

THE CHEMISTRY OF THE SYDNONES

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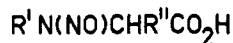
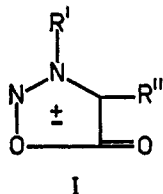
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I. INTRODUCTION

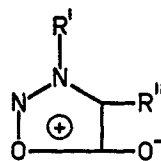
The sydnones (I) constitute a well-defined class of anhydro compounds obtained by the action of certain dehydrating agents, notably acetic anhydride, on the N-nitroso derivatives (II) of N-substituted α -amino acids. These compounds are of interest because of the problem of their electronic structure and also because of the varied types of biological activity displayed by some of them.



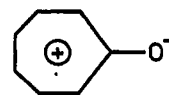
II

The chemistry of the sydnones, as members of a group of similar heterocyclics for which no single, satisfactory electronic structure can be written, was reviewed in 1957 by Baker and Ollis (4). The present review is concerned mainly with developments during the period since then and concentrates on the sydnones and their formal derivatives, the sydnone imines.

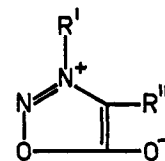
The chemical and physical properties of the sydnones cannot be adequately explained by any single valency structure, and the satisfactory representation of these compounds has given rise to much controversy (2, 54, 59, 92, 111). One or other of a number of possible hybrid structures may be employed, and at present the most frequently used is probably the 'mesoionic' structure (III) proposed by Baker and Ollis (3). In III the available π -electrons are distributed so that a sextet is associated with the ring as a whole, while a lone pair is assigned to the exocyclic oxygen atom. This arrangement, which results in a net separation of charges, is considered to confer aromatic character to the ring system.



III



IV



V

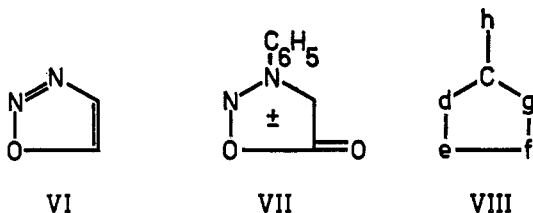
While this description has some aesthetic appeal,

by analogy, perhaps, with the case of tropone (IV), it is by no means certain that III offers an accurate picture of the sydnone system, and various objections to it have been raised. These will be referred to from time to time.

It has also been suggested that the sydnones should be discussed on the basis of the extreme zwitterionic structure (V) with the reservation that they are mesomeric betaines, and the contribution of several additional structures must be understood (58, 60). Use of the term betaine in connection with sydnones, however, has disadvantages in view of their physical properties (section IVA). The structural aspects of sydnones have been the subject of a short review in Czech (116).

For the purposes of this review, the earlier, more noncommittal, formula (I) of Baker and Ollis (8) will be used. This has the advantage that it stresses the lactonic character of the compounds, while leaving open the question of electron distribution in the rest of the molecule.

Formally the sydnones (I) are derivatives of 1,2,3-oxadiazole (VI). Since it is now thought that compounds previously supposed to be 1,2,3-oxadiazoles are, in fact, open-chain α -carbonyl diazo derivatives, the sydnones would appear to be the only known representatives of this ring system (18). On this basis 3-phenylsydnone (VII), for example, has been given the systematic nomenclature ψ -5-keto-3-phenyl-3,5-dihydro-1-oxa-2,3-diazole (5), where the symbol



ψ reflects the uncertainty about electron distribution referred to above. An alternative nomenclature based on the betaine structure (V) is anhydro-5-hydroxy-3-phenyl-1-oxa-2,3-diazolium hydroxide (58).

The name 'sydnone,' although of trivial origin (30), appears to have become accepted through usage and is employed by *Chemical Abstracts*. In view of the number and variety of the compounds which are now known, the convenience of the name outweighs, in this case at least, any undesirable aspects of this type of terminology.

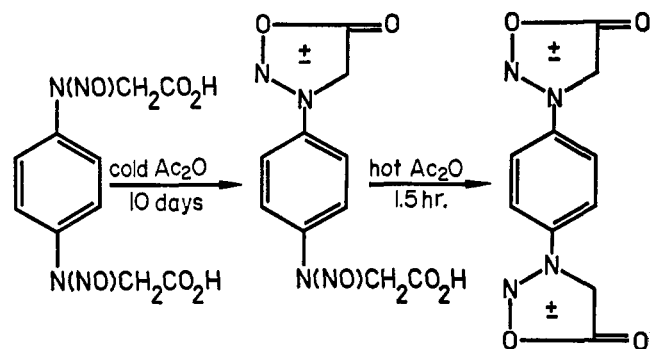
In this connection, however, it is well to remember that sydnones represent only one of some 288 possible five-membered ring systems having similar electronic characteristics, but of which relatively few have yet been prepared (14). These systems are generalized in formula VIII where d, e, f, g, and h are variously R-C, N; R-N, O; S; and R₂C.

II. PREPARATION OF SYDNONES

The original method of preparation by the cyclodehydration of an N-alkyl or aryl N-nitroso- α -amino acid is still the only general route to sydnones (34). The substituent R' in I may be alkyl or aryl but not hydrogen, while R'' may be alkyl, aryl, or hydrogen. Both substituents can be members of an alicyclic ring, and either of them may also contain a functional group such as carboxyl, ester, ether, nitrile, or hydroxyl (83). The probable mechanism of sydnone formation has been discussed by Baker, Ollis, and Poole (6).

The reaction is often effected by heating the nitroso compound with excess acetic anhydride on a water bath for several hours, and this procedure is generally satisfactory with the simple alkyl or aryl derivatives (30). However, in many cases it is better to allow the reaction to proceed for a few days at room temperature when a cleaner product is obtained. Some alkyl sydnones with a functional group in the side chain, are extensively decomposed by hot acetic anhydride.

A number of binuclear sydnones have been prepared by cyclodehydration of the appropriate dinitroso compounds (21, 84, 85, 104). In the case of *p*-phenylene-3,3'-disydnone it has been demonstrated that the reaction proceeds in two discrete stages (104).



Evidently, transmission by the benzene nucleus of the positive charge on the 3-nitrogen of the first sydnone ring deactivates the other nitroso-acid system.

Although acetic anhydride remains the most widely used dehydrating agent, several alternatives have been utilized successfully. These are trifluoroacetic anhydride (6, 21), thionyl chloride (6), and carbonyl chloride (75). Using trifluoroacetic anhydride the reaction, which may require some days with acetic anhydride, is complete in a few seconds. It has also been reported that N,N'-diisopropylcarbodiimide converts N-nitroso-N-phenylglycine into 3-phenylsydnone in aqueous solution at room temperature (75).

Some unusual examples of sydnone formation involving rearrangement of the cyclic anhydrides derived from certain N-alkyl-N-nitroso- α -aminodicarboxylic acids have been observed recently (84-86), but are

not of general preparative significance. These are discussed in the following section.

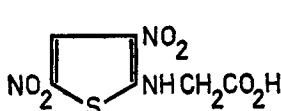
III. UNSUCCESSFUL ATTEMPTS TO PREPARE SYDNONES

The formation of sydnones from the corresponding N-nitroso amino acids is a very general reaction. In a few instances, however, attempts to prepare specific sydnones have failed. The known examples fall into two groups: (A) where the requisite nitroso derivative could not be prepared for some reason, and (B) where an alternative reaction course competed successfully with sydnone formation during the actual dehydration stage.

A. AN N-NITROSO DERIVATIVE CANNOT BE PREPARED

In attempting to prepare a 3-thienylsydnone, Tien and Hunsberger (93) found that N-(3,5-dinitro-2-thienyl)glycine (IX) could not be nitrosated even under conditions applicable to very weakly basic amines.

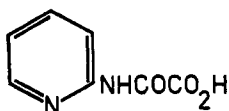
Ohta and Masaki (73) obtained a C-nitroso derivative (X) on nitrosation of N-2-pyridylglycine. With acetic anhydride this compound formed either N-2-pyridyloxamic acid (XI) or N-2-pyridyl-O-acetyl formamidoxime (XII) according to the reaction temperature. It may be noted that N-3-pyridylglycine reacts normally to give the N-nitroso derivative, from which the corresponding sydnone is readily obtained (90, 91).



