for benzene and other polyene aromatics, but distinctly larger than for C—C single bonds, indicating substantial π-bonding between ring carbon atoms.

TABLE II

STRETCHING FORCE CONSTANTS[a]

	K_{CC}	K_{CO}
$C_4O_4^{2-}$	3.95	5.60
$C_5O_5^{2-}$	3.50	6.72
C—C	2.0–2.3	—
Benzene	5.17	—
C=C	7	—
C—O	—	2.8
Acetate ion	2.46	7.20
C=O	—	10.8

[a] Constants in millidynes per angstrom; Urey-Bradley force field. Literature citations are given in Ito and West.[28]

The nonbonded repulsion constant, F_{CC}, between transannular carbon atoms is very large (3.91 mdynes/Å) in $C_4O_4^{2-}$, but drops to 1.52 in $C_5O_5^{2-}$. The value for **1** apparently reflects strong transannular repulsive interactions between the carbon atoms in **1**, which are quite close together and bear partial positive charges. The repulsions are substantially relieved in **2** where the carbon atoms are farther apart.

Salts of the six-membered ring oxocarbons are dark colored and determination of their Raman spectra is difficult. The Raman spectrum of $Rb_2C_6O_6$ has recently been measured by Whatley using a laser source,[29] but vibrational assignments and normal coordinate analysis for **3** have not been carried out. However, predictions have been made concerning the structures of rhodizonate salts based only on their infrared spectra. $Rb_2C_6O_6$ shows a very simple infrared spectrum, resembling that of squarate and croconate salts, whereas $K_2C_6O_6$ has a rich and complex spectrum. We therefore suggested that **3** would be planar and symmetrical in $Rb_2C_6O_6$, but that the anion would be nonplanar in $K_2C_6O_6$.[31] The X-ray results (Section III,B) fully confirm these suggestions.

The infrared spectrum provides the only structural evidence yet available for **4**.[30,31] $K_4C_6O_6$ exhibits a relatively simple spectrum (Table III), consistent with a relatively symmetrical structure for the anion in this salt also. However, two strong bands are found in the C=O stretching region, making the fully symmetrical D_{6h} structure unlikely.

TABLE III

INFRARED SPECTRA OF $K_4C_6O_6$

Frequency (cm^{-1})	Intensity	Comment
725	Weak	—
765	Very weak	—
1310	Medium	Fundamental?
1530	Strong	Fundamental
1600	Strong	Fundamental

B. X-RAY CRYSTAL STRUCTURES

Salts of the oxocarbon anions **1**, **2**, and **3** have all been studied recently by X-ray crystallography. The structure of diammonium croconate was determined in 1963 by Baenziger *et al.*[32,33a] Later, McIntyre and Werkema deter-

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[31] H. Y. Niu, Ph.D. Thesis, Univ. of Wisconsin, 1961.

[32] N. C. Baenziger, J. J. Hegenbarth, and D. G. Williams, *J. Am. Chem. Soc.* **85**, 1539 (1963).

[33a] N. C. Baenziger and J. J. Hegenbarth, *J. Am. Chem. Soc.* **86**, 3250 (1964).

mined the structure of dipotassium squarate monohydrate,[34] and Neuman and Dahl studied $K_2C_6O_6$ and $Rb_2C_6O_6$.[35]

The oxocarbon anions have planar, D_{nh} structures in all of the salts studied except for $K_2C_6O_6$. Bond lengths for the symmetrical anions are listed in Table IV, along with bond orders calculated from the accepted bond distance–bond order relationships.[33a] Substantial delocalization into the carbocyclic ring is indicated for all three anions, which have C—C π bond orders of about 0.3–0.4. It is interesting that the shortest C—C distance is found for croconate ion. The slightly increased distance in **1** might reflect transannular repulsion, or angle strain and resulting rehybridization in the four-membered ring. However, the difference is so slight that it may be a reflection of crystal forces rather than differences in the free anion.

TABLE IV

BOND LENGTHS AND BOND ORDERS[a] IN OXOCARBON ANIONS

Anion	Compound	r_{CC} (Å)	p_{CC}	p_{CC} (calcd.)	r_{CO} (Å)	p_{CO}	p_{CO} (calcd.)	Ref.
1	$K_2C_4O_4 \cdot H_2O$	1.469	0.38	0.41	1.259	0.78	0.69	34
2	$(NH_4)_2C_5O_5$	1.457	0.44	—	1.262	0.78	—	33a
3	$Rb_2C_6O_6$	1.488	0.27	0.38	1.213	1.0	0.75	35

[a] Calculated values for π-bond orders were obtained[33b] using parameters of Baenziger and Hegenbarth.[33a]

The rhodizonate ion has significantly longer C—C and shorter C—O distances, indicating less π-bonding in the ring in this species. In $Rb_2C_6O_6$, the C—O bond order is remarkably high, attaining the full double-bond value of 2. The bond order in the ring can nevertheless be greater than 1, because the anion bears negative charges which can contribute to the π system.

The three compounds $K_2C_4O_4H_2O$, $(NH_4)_2C_5O_5$, and $Rb_2C_6O_6$ share some common structural features. These substances all form layer-type structures with the planar anions arranged in stacks; parallel, or nearly parallel, but with the center of one anion slightly displaced from the next. This arrangement is illustrated for the squarate salt in Fig. 4. A most interesting finding is that carbon atoms of anions in adjacent layers approach each other quite closely—the separation distance is 3.30 Å in $Rb_2C_6O_6$ and 3.24 Å in the squarate salt. This is closer than the van der Waals' distance, and McIntyre and Werkema[34]

[33b] E. Patton and R. West, unpublished studies.

[34] W. M. McIntyre and M. S. Werkema, *J. Chem. Phys.* **42**, 3563 (1964).

[35] M. A. Neuman, *Dissertation Abstr.* **26**, 6394 (1966).

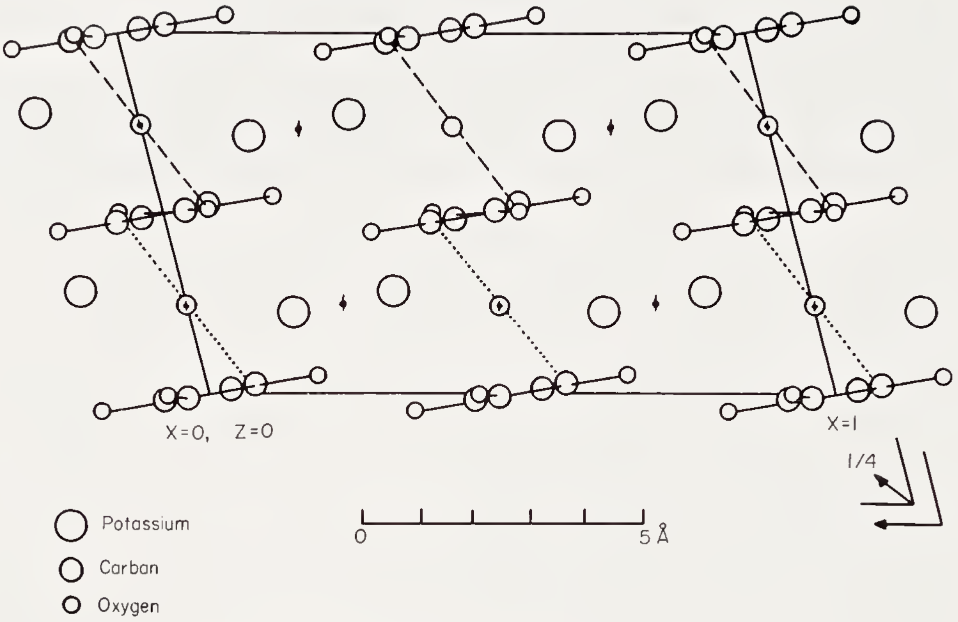

FIG. 4. Arrangement of cations and anions in potassium squarate monohydrate according to McIntyre and Werkema.[34] Note stacking of the $C_4O_4^{2-}$ anions. The dotted and dashed lines represent O—H—O hydrogen bonds, behind and in front of the plane of the paper, respectively.

suggest that interionic charge-transfer complexing takes place between the aromatic anions. High anisotropic electrical conductivity has been found for other layer structures with close layer separations in which charge transfer can take place, such as graphite (3.40 Å) and cesium tetracyanoquinodimethanide (3.20 Å). No striking electrical conductivity was found for $K_2C_4O_4 \cdot H_2O$, but data are lacking for other oxocarbon salts. Studies of the electronic spectra of solid oxocarbons would also be useful in detecting interionic charge-transfer interactions if they are present.