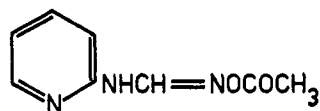
IX



X



XI



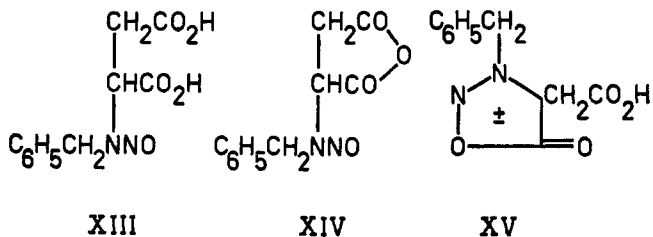
XII

B. ANOTHER REACTION COMPETES WITH SYDNONE FORMATION

Unlike the 2-pyridyl analog N-4-pyridylglycine is reported to form an N-nitroso derivative, which, however, did not produce the expected sydnone, $C_7H_{13}N_3O_2$, with acetic anhydride, but instead gave a colorless crystalline substance, $C_{10}H_{13}N_3O_2$, of unknown structure (72). Apparently another reaction intervenes in this case although it is also possible, on the evidence presented, that the nitroso compound in question was not an N-substituted derivative.

The first definite example of sydnone formation being rejected in favor of an established alternative reaction was provided by Brookes and Walker (19). N-Benzyl-N-nitroso-DL-aspartic acid (XIII) formed

the cyclic anhydride (XIV) rather than the isomeric 3-benzyl-4-carboxymethylsydnone (XV) on treatment with acetic anhydride at room temperature.

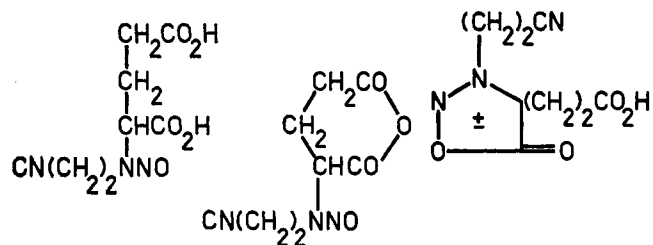


XIII

XIV

XV

This result is not due to any inherent instability of sydnone XV, which has since been synthesized in an unambiguous manner (86). Similarly, N-β-cyanoethyl-N-nitroso-L-aspartic acid gave the corresponding anhydride with retention of optical activity (86). In the case of N-β-cyanoethyl-N-nitroso-L-glutamic acid (XVI) the six-membered cyclic anhydride (XVII) was the major product (46%), but a small quantity (8%) of 3-β-cyanoethyl-4-β-carboxyethylsydnone (XVIII) was also formed (84).



XVI

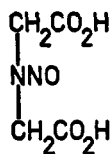
XVII

XVIII

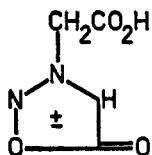
Sydnone formation is not necessarily suppressed in all cases where a similar competitive situation exists, and several instances are known in which sydnones are formed in preference to the isomeric cyclic anhydrides.

Treatment of N-nitrosoiminodiacetic acid (XIX) with cold acetic anhydride gave 3-carboxymethylsydnone (XX) rather than the corresponding anhydride, N-nitrosomorpholin-2,6-dione (XXI) (81). N-Phenyliminodiacetic acid, by comparison, forms the expected morpholindione with acetic anhydride (15). The unsymmetrical iminodiacetic acid derivative (XXII) likewise gave a mixture consisting of 3-carboxymethyl-4-phenylsydnone (XXIII) (50%) and 3-α-carboxybenzylsydnone (XXIV) (30%) (84).

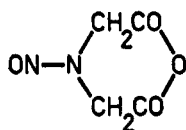
A very close balance between sydnone and cyclic anhydride formation has been observed with N,N'-di-β-cyanoethyl-N,N'-dinitroso-α,α'-diaminoglutaric acid (XXV) (85). This compound consisted of a mixture of *meso* and *DL* diastereoisomers. Treatment of the mixture with acetic anhydride gave 3,3'-di-β-cyanoethyl-4,4'-methylenedisynone (XXVI), whereas the individual diastereoisomers each gave the



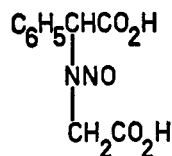
XIX



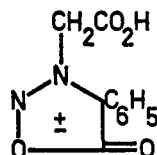
XX



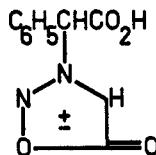
XXI



XXII

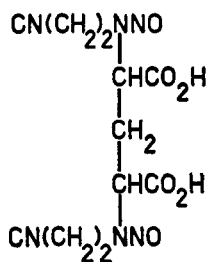


XXIII

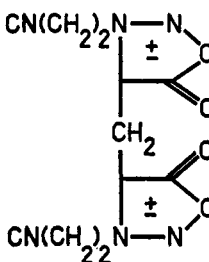


XXIV

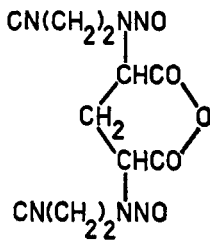
cyclic anhydride (XXVII) predominantly. The latter was readily converted into the sydnone on warming with acetic anhydride.



XXV

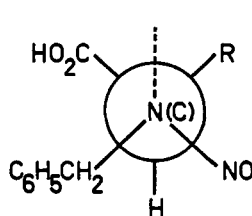


XXVI

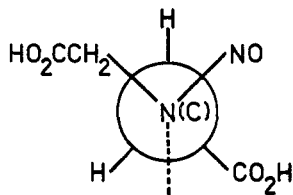


XXVII

It has been suggested that the particular reaction course followed in these competitive situations is governed to some extent by conformational factors (84). The preferred conformation of the aspartic and glutamic derivatives, XIII and XVI, respectively, may be represented by a Newman projection (XXVIII) in which the groups about the C α -N bond are so arranged that the largest are in a *trans* orientation. The group R is CH₂CO₂H in XIII and (CH₂)₂CO₂H in XVI. In this configuration the nitroso and α -carboxyl groups are not suitably placed for participation in sydnone formation, for which a more strained conformation would first have to be adopted by rotation about the C-N bond.



XXVIII

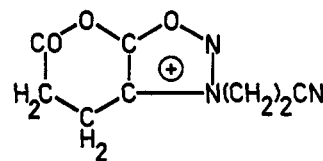


XXIX

In the case of N-nitrosoimino diacetic acid (XIX), on the other hand, the most favorable conformation

is XXIX, in which the bulky groups are again *trans*, but the nitroso group is now able to participate in sydnone formation without any initial radical change in configuration.

It is convenient at this point to consider the unusual hydrolytic behavior of several of these cyclic anhydrides. The glutamic derivative (XVII) reacted with water at room temperature with formation of 3- β -cyanoethyl-4- β -carboxyethylsydnone (XVIII) in 35% yield, in addition to the expected glutamic acid (XVI) (84). Similarly, N-benzyl-N-nitroso-DL-aspartic anhydride (XIV) gave the corresponding sydnone (XV) in 30% yield when dissolved in boiling water (86). With aqueous acetone at room temperature a 3-4% yield of XV was obtained. N- β -Cyanoethyl-N-nitroso-L-aspartic anhydride also formed a sydnone (2-5%) on hydrolysis at room temperature. These results suggest that the nitroso group may be involved in neighboring group participation in the hydrolysis of the anhydride ring, probably by way of a mesomeric bicyclic cation such as XXX.



XXX

Although this method of sydnone formation is not of preparative importance, it does provide the most convenient route to 3- β -cyanoethyl-4- β -carboxyethylsydnone (XVIII).

IV. PHYSICOCHEMICAL PROPERTIES

Some of the physicochemical properties of sydneses, such as dipole moments, have already been discussed by Baker and Ollis (4) and will not be considered here except where new work has appeared since 1957.