Dipotassium rhodizonate has a structure quite different from the other oxocarbon salts; in fact the structure is unique. The formula for the solid should really be written $K_4(C_6O_6)(C_6O_6)$, for the crystals contain equal numbers of two isomeric kinds of $C_6O_6^{2-}$ ions with different nonplanar structures![35] Half of the anions have the chair cyclohexane structure with D_{3d} symmetry and the other half have a structure with much lower C_2 symmetry (Fig. 5). The distortions from planarity probably reflect crystal forces caused by attraction between oxygens and potassium cations, bending the anions out of the preferred planar form. Similar distortion from planarity may take place in sodium and lithium croconates, which show infrared bands additional to those found for the dipotassium salt.[28]

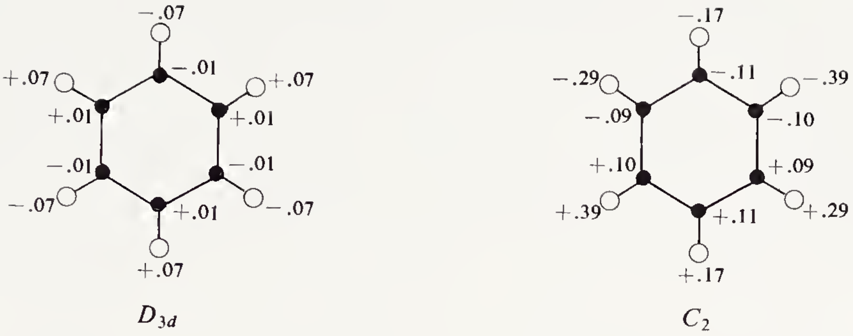

FIG. 5. Schematic drawing showing the two types of $C_6O_6{}^{2-}$ anions found in equal numbers in $K_2C_6O_6$. Carbon atoms are indicated by ● and oxygen atoms by o. The numbers give distance for each atom from the mean plane through the anion.[35]

C. ELECTRONIC SPECTRA

The ultraviolet and visible spectra of croconates and rhodizonates have been studied on numerous occasions. Recently, a definitive paper has appeared on the electronic spectra of croconic acid and the croconates, giving references to the earlier literature.[36] The electronic spectra of squaric acid and the squarates has also been carefully investigated.[37] There are early papers on the spectra of rhodizonic acid and rhodizonates,[38] but definitive recent work is lacking.

The color of the oxocarbon anions deepens as ring size increases. Alkali metal squarates are colorless and croconates are yellow. The rhodizonates exhibit strong dichroism, appearing green by reflected light but red by transmitted light or when finely ground. The electronic absorptions of the anions **1**, **2**, and **3** in aqueous solution are shown in Fig. 6. The principal absorption bands for the three ions are strikingly similar, each consisting of a strong, relatively sharp band with a shoulder at higher energy. As expected from the colors, the absorptions move to longer wavelength as ring size increases. The maxima in nanometers and extinctions (ϵ) are, for $C_4O_4{}^{2-}$, 269 (2.87×10^4); for $C_5O_5{}^{2-}$, 363 (3.60×10^4); and for $C_6O_6{}^{2-}$, 483 (3.36×10^4).

As the pH is lowered, bands for the monoanion and neutral acid appear at shorter wavelengths. For instance, as solutions of **2** are made more acidic, a new band is found first for $HC_5O_5{}^-$ at 324 nm and later for $H_2C_5O_5$ at 299 nm[37] (Fig. 7). Two isosbestic points are found at about 325 and 310 nm.

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[36] B. Carlqvist and D. Dyrssen, *Acta Chem. Scand.* **16**, 94 (1962).

[37] D. T. Ireland and H. F. Walton, *J. Phys. Chem.* **71**, 751 (1967).

[38] G. Schwartzenbach and S. Suter, *Helv. Chim. Acta* **24**, 617 (1941).

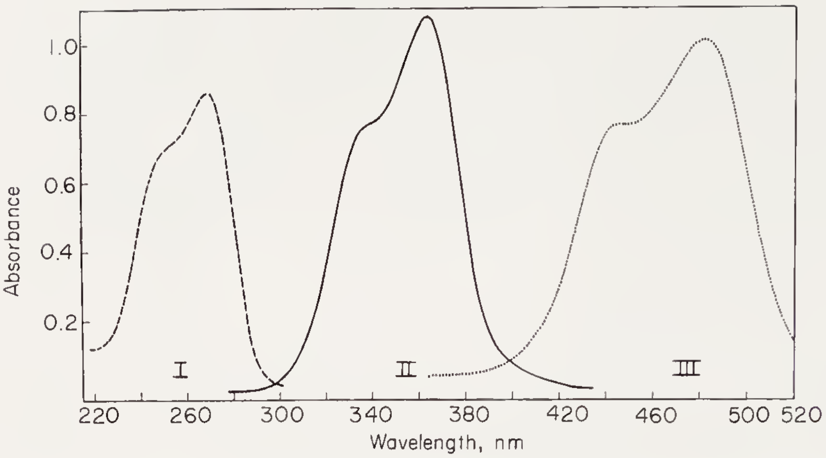


FIG. 6. Principal absorption bands in the electronic spectra of the oxocarbon anions, all 3×10^{-5} *M* in water.[39] Squarate (I); croconate (II); rhodizonate (III). Note doubling which may be due to Jahn-Teller distortion in the excited state.

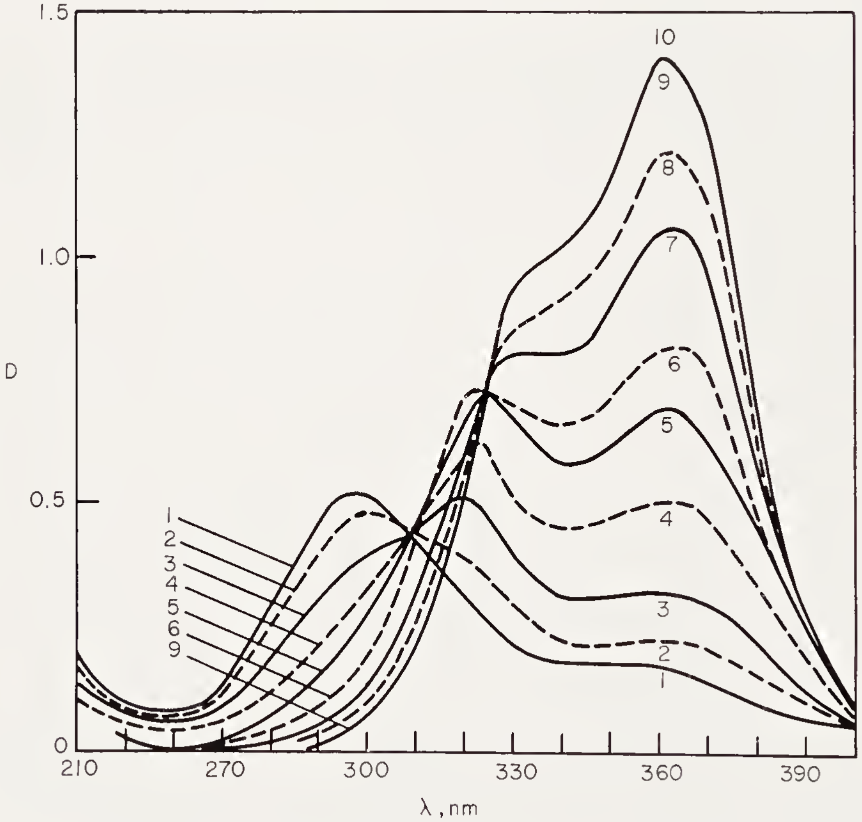
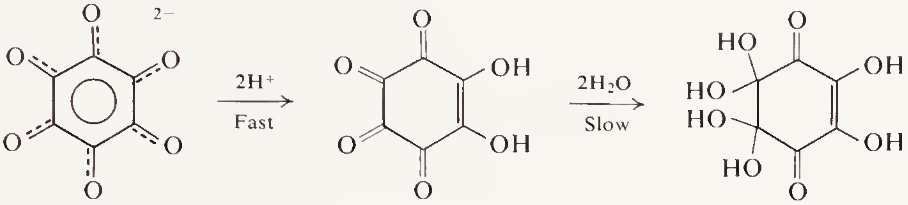


FIG. 7. Absorption spectrum of croconate ion in water as a function of pH, according to Carlqvist and Dyrssen.[36] The numbers on the curves refer to different [H^+]: 1, 1.98 *M*; 2, 0.98 *M*; 3, 0.50 *M*; 4, 0.22 *M*; 5, 0.11 *M*; 6, 0.050 *M*; 7, 0.022 *M*; 8, 0.01 *M*; 9, 0.001 *M*; 10, 10^{-6} *M*. Curve 1 has a maximum at 299 mμ and curve 9 at 363 mμ.

Doubling of the principal absorption is observed only for the dianions; this may be due to Jahn-Teller distortion in the electronic excited state, which is probably degenerate.

An interesting effect is found when $C_6O_6^{2-}$ is acidified. There is an immediate change in the spectrum, followed by a slow change extending over several minutes.[33b, 38] Probably the rhodizonic acid originally formed undergoes a slow hydration[33b]:



3

Rhodizonic acid is known to crystallize from water as a dihydrate of the type shown, and the two molecules of water can be removed only with difficulty.[39]

D. DIAMAGNETIC ANISOTROPY

If oxocarbon rings are aromatic, they, like other aromatic rings, should show "ring currents" and enhanced diamagnetism. Unfortunately, the NMR method used to detect ring currents in polyene aromatics fails for oxocarbons because there are no protons in the anions.[40]

The diamagnetic anisotropy of one salt, diammonium croconate, has, however, been studied by Ma and West using the classical single-crystal method of Krishnan.[41] The compound crystallizes from water as monoclinic needles. Crystals about 1 cm in length and weighing about 10 mg were used for the experiment. The difference between the two axes of the susceptibility ellipsoid perpendicular to the needle axis was so small that it could not be determined, but the difference between these two axes and the remaining one was easily measured. The results gave $X_1 - X_3 = X_2 - X_3 = 51 \pm 2 \times 10^{-6}$ in cgs units.[42] The value 51×10^{-6} may be taken, as a good approximation, to be ΔK, the

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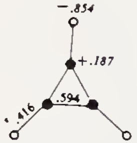
[39] B. Eistert and G. Bock, *Angew. Chem.* **70**, 595 (1958).

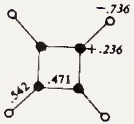
[40] No NMR studies of any sort have been reported for oxocarbon anions, but investigations of ^{13}C and ^{17}O NMR in these species would be of considerable interest.

[41] K. S. Krishnan, *Phil. Trans. Roy. Soc. London* **A231**, 235 (1953); **A232**, 99 (1933); **A234**, 265 (1935).

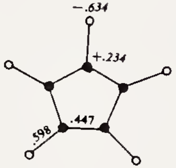
[42] R. S. Ma and R. West, unpublished studies; R. S. Ma, M.S. Thesis, Univ. of Wisconsin, 1963.



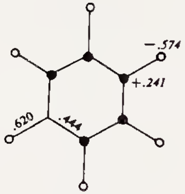
II −2: 0.280



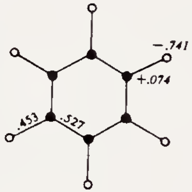
III −2: 0.240



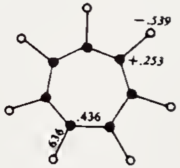
IV −2: 0.231



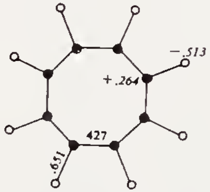
V −2: 0.227



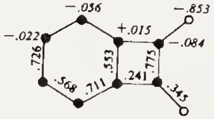
VI −4: 0.209



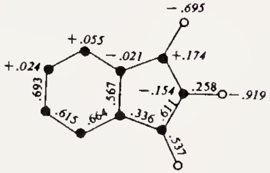
VII −2: 0.223



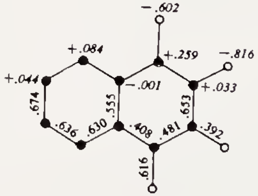
VIII −2: 0.220



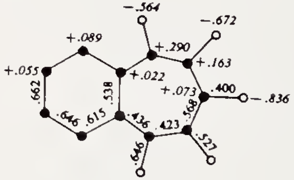
IX −2· 0.250



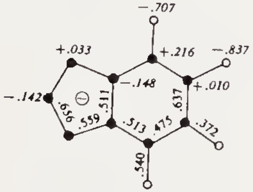
X −2: 0.284



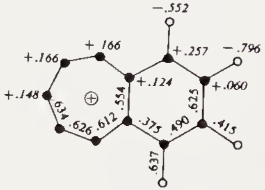
XI −2: 0.292



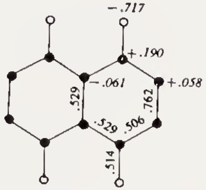
XII −2: 0.289



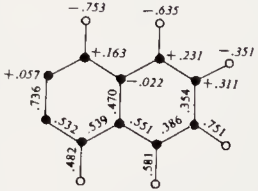
XIII −3: 0.215



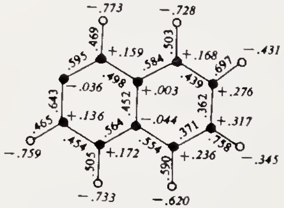
XIV −1: 0.375



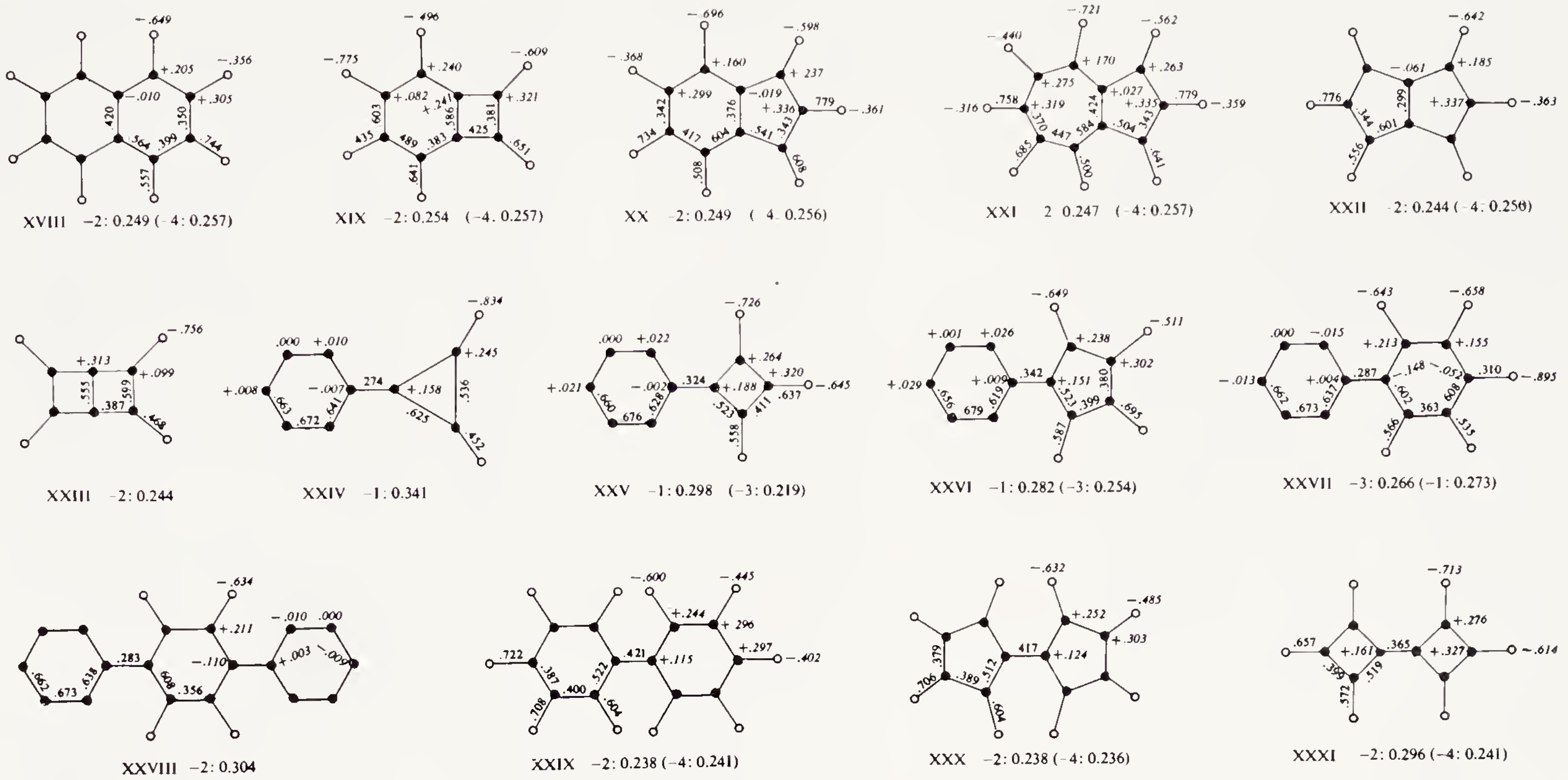
XV −2: 0.298



XVI −2: 0.272 (−4: 0.271)



XVII −3: 0.263



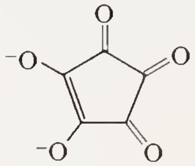
XVIII −2: 0.249 (−4: 0.257)
XIX −2: 0.254 (−4: 0.257)
XX −2: 0.249 (−4: 0.256)
XXI −2: 0.247 (−4: 0.257)
XXII −2: 0.244 (−4: 0.250)
XXIII −2: 0.244
XXIV −1: 0.341
XXV −1: 0.298 (−3: 0.219)
XXVI −1: 0.282 (−3: 0.254)
XXVII −3: 0.266 (−1: 0.273)
XXVIII −2: 0.304
XXIX −2: 0.238 (−4: 0.241)
XXX −2: 0.238 (−4: 0.236)
XXXI −2: 0.296 (−4: 0.241)

FIG. 8. Results of MO calculations for various oxocarbons.[27] The number below each drawing is the delocalization energy per π-electron in units of β, for the anionic charge indicated. Numbers on the drawing give π-bond orders and charge densities on the atoms.

molecular diamagnetic anisotropy between the directions parallel and perpendicular to the ring. The molecular diamagnetic anisotropy of croconate ion appears to be very similar to other highly aromatic compounds with similar ring size, such as benzene ($\Delta K = 54 \times 10^{-6}$) or ferrocene[43] ($\Delta K = 49.5 \times 10^{-6}$).