A. GENERAL

The alkyl sydneses are mostly liquids or low-melting solids which can be distilled *in vacuo* without appreciable decomposition. A curious exception appears to be 3-*t*-butylsydnone for which an unexpectedly high melting point (168-170°) has been reported (61). The aryl sydneses are generally highly crystalline solids with melting points ranging to above 300°. Sydneses are more or less soluble in the common organic solvents (except petroleum ether) and are normally sparingly soluble in water. When a functional group such as carboxyl is present in an alkyl side chain, solubility in water tends to increase markedly at the expense of solubility in chloroform, ether, and benzene.

B. INFRARED SPECTRA

The infrared spectra of many sydnones (XXXI) have been obtained, and some definite assignments made (21, 36, 38, 92, 107, 111). The most characteristic feature is the very strong carbonyl stretching band in the range 1718–1770 cm^{-1} . Usually this consists of a single peak, but occasionally multiple peaks occur (21). This effect is due to Fermi resonance splitting and has been studied for the solution spectra of 3-phenyl- and 3-ethylsydnone (17).

The carbonyl absorption of γ -lactones is near 1740 cm^{-1} while that of tropone is at 1638 cm^{-1} , and it has been suggested that this is evidence against the mesoionic structure (III) for sydnones. On the other hand, Zaitsev and Sheinker (114) have measured the integrated absorption of sydnone carbonyl bands for a number of the compounds. The values obtained ($6\text{--}12 \times 10^4$ mole $^{-1}$ l./cm. 2) are greater than those for other carbonyl compounds ($1.5\text{--}5.7 \times 10^4$ mole $^{-1}$ l./cm. 2) and were taken to indicate that the bond is highly polarized as a result of the electron drift required by the mesoionic formula.

Another characteristic band occurs in the spectra of monosubstituted sydnones, namely, the stretching frequency of the ring C–H bond at about 3190 cm^{-1} (21, 38, 92, 111). This medium intensity peak is quite distinct from those arising from alkyl or aryl substituents, and is particularly useful for deciding if a sydnone of ambiguous structure is substituted in the 4-position (84).

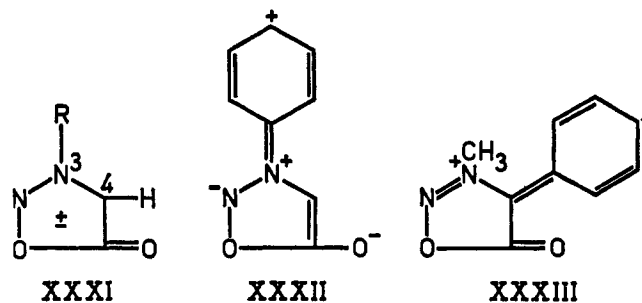
Less definite assignments have been made for bands in the 700–1000 cm^{-1} region. A peak frequently occurring near 870 cm^{-1} is probably due to C–O stretching (17, 92).

Yamada and Kozima (100) have observed that 3-phenylsydnone and iodine apparently form a loose complex in which the carbonyl absorption is displaced slightly to longer wave length.

C. ULTRAVIOLET SPECTRA

Alkyl sydnones give ultraviolet spectra consisting of a single maximum at 290 $\text{m}\mu$ with an intensity of *ca.* ϵ 8000 (42), and this has been advanced as evidence for the aromatic character of the ring system (4). The presence of aryl substituents on the sydnone nucleus results in a bathochromic displacement of this band due to interannular conjugation involving resonance structures such as XXXII (5, 121). Thus 3-phenylsydnone absorbs at 310 $\text{m}\mu$ (ϵ 5600). A phenyl group in the 4-position appears to conjugate more effectively than when in the 3-position. The maximum for 3-methyl-4-phenylsydnone, for example, is at 317 $\text{m}\mu$ (ϵ 7700) (84, 87). In this case the corresponding resonance structures (as XXXIII) are probably more stable than any of the tetrapolar

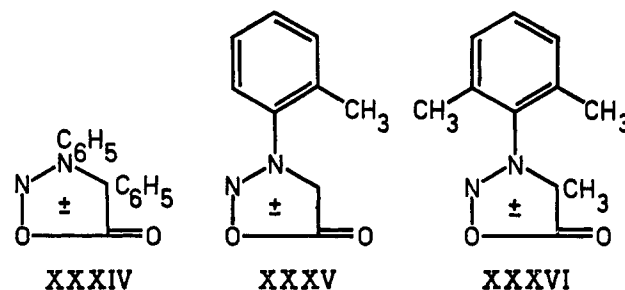
forms (XXXII) which must be written for 3-aryl sydnones.



The presence of two aryl substituents as in 3,4-diphenylsydnone (XXXIV) causes a still greater bathochromic shift (340 $\text{m}\mu$, ϵ 8900).

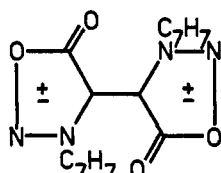
In addition to the sydnone band the aryl sydnones exhibit benzenoid K absorption in the region 240–290 $\text{m}\mu$ (ϵ *ca.* 10,000). Superposition of the two sets of maxima produces a minimum (*ca.* 285 $\text{m}\mu$), the position of which varies markedly with the degree of conjugation (35).

Conjugation involving the sydnone ring is subject to steric effects of the kind encountered with other unsaturated systems. In 3-*o*-tolylsydnone (XXXV) the coplanarity of the two rings is affected by the *ortho* methyl group with the result that the above minimum is displaced to shorter wave length (255 $\text{m}\mu$) and greatly reduced in intensity (121). This effect reaches an extreme with 3-(2',6'-dimethylphenyl)-4-methylsydnone (XXXVI) in which interannular conjugation is severely inhibited, and the spectrum tends to resemble that of an alkyl sydnone (42, 121).



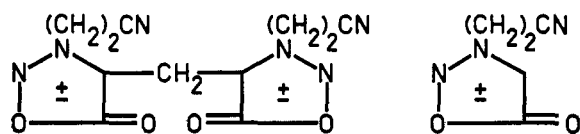
An unusually large bathochromic shift has been observed in the case of 3,3'-dibenzyl-4,4'-disydnone (XXXVII) with a maximum at 350 $\text{m}\mu$ (ϵ 14,700) (84). This value is surprising in view of the 'diphenyl' type of resonance inhibition which might be expected for this structure. It is possible that strong electrostatic attraction between the negatively biased carbonyl oxygens and the positive ring nitrogens tends to hold the molecule in an almost planar configuration.

There is some evidence that two sydnone nuclei can interact electronically across a methylene bridge (85, 119). The sydnone absorption of 3,3'-di- β -cyanoethyl-4,4'-methylenedisydnone (XXXVIII) occurs at 303



XXXVII

$m\mu$ (ϵ 10,100), whereas that of 3- β -cyanoethylsydnone (XXXIX) is at 292 $m\mu$ (ϵ 4000) (85).



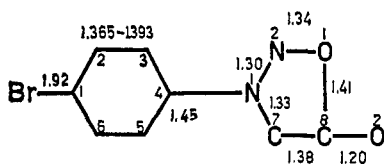
XXXVIII

XXXIX

D. X-RAY DIFFRACTION

A preliminary X-ray investigation of several 3-aryl sydrones was carried out by Schmidt, who concluded that the two ring systems were probably coplanar in the crystal (78). More recently, a detailed structure analysis of 3-*p*-bromophenylsydnone (XL) has been completed (9, 10).

Contrary to the findings of Schmidt, the rings, which are individually planar, are twisted about the C-4-N-1 bond to contain a dihedral angle of 27°. The different bond lengths obtained are shown in XL. It is noteworthy that the length of the exocyclic C-O bond is close to that of a normal carbonyl group. This is difficult to reconcile with the mesoionic structure (III) in which this should possess very little double-bond character if the nucleus were truly aromatic.



XL

E. POLAROGRAPHY

Zuman has found that sydrones are suitable materials for polarographic study as good waves are readily

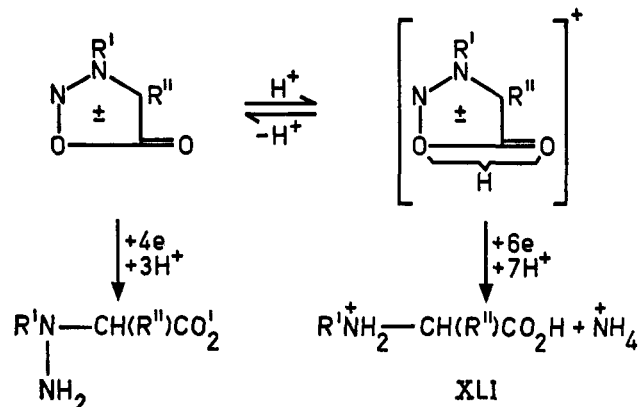
TABLE I

PROTON MAGNETIC RESONANCE OF SYDRONES^a

Sydnone	$\tau_{\text{sydnone H}}$	$\tau_{3\text{-alkyl H}}$	$\tau_{4\text{-alkyl H}}$	$\tau_{\text{phenyl H}}$
3-Phenyl	3.22	2.30
3-Benzyl	3.81	4.64	...	2.56
3-Hexadecyl	3.67	5.73 ^b
3-Methyl-4-phenyl	...	5.87	...	2.50
4-Methyl-3-phenyl	7.83	2.32
3-Benzyl-4-carbo-methoxymethyl	...	4.50	6.46	2.64

^a The spectra were obtained in CDCl_3 solution with tetramethylsilane as internal reference. ^b Triplet with $J = 7$ c.p.s.

obtained, and a wide range of the compounds has been investigated (115, 117-120). The course of reduction at the cathode may be summarized as



At pH values greater than 7.5 reduction occurred by a four-electron process to give the anion of an unsymmetrical hydrazino acid. Under acidic conditions (pH < 6), on the other hand, six-electron waves were obtained with formation of anions of N-substituted amino acids (XLI) and ammonium ion (74, 118). Ordinary chemical reduction of 3-phenylsydnone with zinc and acetic acid gives N-phenylglycine and ammonia (32).

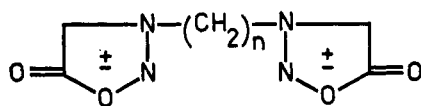
The four-electron waves observed under alkaline conditions are independent of pH and can be utilized to study the effect of variations of the substituents R' and R'' (121). The half-wave potentials of *meta* and *para* substituted 3-phenylsydrones can be expressed by a modified Hammett equation

$$\Delta E_{1/2} = \rho_{\pi, R} \sigma_x$$

Here $\Delta E_{1/2}$ is the difference between the observed potential and that of 3-phenylsydnone, while $\rho_{\pi, R}$ and σ_x are the reaction and substituent constants, respectively (120).

The fact that the results follow a Hammett relationship indicates that the substituents exert a polar effect only. With *ortho* substituted derivatives such as 3-*o*-tolylsydnone (XXXV), however, the half-wave potential is displaced in a negative direction by an amount (-0.085 v.) which is considerably greater than that predicted for a purely polar effect (-0.03 v.) (121). This has been ascribed to steric inhibition of coplanarity affecting the interannular resonance, and as in the case of the ultraviolet spectra of hindered sydrones (section IVD), the effect is greatest with 3-(2',6'-dimethyl)phenyl-4-methylsydnone (XXXVI) (-0.24 v.). Whereas these results clearly demonstrate the operation of resonance interaction with 3-phenyl groups, it was also claimed that the polarographic data prove that no such interaction occurs with the 4-phenyl group in 3,4-diphenylsydnone (121). This conclusion is contrary to the ultraviolet spectral data and also to chemical evidence (section VA).

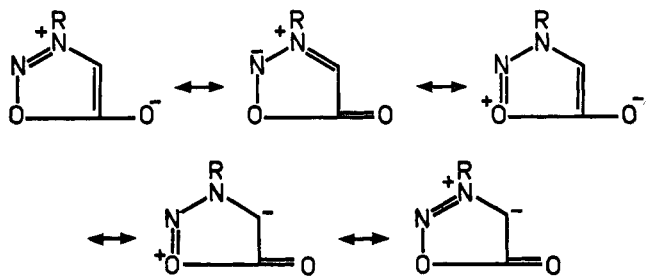
In the case of 3,3'-polymethylenedisynones (XLII) the protonated form (strongly acid conditions) is reduced in one twelve-electron step. Under other conditions two discrete four-electron steps make up an eight-electron wave. This effect is greater with a short carbon chain (XLII, $n = 2$), and may be due interaction between the sydnone rings so as to facilitate preferential attack on one nucleus (119).



XLII

F. MAGNETOCHEMISTRY

The diamagnetic susceptibilities of eight sydnones have been determined by Matsunaga (66). An average value of 38.7×10^{-6} c.g.s. unit was obtained for that portion of the susceptibility due to the sydnone ring. Calculated values based on the five ionic canonical forms (XLIII) gave an average of 24.6×10^{-6} c.g.s. unit. There is therefore an exaltation of 14.1×10^{-6} c.g.s. unit due to mesomerism in the nucleus. This is comparable with the corresponding values for thiophene (17.9×10^{-6}), furan (13.4×10^{-6}), and pyrrole (14.4×10^{-6}).



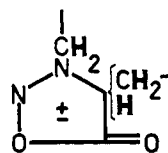
XLIII

G. N.M.R. SPECTRA

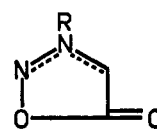
Proton magnetic resonance spectra of a number of sydnones have been obtained in an effort to throw more light on the electronic nature of the ring system, and, in particular, to observe any indications of an aromatic ring current (89). A selection of the results are collected in Table I, which includes τ -values for 3- and 4-alkyl protons, the protons of any attached phenyl groups, and sydnone ring protons (XLIV).

The resonance of 3-alkyl protons occurs at considerably lower field than that of 4-alkyl protons owing to the strong deshielding effect of the positively charged 3-nitrogen atom. The τ -values for the ring protons of various aromatic five-membered heterocyclics, such as thiophene, are in the range 1.0-3.4 (99). By comparison, the sydnone ring proton values are at unexpectedly high field and are difficult to reconcile

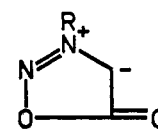
with the mesoionic formulation of these compounds. In the mesoionic structure the positive charge associated with the ring should exert a very marked deshielding effect. It has been suggested that sydnones might be better represented as cyclic azomethine imines (XLV) (48), in which a mesomeric azomethine-imine system and a lactone moiety coexist in a strongly localized state (89). The important contributing structure (XLVI) would place a negative charge on the 4-position with consequent shielding of the attached proton.



XLIV



XLV

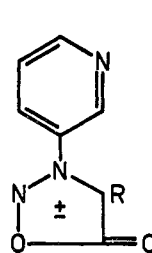


XLVI

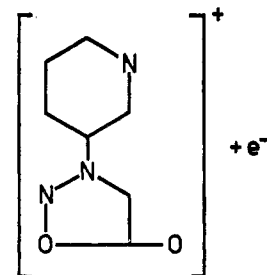
Daeniker and Druey (22) obtained a value of 6.34 p.p.m. (τ 3.66) for the ring proton resonance of 3-*n*-butylsydnone, and considered that this value, in conjunction with those for several sydnone imine derivatives at somewhat lower field, tended to support the mesoionic structure.

H. PHOTOTROPY

Of the numerous sydnones which are known, one, 3-3'-pyridylsydnone (XLVII), is unique in that it exhibits to a marked degree the phenomenon of phototropy (photochromism) (90, 91). The compound is a colorless, crystalline solid which becomes deep blue on exposure to daylight. The color fades slowly in the dark or more rapidly on heating, or by application of an electric field (67). The process can be repeated several times without appreciable fatigue, although eventually fatigue occurs, apparently due to progressive decomposition (67). Both forms of XLVII give identical infrared spectra (91).



XLVII, R = H
XLVIII, R = CH₃ or C₆H₅



XLIX

Several 3-3'-pyridylsydnones closely related to XLVII have been prepared but are not phototropic. These include the methyl and phenyl analogs (XLVIII) (71) and some 4-mercuri derivatives (92). It has

been claimed that a number of 3-benzylsydnones and 3,3'-polymethylenedisynones are slightly phototropic (67).

The behavior of XLVII has been investigated by electron spin resonance (40). After irradiation a signal developed gradually at a rate dependent on temperature and the presence of air. Later work indicated that two species are formed on irradiation, one colored and the other paramagnetic (68).