IV. Molecular Orbital Calculations

The first theoretical treatment of the oxocarbon anions was of the simple Hückel π-electron type, neglecting overlap.[27] In calculating resonance energies, the hypothetical localized structures used were those in which the negative charges were localized on individual oxygen atoms. For example, the localized structure employed for croconate ion was:



The parameters $h = 1.0$ and $k = 0.8$ were used in these calculations. Charge densities, bond orders, and delocalization energies per π-electron for 30 typical examples are given in Fig. 8. Unpublished calculations on more than 50 additional examples bear out the main conclusion evident from the data in Fig. 8. Substantial delocalization energy is predicted for nearly every conceivable oxocarbon anion, regardless of ring size or symmetry, in at least one and often in several states of ionization.[44a]

It is interesting that the predicted delocalization energy of the monocyclic oxocarbon anions drops sharply from $C_3O_3^{2-}$ to $C_4O_4^{2-}$, and then falls only slowly with increasing ring size (Fig. 8). There is no alternation of aromatic stabilization with ring size such as is found for the cyclic polyenes.

Ring strain and electron repulsions are, of course, neglected in the simple Hückel approach; these would tend to destabilize both small and large rings relative to those of intermediate size. In fact, however, structural and other data indicate that **1** and **2** have about equal stability and are more "aromatic" than **3** or **4**. The slightly larger resonance energy for **1** than for **2** may be approximately compensated by destabilization due to ring strain or 1,3-carbon–carbon repulsion in **1**. Ring strain should be much greater in the unknown "deltate ion,"[44b] $C_3O_3^{2-}$, where the internuclear angles are compressed

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[43] L. N. Mulay and Sister M. E. Fox, *J. Am. Chem. Soc.* **84**, 1308 (1962).

[44a] R. West and D. L. Powell, unpublished studies.

[44b] For the unknown oxocarbon acid $H_2C_3O_3$, the name "deltic acid" is suggested, from the triangular Greek letter delta.

to 60° from the preferred value (for sp^2-π carbons) of 120°. In the large oxocarbon rings, O–O nonbonded repulsions become significant. These may be important in destabilizing **3** relative to **2**, and should surely be manifest in seven- and higher-membered oxocarbon rings, which are expected to be nonplanar. Nevertheless it seems likely that the oxocarbon anions from $C_3O_3^{2-}$ to $C_8O_8^{2-}$ will all eventually be isolated.

The Hückel π-electron energy levels for the monocyclic oxocarbons from C_3 through C_8 are shown diagrammatically in Fig. 9. The highest filled level

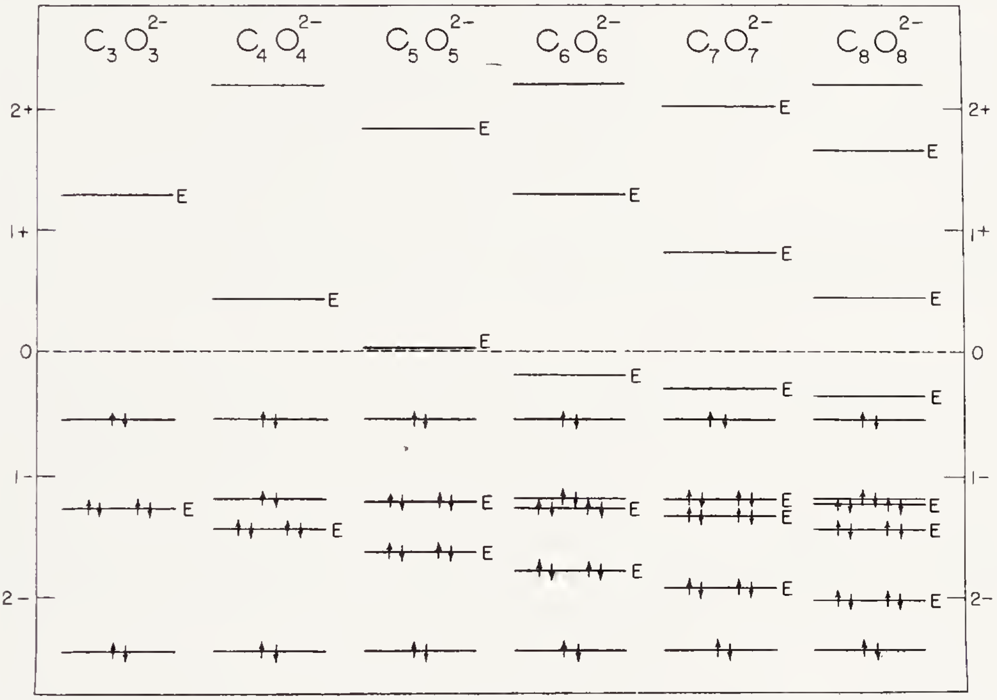


FIG. 9. π-Electron energy levels for the monocyclic oxocarbon anions from Hückel MO calculations,[27] in units of β. Electrons are indicated by arrows and degenerate levels by *E*.

in the dianions is a singlet lying at the same energy for all of the monocyclic oxocarbons. The lowest unfilled level is degenerate and lies at successively lower energy as ring size increases. The closer spacing of levels as ring size increases is in good semiquantitative agreement with the lowering of the excitation energy from **1** to **2** to **3**.[27]

The low energy for the degenerate unfilled level in larger oxocarbon rings suggests that they may easily form anions with charge greater than 2–. The delocalization energy per π-electron for various charges is shown in Fig. 10, for the four-, five-, and six-membered rings. Because charge repulsions are ignored, these calculations make $C_nO_n^{4-}$ ions appear more stable than they

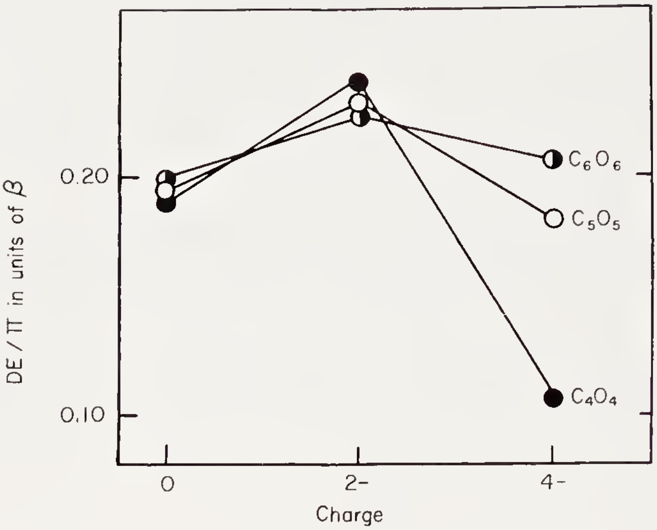
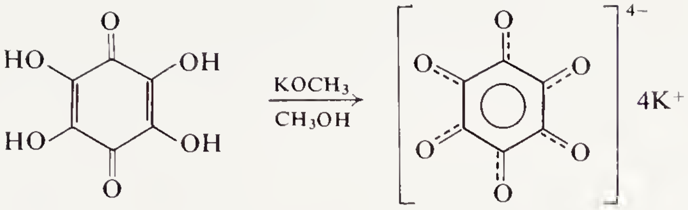


FIG. 10. Delocalization energy (DE) per π-electron, in units of β, as a function of charge for the monocyclic oxocarbon anions. Data from Hückel MO calculations.

really are. However, considerations of this sort led directly to the synthesis of $K_4C_6O_6$, the only known oxocarbon salt with charge 4− on the anion.[7]

After the crystal structure of $(NH_4)_2C_5O_5$ was determined, Baenziger and Hegenbarth[33a] carried out similar Hückel LCAO–MO calculations for croconate ion, with and without overlap. Parameters h and k were varied to give the best fit with the experimental bond orders, as determined from bond lengths (Table IV). The best agreement was obtained with $h = 0.2$ to 0.4 and $k = 1.4$ to 1.6. These parameters gave atomic charges $q_c = 1.00, q_o = 1.40$ compared to $q_c = 0.77$, $q_o = 1.63$ from the earlier Hückel calculations. Very little change is introduced into these values by the inclusion of overlap. The improved Hückel parameters also produced delocalization energies 30% larger than those obtained earlier. Application of the Baenziger-Hegenbarth parameters[33a] to squarate ion gives π bond orders which agree fairly well with those found (Table IV), but the same calculation for rhodizonate gives too high a value for the C—C bond order and too low for C—O (Table IV). Nevertheless, these values are probably suitable starting parameters for Hückel MO calculations on oxocarbons.