According to Cohen and Schmidt (20) the phototropy of XLVII is due to the separation of the molecule into a cation (XLIX) of unspecified structure and an electron which diffuses into the crystal lattice.

I. SURFACE PROPERTIES

The appreciable water solubility of several sydnones of low molecular weight points to the hydrophilic nature of the ring system as a whole, and a sydnone containing a long-chain alkyl substituent would be expected to form a stable unimolecular film at a water-air interface (1). In order to observe the effect of

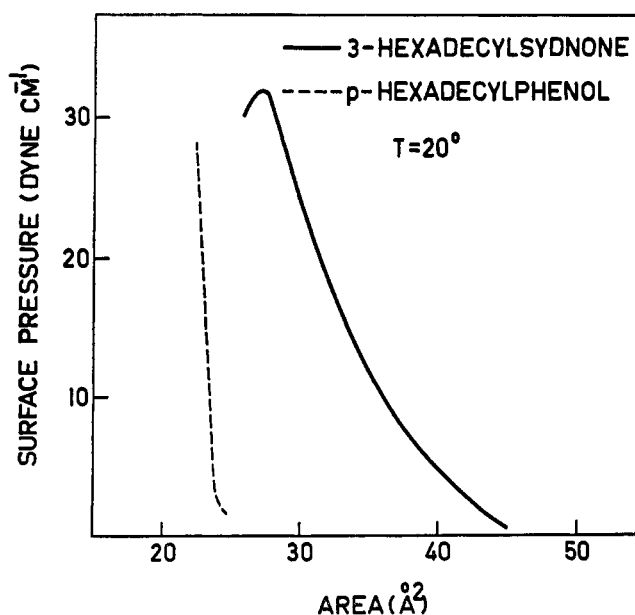
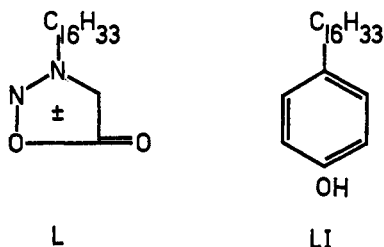


Fig. 1.—Surface pressure-area curve for the 3-hexadecylsydnone monolayer.

the sydnone nucleus on the properties of such a film 3-hexadecylsydnone (L) was selected, and the surface pressure-area curve of its monolayer is given in Fig. 1 (80).



The corresponding curve for *p*-hexadecylphenol (LI) is also given as being more or less typical of the monolayers from many 16-carbon derivatives having polar head groups of approximately the same size as the sydnone ring system (1).

Whereas the phenol (LI) and other hexadecyl compounds form a condensed film of low compressibility, the sydnone film is very similar to the liquid-expanded type of monolayer obtained with shorter chain lengths or elevated temperatures (1). The expanded nature of the film indicates that the lateral cohesion within the monolayer is considerably reduced, probably owing to strong electrostatic repulsion between the sydnone nuclei, and this was taken as support for the highly polar mesoionic structure (III) for sydnones.

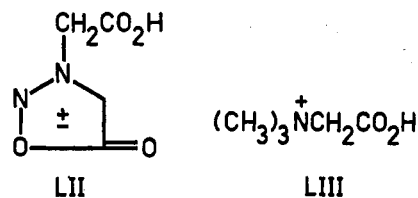
Unfortunately, surface potential measurements were not recorded for this monolayer.

J. MISCELLANEOUS

There are a few examples of other physicochemical properties in the sydnone series.

a. Hearne and LeFèvre (45) found that the observed molar Kerr constants of sydnones agreed with calculated values, and that the agreement was apparently unaffected by the possible existence of mesoionic character in the compounds. These authors give a value of 5.4 cm.³ as the portion of the molar refraction of sydnones representing the exaltation of polarizability due to mesomerism in the nucleus.

b. The dissociation constant pK_a of 3-carboxymethylsydnone (LII) was found to be 1.7, which is comparable with the value (1.83) for the conjugate acid of trimethylbetaine (LIII) (52). This figure reflects the large positive charge on the 3-nitrogen atom of the ring.



V. CHEMICAL BEHAVIOR

In recent years there have been considerable developments in sydnone chemistry, and the various aspects will be discussed under appropriate headings. Except where relevant, the earlier reactions, which have been covered by Baker and Ollis (4), are not considered.

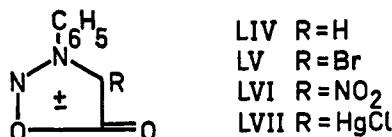
A. ELECTROPHILIC SUBSTITUTION

The single ring hydrogen in 3-phenylsydnone (LIV) is readily replaced by other groups under reaction conditions which often resemble those used for electrophilic substitution in benzene and other aromatic

compounds. This similarity is also a strong point in favor of the mesoionic representation of sydnones as aromatic derivatives (4). Most of the work has been carried out with 3-phenylsydnone, and a promising field of study concerning the influence of substituents in the phenyl group on the reactivity of the 4-position lies open.

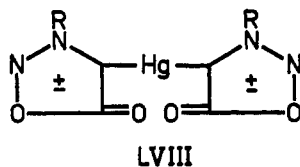
3-Phenylsydnone (LIV) is converted into 4-bromo-3-phenylsydnone (LV) on treatment with bromine in acetic anhydride at 0°, or with N-bromosuccinimide in boiling chloroform (5). Bromine in acetic acid in the presence of sodium acetate has also been used (55), as well as bromine in aqueous potassium bromide (33, 69). The relative efficiencies of different bromination procedures have been compared and were found to decrease in the following order (53): Br₂ in Et₂O-NaHCO₃ > N-bromosuccinimide ≈ N-bromoacetamide > Br₂ in CHCl₃/CaCO₃ > Br₂ in Ac₂O > IBr in CHCl₃-CaCO₃.

Similarly, 3-phenylsydnone can be chlorinated by chlorine in acetic anhydride (6) and iodinated by iodine in aqueous potassium iodide (69).



Treatment of 3-phenylsydnone with nitric acid or potassium nitrate and concentrated sulfuric acid at or below 0° produces the 4-nitro derivative (LVI) (6, 19). Unsuccessful efforts to nitrate the sydnone ring have also been reported (21).

Mercuriation of sydnones with mercuric chloride results in the formation of either a mercuri derivative (as LVII) or a mercuri disydnone (LVIII) according to the reaction conditions, *e.g.*, temperature (69, 92, 111). Mercuric acetate gives a 4-acetomercuric derivative (111).

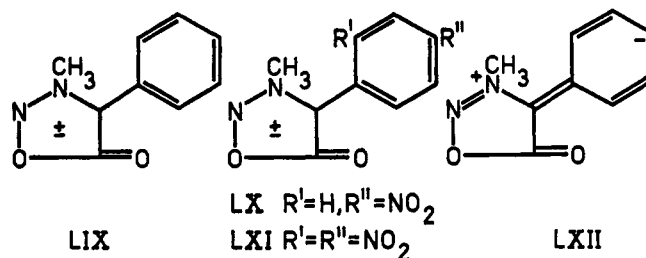


3-Ethylsydnone and several 3-aryl sydnones have been sulfonated using sulfur trioxide-dioxane complex in ethylene dichloride with formation of the corresponding sydnonesulfonic acids, which were isolated as the barium salts (111). Acetylation of the sydnone ring was effected with acetic anhydride and boron trifluoride etherate (107). Finally, there is a report that the formyl group can be introduced by the action of N-methylformanilide and phosphorus oxychloride (92).

Apart from electrophilic attack at the 4-position of the sydnone ring there is also the possibility of sub-

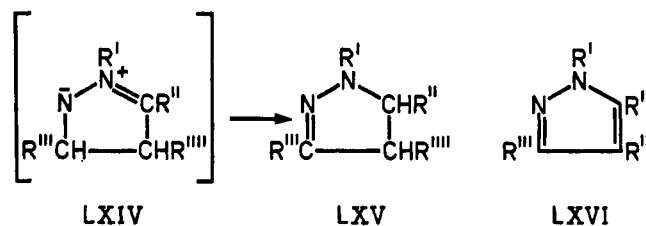
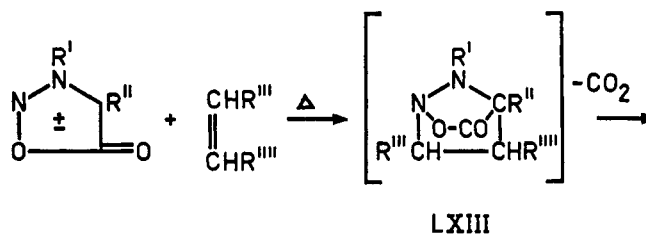
stitution in aromatic groups attached to the ring. Baker, Ollis, and Poole (6) referred to the nonreactivity of the aryl group in 3-phenylsydnone during the nitrations and halogenations discussed above. Such deactivation is not unexpected owing to the positive charge located on the 3-nitrogen (*cf.* structure XXXII).