The Hückel energy levels of Fig. 9 show the lowest unfilled level for the dianions as doubly degenerate. The monocyclic oxocarbon tetraanions are therefore predicted to be diradicals. The only known example is $K_4C_6O_6$, prepared by West and Niu from dilute solutions of tetrahydroxy-*p*-benzoquinone and potassium methoxide in anhydrous methanol with rigorous exclusion of oxygen[7]:



The product is a black solid which, contrary to expectation, is diamagnetic. This finding led Kaufman and Sadô to carry out more refined calculations of the Pariser-Parr-Pople self-consistent field type on the $C_6O_6{}^{m-}$ system.[45,46] The energy levels obtained from these calculations are critically dependent on the input parameters, and indeed they appear quite unrealistic for the charged species, probably because variations in valence state ionization potentials and electron repulsion integrals with charge have not been taken into account. Kaufman concluded that simple configuration interaction with excited states would be unlikely to remove the degeneracy of the lowest antibonding levels in $C_6O_6{}^{2-}$, and that a Jahn-Teller-like distortion of the anion would be a more reasonable explanation of the observed diamagnetism of $K_4C_6O_6$.[45]

Pariser-Parr-Pople calculations on croconate ion have also been published by Cignitti.[47] Here again, the results depend crucially on the values chosen for core and penetration integrals, which cannot accurately be evaluated. It is fair to say that SCF and other advanced π-electron calculations for oxocarbons have generally given disappointing results, particularly considering the usefulness of the simple Hückel calculations.[32,33a] Very probably, σ and/or nonbonding electrons will have to be included in advanced molecular orbital calculations before further progress will be rewarding.[46]

V. The Oxocarbon Acids

A. PROPERTIES

The known neutral molecules from which the monocyclic oxocarbon anions can be derived are squaric (**9**), croconic (**10**), and rhodizonic (**11**) acids, and tetrahydroxy-*p*-benzoquinone (**12**). All are now believed to have the α-enediol structures shown,[3] although no crystal structure studies have been made.

The compounds are crystalline solids; their colors deepen with increasing ring size (as is also true for the anions). Squaric acid is colorless, **10** is pale-yellow, **11** is red, and **12** is violet. Croconic and rhodizonic acids are highly soluble in water and moderately soluble in polar organic solvents, but **9** and

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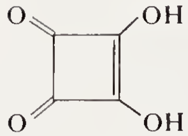
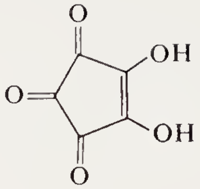
[45] J. J. Kaufman, *J. Phys. Chem.* **68**, 2648 (1964).

[46] A. Sadô, unpublished work.

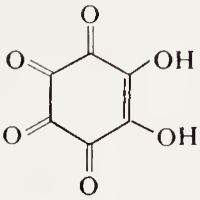
[47] M. Cignitti, *Theoret. Chim. Acta* **5**, 169 (1966).



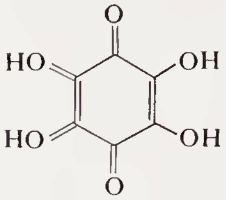
9



10



11



12

12 are sparingly soluble in water, probably because extensive hydrogen bonding association takes place in the crystals. Because of their insolubility, **9** and **12** are very easy to separate from aqueous solutions, but **10** and **11** are isolated only with difficulty. Ion-exchange chromatography[31] and dioxane extraction[24] have been used to separate **10** and **11** from aqueous solutions containing other soluble salts.

The oxocarbon acids are quite strong, and the first and second ionization constants are close together, reflecting the aromatic stabilization gained in ionization to the dianion. Table V gives the p*K* values for the four parent compounds.

TABLE V

p*K* Values for Oxocarbon Acids

Species	pK_1	pK_2	Ref.
$C_4O_2(OH)_2$, **9**	1.7	3.2	37
$C_5O_3(OH)_2$, **10**	0.5	1.5–2.0	36, 48
$C_6O_4(OH)_2\cdot 2H_2O$, **11**	3.1	4.9	38
$C_6O_2(OH)_4$, **12**	4.8	6.8	49a

Compounds **9–12** all give colors with ferric chloride as expected for enols. Compounds **10** and **11** react readily with carbonyl reagents such as hydrazines.

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[48] P. Souchay and M. Fleury, *Compt. Rend. Acad. Sci.* **252**, 737 (1961).

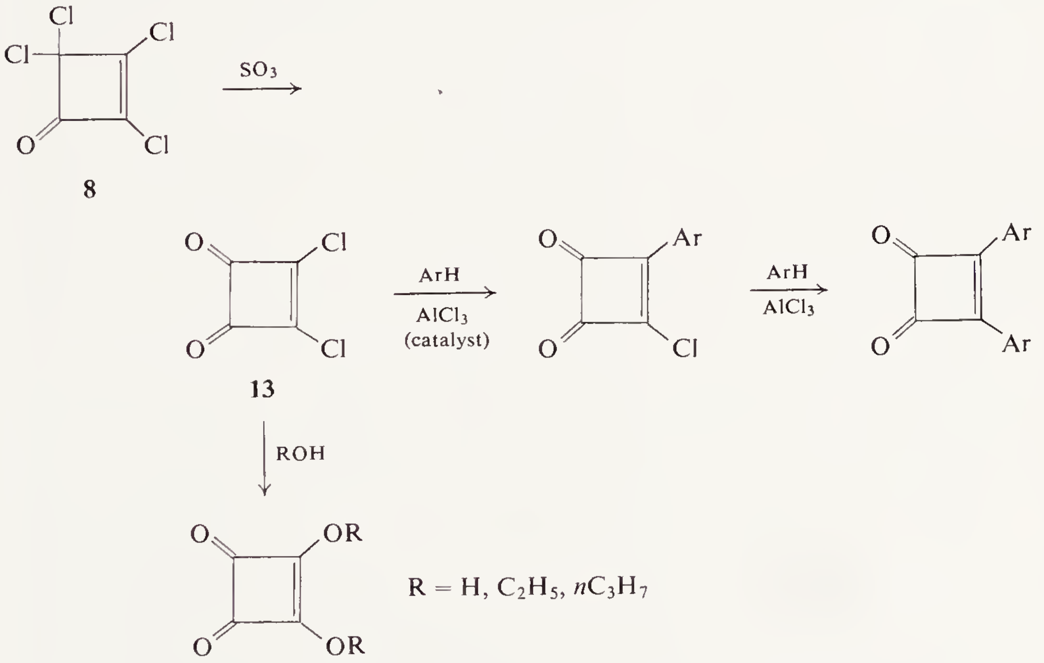
[49a] P. W. Preisler, L. Berger, and E. S. Hill, *J. Am. Chem. Soc.* **69**, 326 (1947); **70**, 871 (1948).

Squaric acid, however, which has both C=O groups adjacent to the double bond and hence is less reactive, does not give positive tests with carbonyl reagents.

B. DERIVATIVES

"Esters" (actually enol ethers) of squaric acid and croconic acid have been prepared[2,3]; those of squaric acid can be obtained simply by heating the acid with alcohols, for it serves as its own acid catalyst for esterification. The same reaction should take place for **10**. These esters readily undergo hydrolysis back to the parent acids.

Other acid derivatives have recently been prepared for squaric acid. Dichlorocyclobutenedione (**13**), the "acid chloride" of squaric acid, has been made by the action of SO_3 on perchlorocyclobutenone (**8**).[26] Compound **13** is highly reactive and behaves much like a typical acid chloride, undergoing hydrolysis to **9**, alcoholysis to enol ethers of **9**, and reacting with aromatic compounds in Friedel-Crafts reactions to give mono- or diarylcyclobutenediones:



$R = H, C_2H_5, nC_3H_7$

Ammonolysis of the dimethyl ester of **9** yields diaminocyclobutenedione, formally the diamide of squaric acid. Similar derivatives could probably be made for **10** and **11**.

The oxocarbon acids undergo numerous interesting condensation reactions, especially with amines and active hydrogen compounds. Many of the products are intensely colored and may find use as dyestuffs; their chemistry has been treated in recent reviews.[2,49b] The oxocarbons also serve as complexing agents for many metals. The complexes of squarate and croconate with divalent metals have recently been characterized,[50] and the structures of the divalent metal croconates, which form linear coordination polymers, have been established by X-ray crystallography.[51]

C. OXIDATION AND REDUCTION PRODUCTS

The oxidation products of **10** and **11** have long been known under the names of leuconic acid ($C_5H_{10}O_{10}$) and triquinoyl octahydrate ($C_6H_{16}O_8$), respectively.[2] These compounds are obtained by treating the parent acids or their alkali salts with oxidants, such as free halogens or nitric acid. The analogous four-membered ring compound, $C_4(OH)_8$, was synthesized from squaric acid with bromine or nitric acid in 1963.[52] All of the oxidation products can be reduced back to the parent oxocarbon acids with SO_2.

The structure of $C_4(OH)_8$ has been studied both by vibrational spectroscopy[52] and X-ray crystallography,[53] and it has been established that the compound is octahydroxycyclobutane. The infrared spectra of octahydroxycyclobutane, leuconic acid, and triquinoyl are all similar; none of the compounds shows C=O absorption. It is highly probable that all three compounds have the fully hydroxylated structures shown in Fig. 11.

Recently, the mass spectra of the monocyclic oxocarbon acids **9**, **10**, **11**, and **12**, and of their oxidation products have been studied by Skujins *et al.*[54] All of these compounds, as a characteristic feature of their fragmentation, show loss of carbon monoxide followed by ring closure to give the next smaller ring. Parent ion peaks were found for **9**, **10**, **11**, and **12**, but not for their oxidation products.

Reduction of the oxocarbons is well understood only for the six-membered ring compounds. Rhodizonate ion or rhodizonic acid can be reduced with SO_2 or other mild reagents, first to tetrahydroxy-*p*-benzoquinone and later to hexahydroxybenzene. The reduction has been studied potentiometrically; it takes place in successive two-electron steps and is essentially reversible.[49a,55]

Croconic acid also apparently undergoes successive two-electron reduction, but it seems likely that two different products are obtained in the first step.[2,56]

[49b] H. E. Sprenger and W. Ziengenbein, *Angew. Chem. Int. Ed. Engl.* **7**, 530 (1968).

[50] R. West and H. Y. Niu, *J. Am. Chem. Soc.* **85**, 2586, 2589 (1963).

[51] M. D. Glick, G. L. Downs, and L. F. Dahl, *Inorg. Chem.* **3**, 1712 (1964).

[52] R. West, H. Y. Niu, and M. Ito, *J. Am. Chem. Soc.* **85**, 2584 (1963).

[53] C. M. Bock, *J. Am. Chem. Soc.* **90**, 2748 (1968).

[54] S. Skujins, J. Delderfield, and G. A. Webb, *Tetrahedron* **24**, 4805 (1968).

[55] P. Souchay and F. Tatibouet, *J. Chim. Phys.* **49**, C-108 (1952).

[56] M. Fleury, *Compt. Rend. Acad. Sci.* **258**, 1512 (1964).

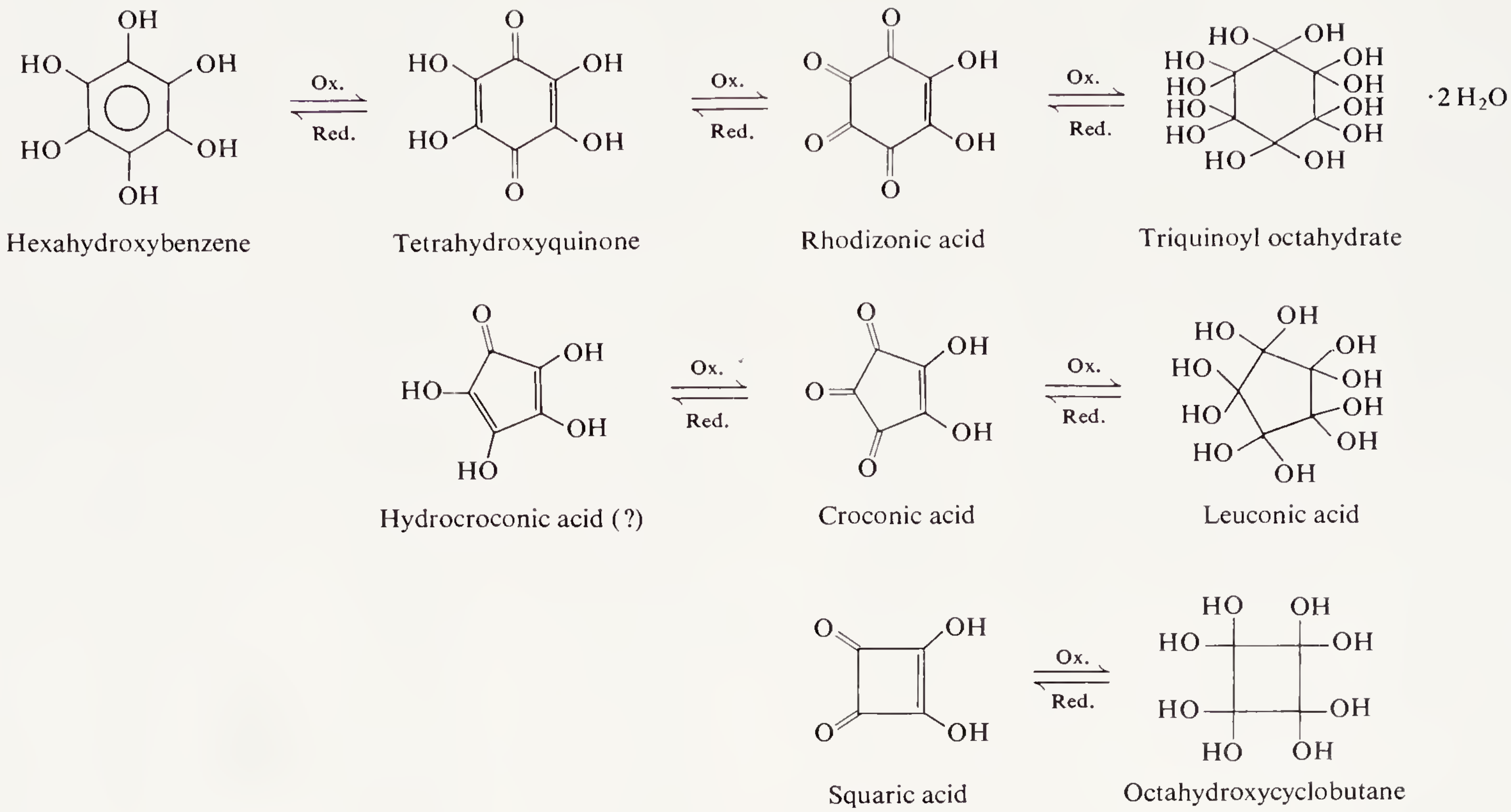
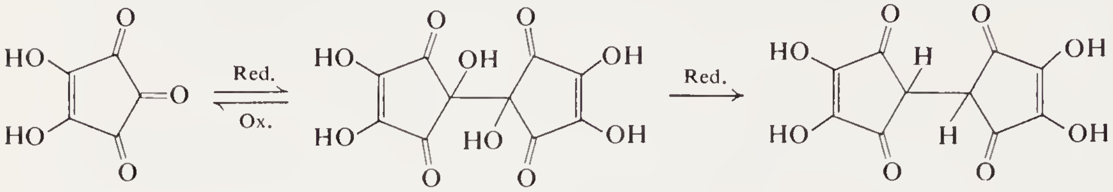


FIG. 11. Oxidation–reduction equilibria among the monocyclic oxocarbon acids.

One of these is probably "hydrocroconic acid" (Fig. 11), which may also be produced on chemical reduction with SO_2, Zn, or $SnCl_2$.[7] Recently, Prebendowski and Rutkowski have shown that interesting bimolecular reduction products are obtained when croconate is treated with hydrogen iodide[57]:



14

These compounds are of interest as possible precursors for "biaryl"-type oxocarbon anions.

Reduction of squaric acid has not been reported. The neutral reduction product, tetrahydroxycyclobutadiene, would of course be expected to be highly unstable. Oxidation and reduction products in the monocyclic oxocarbon series are summarized in Fig. 11.

VI. Oxocarbon Anion-Radicals

Aromatic compounds of many types form delocalized, charged radical species. Especially well-studied are the aromatic anion-radicals. It is of interest, then, to see whether oxocarbons will also form delocalized, aromatic odd-electron species. To date, there is only preliminary evidence that such species may exist.

Upon oxidation in air, the diamagnetic compound $K_4C_6O_6$ gave a green, strongly paramagnetic product which exhibited a single broad line in the ESR spectrum with $g = 2.003$. This intermediate could not be isolated, but underwent further rapid oxidation forming dipotassium rhodizonate. The structure $C_6O_6{}^{3-}$ was suggested for the green compound, which would thus be a trianion-monoradical.[7]

Another indication of an oxocarbon radical came from studies of the reaction of carbon monoxide with metallic potassium. When the reaction products were heated to 250°C and examined by ESR spectroscopy, a single-line spectrum was observed, attributed to the pentaanion-monoradical $C_6O_6{}^{5-}$.[58]

It is likely that further oxocarbon anion-radicals will be detected and studied in the future. A sequence of anions differing by one unit of charge is

---

[57] S. Prebendowski and Z. Rutkowski, *Roczniki Chem.* **31**, 81 (1957).