It has been found, however, that a phenyl group in the 4-position is activated for electrophilic substitution. 3-Methyl-4-phenylsydnone (LIX) is readily converted into a 4'-nitro derivative (LX) on treatment with nitric acid in acetic acid at room temperature (82). Traces of 2'- and 3'-nitro compounds were also detected. With mixed nitric-sulfuric acid, or fuming nitric acid, at 0°, the 2',4'-dinitro compound (LXI) is produced. The reactivity of this phenyl group is probably due to contributing structures such as LXII, which place a negative charge on the *ortho* and *para* positions (82).



B. ADDITION-ELIMINATION REACTIONS

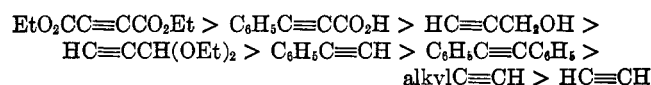
Vasil'eva, Yashunskii, and Shchukina (96) found that by heating sydnones with nitriles or esters of α -unsaturated acids, either pyrazole or pyrazoline derivatives, or mixtures of both, were formed with elimination of carbon dioxide. This reaction has been studied extensively by the Russian workers (95, 97, 98, 110) and by Huisgen (49). The probable mechanism is given in the following scheme (49).



The olefin combines with the 2- and 4-positions of the sydnone ring to form an unstable adduct (LXIII). Separation of carbon dioxide leads to an intermediate

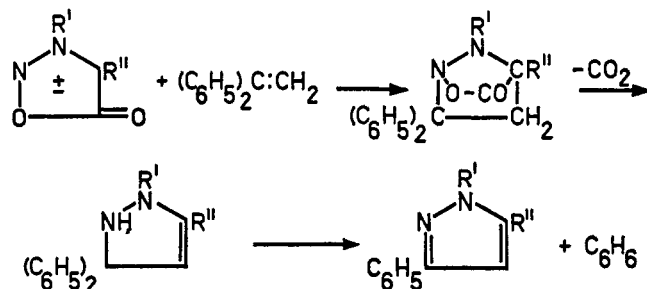
(LXIV) which tautomerizes to a Δ^2 -pyrazoline derivative (LXV). When unsaturated nitriles are used, the initially formed pyrazoline loses hydrogen cyanide to an extent dependent on the reaction conditions, and a pyrazole (LXVI) is also formed. Pyrazoles are obtained directly by heating sydrones with substituted acetylenes in xylene at 120° (50).

The addition of acetylenes proceeds more readily than does the olefin reaction and is facilitated by polar groups adjacent to the triple bond. The following order of decreasing reactivity has been observed (50)

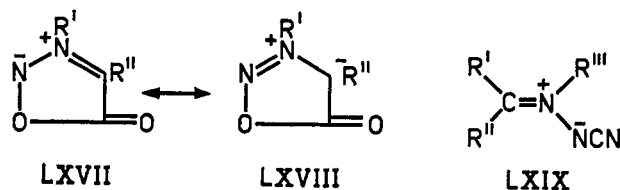


A wide range of pyrazole derivatives have been prepared in this way in yields generally better than 70%.

The reaction of 1,1-diphenylethylene with sydrones also produces a pyrazole directly. In this case benzene is eliminated, evidently from a transitory Δ^4 -pyrazoline intermediate (49).



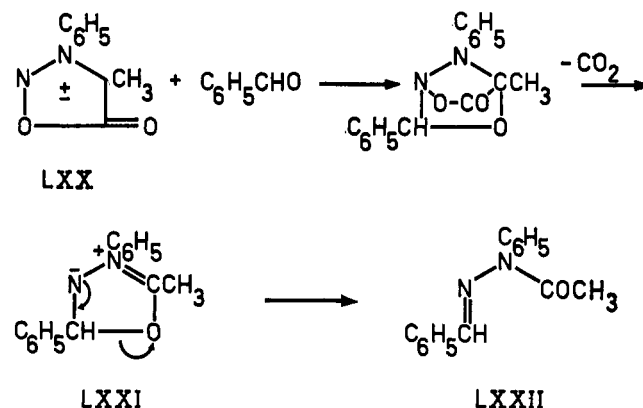
Huisgen (46) has classified the reaction of sydrones with unsaturated compounds as a representative of the extensive group of "1,3-dipolar" additions. On this basis the behavior of sydrones is compared with that of the azomethine imines (LXLX), a recently discovered class of zwitterionic compound which undergo similar addition reactions very readily (47, 48, 51). Of the various canonical forms which contribute to the electronic structure of the sydrone nucleus, there are two, LXVII and LXVIII, which taken together comprise, in effect, a cyclic azomethine-imine system, and the sydrones can be considered as resonance-stabilized



azomethine imines (50). It is possible that these two structures contribute rather more to the actual electronic distribution than has generally been considered (89).

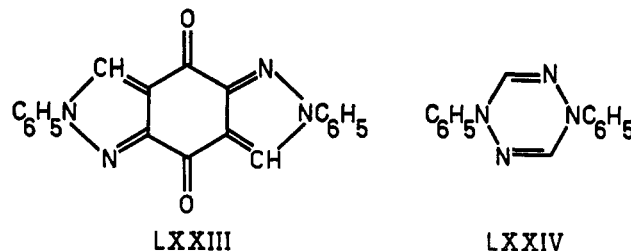
The addition of a carbonyl group to the sydrone ring has also been observed, but a different reaction course is followed. Benzaldehyde and 3-phenyl-4-methyl-

sydnone (LXX) react with formation of benzal (α -acetyl)phenylhydrazine (LXXII) (46). The cyclic



addition-elimination intermediate (LXXI) presumably undergoes the electron shifts shown with subsequent ring opening.

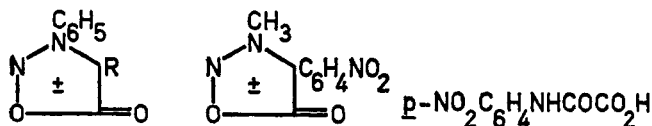
The condensation of 3-phenylsydnone and *p*-benzoquinone to give a compound of probable structure LXXIII (41) and the mutual reaction of two molecules of 3-phenylsydnone in the presence of P_2S_5 with formation of 1,4-dihydro-1,4-diphenyl-1,2,4,5-tetrazine (LXXIV) (7) are related reactions and probably have a similar mechanism.



C. OXIDATION

Hashimoto and Ohta (44) attempted to oxidize the methyl group of 3-phenyl-4-methylsydnone (LXXV) with both potassium permanganate in acetone and hydrogen peroxide in acetic acid, but instead of the expected sydrone carboxylic acid, acetophenone was isolated from the reaction mixture. Similarly 3-phenylsydnone formed a small amount of benzaldehyde with the peroxide reagent, but with permanganate, 3,4-diphenylsydnone (LXXVI) was produced. The latter sydrone was not affected by either reagent. It seems that in these reactions free phenyl radicals are generated by oxidation of the sydrone ring followed by attack at the 4-position of other intact molecules. This topic clearly merits further study.

Oxidation of sydrones with fuming nitric acid may result in complete destruction of the ring. Thus *p*-nitrobenzoic acid was obtained by warming 3-methyl-4-*p*-nitrophenylsydnone (LXXVII) with this reagent (82). On the other hand, 3-phenyl-4-chlorosydnone (LXXVIII) gave *p*-nitrooxanilic acid (LXXIX) (56).