[58] W. Büchner and E. Lucken, *Helv. Chim. Acta* **47**, 2113 (1964).

possible for each of the monocyclic oxocarbons. All the species with odd-numbered net charge would be radicals:

$$C_6O_6^{6-} \rightleftarrows \mathit{C_5O_6^{5-}} \rightleftarrows C_6O_6^{4-} \rightleftarrows \mathit{C_6O_6^{3-}} \rightleftarrows C_6O_6^{2-} \rightleftarrows \mathit{C_6O_6^{1-}}$$

$$\mathit{C_5O_5^{5-}} \rightleftarrows C_5O_5^{4-} \rightleftarrows \mathit{C_5O_5^{3-}} \rightleftarrows C_5O_5^{2-} \rightleftarrows \mathit{C_5O_5^{1-}}$$

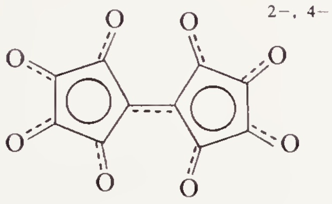
$$C_4O_4^{4-} \rightleftarrows \mathit{C_4O_4^{3-}} \rightleftarrows C_4O_4^{2-} \rightleftarrows \mathit{C_4O_4^{1-}}$$

VII. Polycyclic Oxocarbons

Many kinds of polycyclic oxocarbons can be imagined, but very few examples are known. Of the possible types of structures, four will be considered here.

A. Polyaryls Consisting of Oxocarbon Rings

Such structures as **15** or **16** would be examples:



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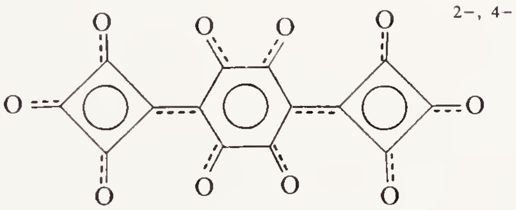


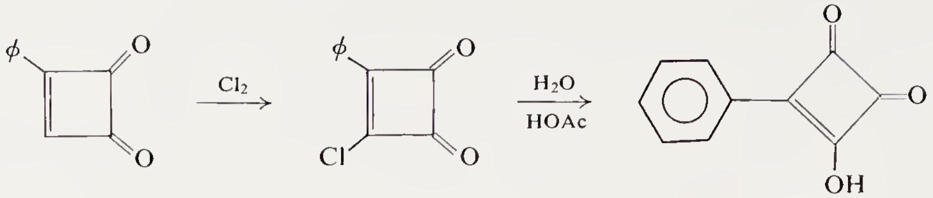
16

Anions of this general kind are completely unknown, although molecular orbital calculations predict stability in some oxidation state for nearly every imaginable structure of this type.[27,44a] The synthesis of such substances is a challenging area of oxocarbon chemistry.

B. Polyaryls Containing Benzenoid and Oxocarbon Rings

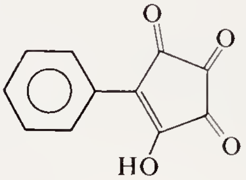
Several compounds of this class are known. Smutny *et al.* have prepared and studied phenylhydroxycyclobutadienoquinone (**17**) and related, less highly oxygenated compounds.[59a] Compound (**17**) is prepared by chlorination and hydrolysis of phenylcyclobutenedione:

[59a] E. J. Smutny, M. C. Caserio, and J. D. Roberts, *J. Am. Chem. Soc.* **82**, 1793 (1960).



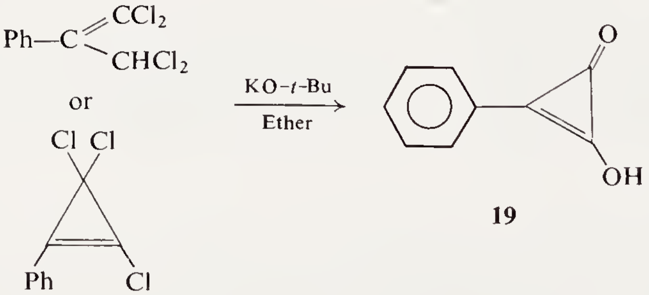
17

Compound **17** is a very strong acid with p$K_a = 0.37$, quite like the monocyclic oxocarbons. Hückel-type molecular orbital calculations for **17** and for other phenylcyclobutadienoquinones were carried out, and 1,3 cross-ring interactions were invoked as stabilizing the molecules. Good evidence for such constructive interactions is lacking, however.[59b] In this connection, the properties of the unknown phenylhydroxycyclopentenetrione (**18**) would be of special interest:



18

Recently, phenylhydroxycyclopropenone or "phenyldeltic acid" (**19**) has been thoroughly studied by Farnum *et al.*[60] and a few other arylhydroxycyclopropenones have been prepared.[61] The reactions of 2-phenyltetrachloropropene or 1-phenyl-2,3,3-trichlorocyclopropene with potassium *t*-butoxide in ether affords **19**, but in very low yield:



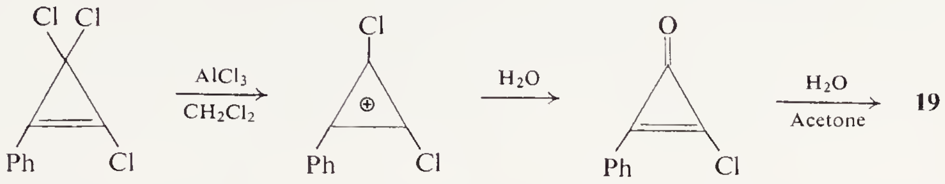
19

[59b] In the monocyclic series, $C_5O_5^{2-}$, in which such transannular stabilization is most unlikely, seems if anything slightly more stable than $C_4O_4^{2-}$ in which such cross-ring interactions might take place. Moreover, the vibrational analysis suggests strong 1,3 repulsive rather than attractive forces in $C_4O_4^{2-}$ (Section III,A).

[60] D. G. Farnum, J. Chickos, and P. G. Thurston, *J. Am. Chem. Soc.* **88**, 3075 (1966).

[61] S. W. Tobey, J. Chickos, and R. West, unpublished studies.

Better yields are obtained by the slow hydrolysis of phenyldichlorocyclopropenium ion as described by West *et al.*[62]:

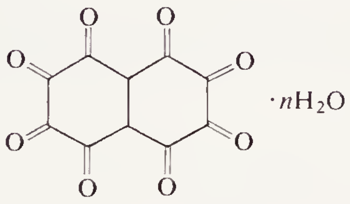


This new synthesis should make compounds of this series much more easily available.

Compound **19** is also a strong protonic acid, with p$K_a \sim 2$. The infrared spectrum of the sodium salt shows strong, sharp bands at 1870 and 1550 cm^{-1}, attributable to the in-phase and out-of-phase C=O stretching modes in the delocalized anion. Compound **19** has been converted to a methyl ether, which undergoes ring opening on attempted solvolysis. Phenylhydroxycyclopropenone itself also undergoes ring-opening reactions easily.[60]

C. Fused-Ring Anions Consisting of Oxocarbon Rings

No such substances are yet known with certainty, but possible precursors are available. A recent patent claims the synthesis of fully oxygenated compounds such as **20** and **21** from photolysis of triquinoyl[63]:



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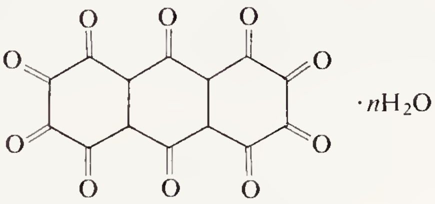


21

If the structures of these compounds are as represented, study of their reactions will be of great interest.

Certain sea urchin pigments of the spinochrome and echinochrome series are naphthoquinones in which every position, or every position but one, on the naphthalene nucleus is oxygenated. For example, spinochromes D and E have structures **22** and **23**, respectively.[64,65]

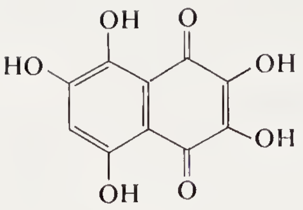
---

[62] R. West, J. Chickos, and E. Osawa, *J. Am. Chem. Soc.* **90**, 3885 (1968).

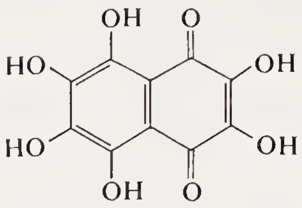
[63] H. E. Worne, U.S. Patent, 3,227,641 (1966).

[64] J. Smith and R. H. Thomson, *Tetrahedron Letters* **1**, 10 (1960).

[65] I. Singh, R. E. Moore, C. W. J. Chang, and P. J. Scheuer, *J. Am. Chem. Soc.* **87**, 4023 (1965).

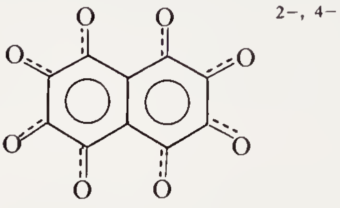


22



23

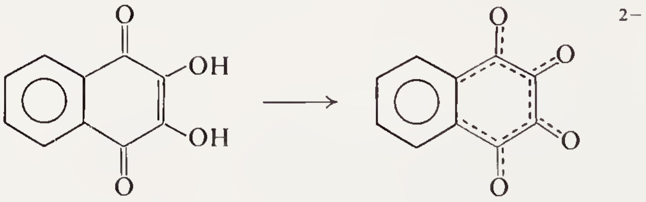
Compound **23**, on further oxidation and treatment with base, should provide oxocarbon anions of the type **24**. The same oxocarbon anions should be available from the reduction of **20**.



24

D. Fused-Ring Compounds with a Benzenoid Ring Fused to an Oxocarbon Ring

One example of this class is well known: the dianion (**26**) of isonaphthazarin (**25**):



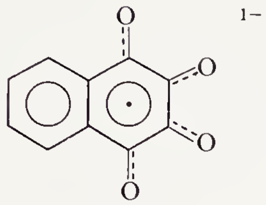
25 **26**

The disodium salt of **26** was first isolated by Bamberger and Kitschelt,[66] and salts have recently been reinvestigated by Bjerke and West.[67] They are unstable, indigo colored substances with $\lambda_{\max} = 640$ nm which undergo air oxidation very easily to an anion-radical, most probably **27**:

---

[66] E. Bamberger and M. Kitschelt, *Ber.* **25**, 133 (1892).

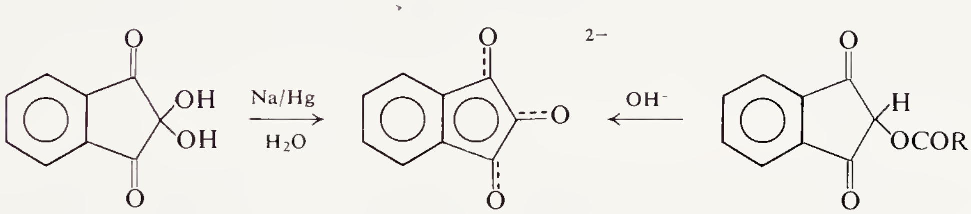
[67] K. A. Bjerke and R. West, unpublished studies; K. A. Bjerke, M.S. thesis, Univ. of Wisconsin, 1964.



27

The anion radical gives a triplet ESR spectrum centered at $g = 2.0044$, with $A_H = 1.7$ gauss. The splitting is believed, from MO calculations, to be due to interaction with the β-protons.

The fused ring oxocarbon dianion **28** appears to be even less stable than its six-membered ring analog **26**. However, the chemistry of **28** is not well understood. As early as 1911 Ruhemann observed that a dark blue solution was produced upon reduction of ninhydrin (**29**) with sodium amalgam in aqueous solution.[68] The blue color was attributed to the dianion, **28**. Later, Riemschneider[69] showed that a similar blue solution was produced by the basic hydrolysis of 2-acetoxy-1,3-diketoindane, **30**:



29 **28** **30**

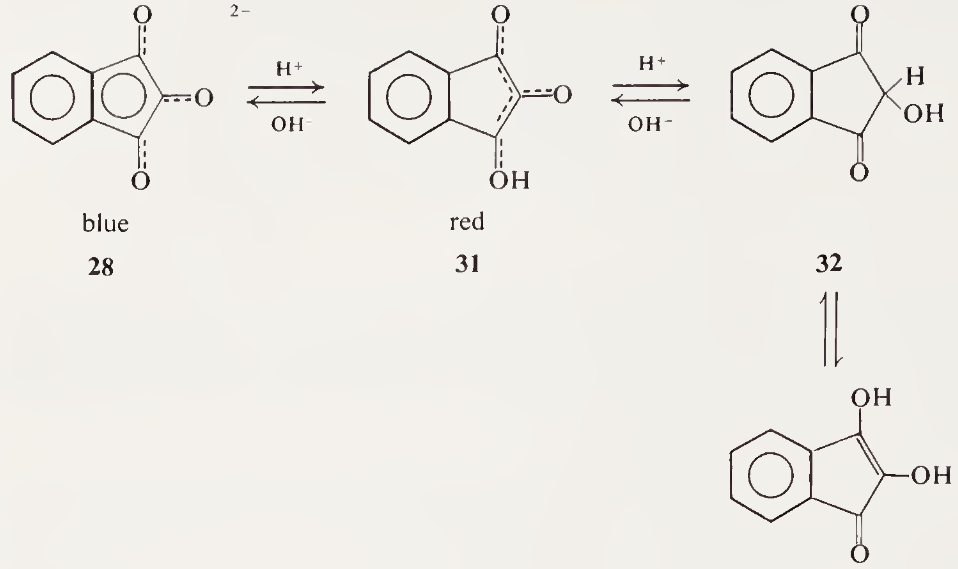
Acidification of the blue solution produced first a red solution thought to be due to the monoanion (**31**) and then a colorless solution from which a beige colored solid was isolated. Riemschneider proposed that the solid was a tautomeric mixture of **32** and **33**. A purer preparation of the same material has been studied recently by Regitz and Heck, who propose on the basis of the infrared spectrum that the solid is exclusively in the diketo form, **32**.[70]

The blue solutions, which may contain **28** are extraordinarily oxygen sensitive, and pure salts of the dianion have apparently never been isolated.

[68] S. Ruhemann, *J. Chem. Soc.* 99, 792 1306 (1911).

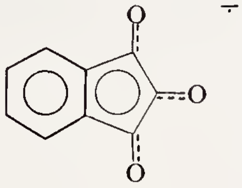
[69] R. Riemschneider, *Monatsh.* 93, 841 (1962).

[70] M. Regitz and G. Heck, *Ber.* 97, 1482 (1964).



28 **31** **32** **33**

Russell and Young[71] have recently studied anion-radicals derived from ninhydrin (**29**). Simple solution of **29** in dimethyl sulfoxide and treatment with base gives a radical whose ESR spectrum indicates splitting by four equivalent protons, $A_H = 0.97$ gauss, thought to be **34**. Reduction of ninhydrin in aqueous solution gives a radical showing coupling by two nonequivalent protons, $A_H = 1.00$ and 0.68 gauss, attributed either to **34** or to its rapidly time-averaged, protonated form, **35**.



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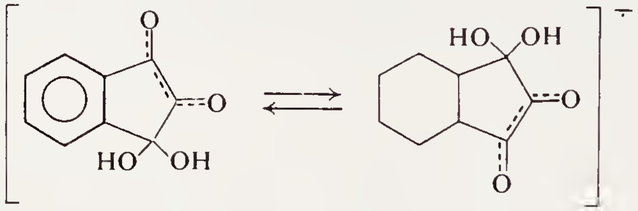
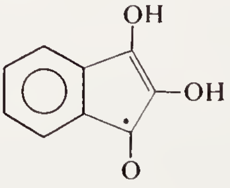


35

In the presence of excess base, a more complex ESR spectrum is observed, attributed to the radical anion **36**:



36

This explanation would require that **36** be a surprisingly weak acid, however.

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[71] G. A. Russell and M. C. Young, *J. Am. Chem. Soc.* **88**, 2007 (1966).

All the evidence indicates that fused-ring oxocarbon anions such as **26** and **28** are relatively unstable and show little aromatic character in the oxocarbon ring. This phenomenon is not unprecedented, as fused-ring compounds generally show reduced aromatic character compared to the two separated rings. For instance, naphthalene is less stable than benzene, and fluorenide anion is distinctly less aromatic than cyclopentadienide.

VIII. Summary

Although oxocarbon anions were among the first aromatic substances ever synthesized, recognition of the unique importance of these species is very recent. With the discovery of the relationships between the oxocarbons and of the aromatic character of the oxocarbon anions, the field of oxocarbon chemistry has both been defined and rejuvenated. Structures are now known for the two "classic" aromatic oxocarbons, rhodizonate and croconate, as well as for the newly synthesized member, squarate ion. But much remains to be done. In the monocyclic series, only anions with ring size 4, 5, and 6 are yet known. Although oxocarbons lack the substitution chemistry of benzenoid aromatics, it appears that the oxocarbons will form numerous condensation derivatives with unusual and interesting electronic structures and properties. Finally, the chemistry of more complex oxocarbons is only beginning. Literally hundreds of possible stable structures await synthesis by the organic chemists of tomorrow.

ACKNOWLEDGMENT

Dr. West thanks the U.S. Public Health Service for a fellowship which made possible the completion of this manuscript. We also thank Dr. James Chickos for helpful suggestions, and Elizabeth Patton for obtaining some of the data reported herein.

Author Index

Numbers in parentheses are footnote numbers. They are inserted to indicate the citation of an author's work when his name is not mentioned on the page.

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