LXXV R=CH₃

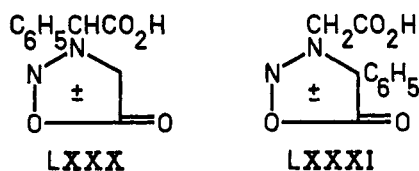
LXXVI R=C₆H₅ LXXVII

LXXVIII R=Cl LXXIX

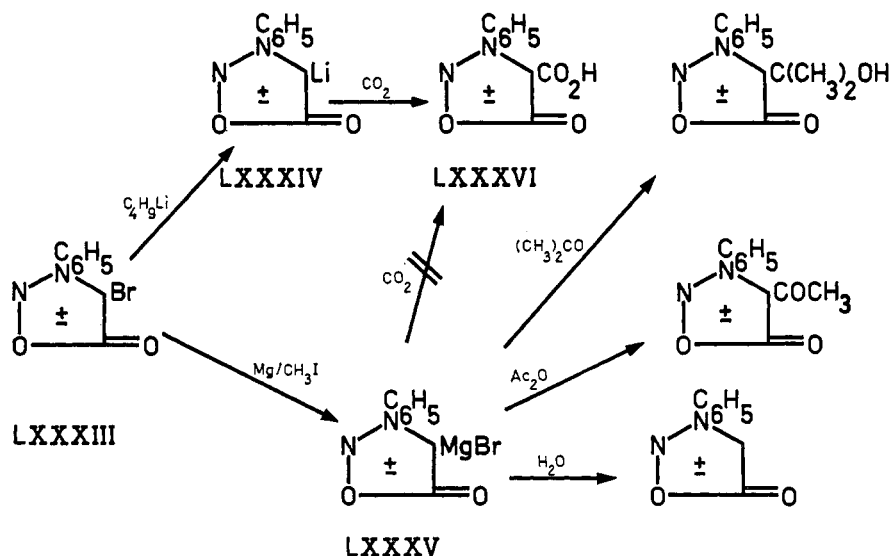
Under the same conditions, 3-phenyl-4-bromosydnone gave unidentified products, while the 4-iodo analog was not oxidized but converted into the 4-nitro derivative. 3-Phenylsydnone was completely degraded with formation of 2,4-dinitrophenol.

D. PYROLYSIS

3- α -Carboxybenzylsydnone (LXXX) is decarboxylated at its melting point (140°) with formation of 3-benzylsydnone (84). Similarly, 3-carboxy-4-phenylsydnone (LXXXI) gives 3-methyl-4-phenylsydnone in low yield.



These results demonstrate the activating effect of

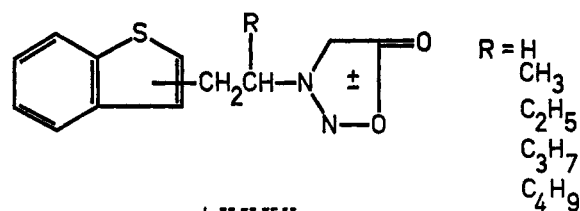


the strongly positive sydnone 3-position on the attached carbon atom.

E. HYDROLYSIS

The behavior of sydnones under both acid and alkaline conditions were among the first reactions of these compounds to be investigated (4). More recently, however, hydrolysis of sydnones by strong acids to give substituted hydrazines has been developed

as a convenient synthesis of otherwise inaccessible monoalkyl hydrazines (21, 34, 38, 108, 113). In this connection, the preparation of β -thianaphthenyl-alkyl hydrazines for use as hypotensive agents from the corresponding sydnones (LXXXII) may be mentioned (37).



LXXXII

Strong acid ion-exchange resins have been used to hydrolyze an ester group in a sydnone alkyl side chain in order to minimize attack on the nucleus (83, 86).

F. REACTIONS OF 4-SUBSTITUTED SYDNONES

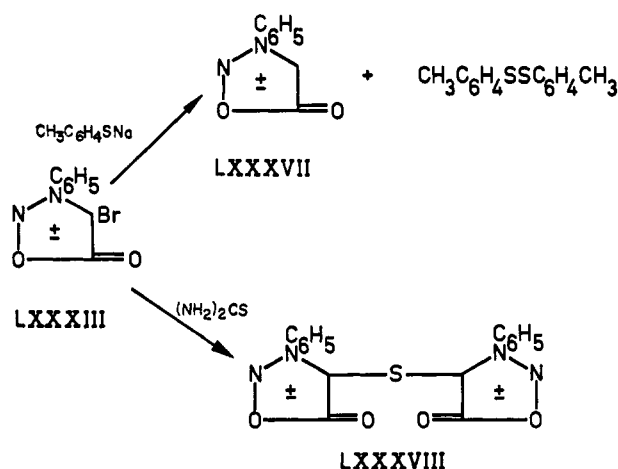
This section is concerned with the reactions of sydnones having a functional group in the 4-position. The most extensively studied of these compounds are the 4-halo sydnones, particularly 3-phenyl-4-bromosydnone (LXXXIII). Much work remains to be done in this field.

In some respects, LXXXIII behaves as a typical aromatic bromo compound. It readily forms organometallic derivatives such as the Grignard compound (LXXXV) and the lithium derivative (LXXXIV).

The reactions of these compounds parallel those of normal organometallic derivatives except that LXXXV fails to react with carbon dioxide (54, 55, 70). The bromine atom in LXXXIII is relatively inert toward silver nitrate, sodium nitrite, sodium phenoxide, and sodium iodide (54).

On the other hand there are some indications that LXXXIII tends to behave on occasion as a positive bromine compound. Reactions in which it acts

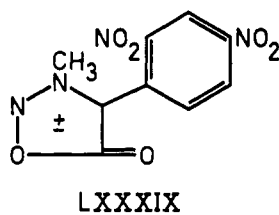
as an oxidizing agent are the following



Treatment of LXXXIII with reducing agents such as sodium *p*-thiocresylate or zinc produces 3-phenylsydnone (LXXXVII), while with thiourea the sulfide (LXXXVIII) is obtained. The bromosydnone also liberates iodine from acidified potassium iodide solution (54, 70).

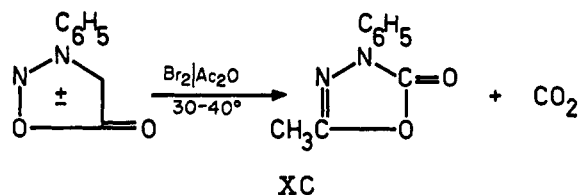
3-Phenylsydnone-4-carboxylic acid (LXXXVI) forms a methyl ester, amide, hydrazide, and azide in the normal way (55). With thionyl chloride it formed a moderately stable acid chloride (63). Attempts to prepare 3-phenyl-4-aminosydnone by the Curtius rearrangement of the azide of LXXXVI were unsuccessful (55), as was reduction of 3-phenyl-4-nitrosydnone (6).

From the limited experimental evidence available, it appears that the presence of electron-donating 4-substituents in the sydnone ring results in instability, while electron-attracting groups have the opposite effect. In this connection it is noteworthy that 3-methyl-4-(2',4'-dinitro)sydnone (LXXXIX) can be recrystallized unchanged from hot concentrated nitric acid (88).

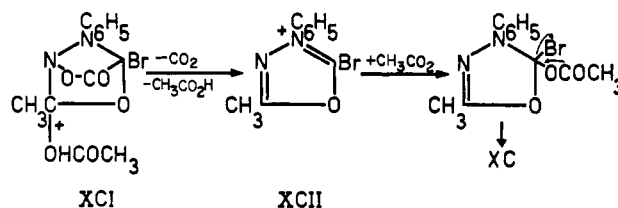


An interesting reaction which almost certainly involves 3-phenyl-4-bromosydnone as an intermediate has been described by Stansfield (79). 3-Phenylsydnone was warmed gently with bromine in acetic anhydride when 2-methyl-4-phenyl-1,3,4-oxadiazol-5-one (XC) was formed with elimination of carbon dioxide.

With propionic and butyric anhydrides, the corresponding ethyl and *n*-propyl derivatives, respectively, were obtained. The reaction is catalyzed by hydrogen



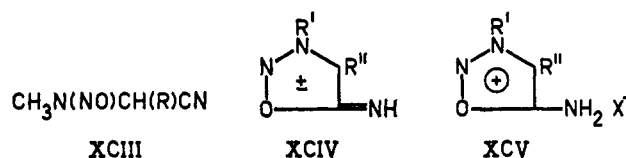
bromide, and in the presence of excess sodium acetate, only 3-phenyl-4-bromosydnone (LXXXIII) was isolated. It is probable that this is essentially an addition-elimination process of the type discussed earlier (section VB), in which a carbonyl group of acetic anhydride and the bromosydnone are involved in a 1,3-dipolar addition according to the following tentative mechanism.



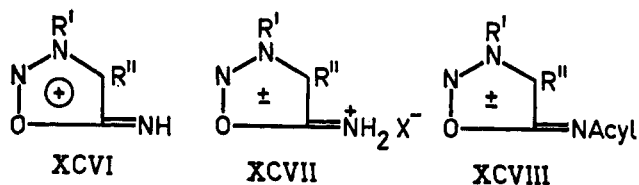
After elimination of carbon dioxide and acetic acid from the adduct (XCI), the resultant immonium intermediate (XCII) could form the observed product (XC) by an exchange step of the type shown. It is also possible that a concerted process occurs in which the exocyclic acetate moiety in XCI is transferred to the 4-position as carbon dioxide leaves.

VI. SYDNONE IMINES

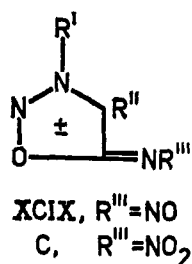
Brookes and Walker (19) found that *N*-methyl-*N*-nitroso- α -aminonitriles (XCIII) reacted with nitric acid to form crystalline derivatives which were shown to be nitrates of sydnone imines (XCIV). Similarly, the sydnone imine hydrochlorides can be prepared by the action of hydrogen chloride on the nitriles (XCIII), and this is the most generally used preparative procedure (22, 57, 94). The sydnone imine ring is also formed in dilute hydrochloric acid (22). Free sydnone imines (XCIV) do not exist, and removal of the acid component from the salts, by an exchange resin for instance, causes opening of the ring (19).



The sydnone imine salts are frequently represented by structure XCV. The cation is seen to be a protonated form of XCVI, which is the analog of Baker and Ollis' mesoionic sydnone structure (III). The uncertainties about the suitability of the latter also apply in the present case, and the alternative noncommittal structure XCVII will be used here (109).



The syndnone imine salts (XCVII) react with acid chlorides or anhydrides under various conditions to form N-acyl derivatives (XCVIII) in which the ring remains intact (23, 24, 57, 82, 94, 102). In this way acetyl, benzoyl, N-phenylcarbamoyl, N-phenylthiocarbamoyl, benzenesulfonyl, and *p*-aminobenzenesulfonyl derivatives of syndnone imines have been prepared. In addition N-nitroso compounds (XCIX) are readily obtained by nitrosation of the salts (57) and N-nitro derivatives (C) by dehydration of syndnone imine nitrates with acetic anhydride (19).



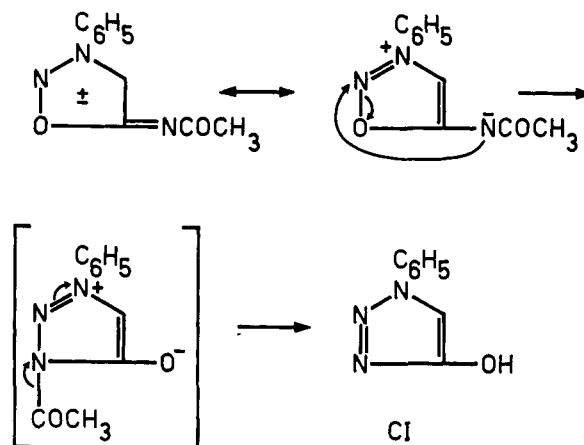
The N-acyl syndnone imines are basic substances (pK_B 10.2–11.5) (23) and form stable salts. They are hydrolyzed by hot aqueous acids to the corresponding syndnone imine salts, with the exception of the carbamoyl derivatives which are stable under these conditions (23).

There are several notable differences between the chemistry of syndnones and syndnone imines. The salts of the latter, unlike syndnones, are stable toward boiling 5 *N* hydrochloric acid (23, 94) but are instantly cleaved by alkalis in the cold with formation of open-chain nitroso amides, $R'N(NO)CH(R'')CONH_2$. With aqueous bicarbonate at 0°, unstable syndnone imine hydrogen carbonates are formed, but these are decomposed on warming (22). Prolonged exposure to hot concentrated hydrochloric acid, on the other hand, causes ring cleavage but apparently without formation of a substituted hydrazine, in marked contrast with the behavior of syndnones. From 3-phenylsyndnone imine hydrochloride, for instance, the only product obtained was some chloroacetic acid. The absence of hydrazine formation in this reaction emphasizes the rather formal nature of the relationship between syndnones and syndnone imines (22).

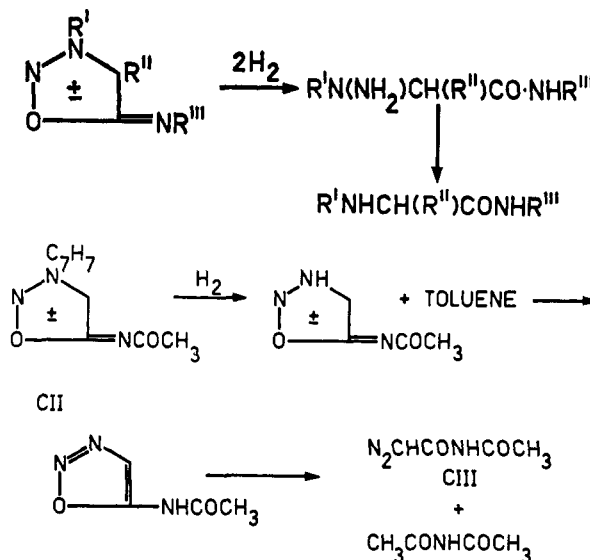
Alkaline hydrolysis of the N-acyl syndnone imines usually results in formation of open-chain amides, as with the syndnone imine salts, but in the case of N-acetyl-3-phenylsyndnone imine an interesting rearrangement also occurred to an appreciable extent with for-

mation of 1-phenyl-4-hydroxy-1,2,3-triazole (CI) (22).

Catalytic hydrogenation of syndnone imine derivatives generally yields aliphatic amides in accordance with the following scheme (22).



With 3-benzyl-N-acetylsyndnone imine (CII), however, the reduction products were toluene and α -diazooacetylacetamide (CIII), accompanied by some N-acetylacetamide formed by further reduction of CIII (25).



Apparently N-debenzylation occurs preferentially in this case with initial formation of a transitory unsubstituted syndnone imine, which presumably was converted into CIII by way of a tautomeric 1,2,3-oxadiazole intermediate and rearrangement of the latter. Similar hydrogenation of 3-benzylsyndnone, unfortunately, gave inconclusive results (25).

The ultraviolet spectra of the syndnone imines closely parallel those of syndnones (section IVC). The alkyl derivatives have a strong absorption maximum at about 290 $m\mu$ (ϵ 8500), which is bathochromically displaced in the aryl compounds (22, 105).

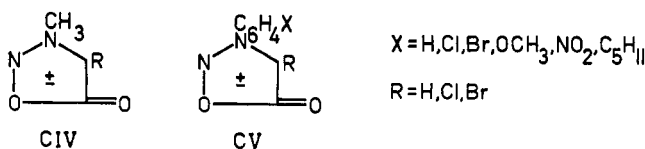
The infrared spectra of the salts (XCVII) exhibit

bands at 1671–1700 and 1588–1606 cm^{-1} (106, 109). Deuteration studies showed that the latter band is due to the exocyclic $=\text{N}^+\text{H}_2$ system, while the other is a $\text{C}=\text{N}$ stretching frequency (109). The spectral results appear to support an azomethine imine type of structure analogous to that suggested for sydnones on the basis of n.m.r. evidence (section IVG).

Polarographic work on sydnone imines has also been reported (65).

VII. BIOLOGICAL ACTIVITY

The fact that sydnones are derived from α -amino acids provides a reasonable basis for the expectation of possible biological activity in suitable derivatives. Initial experiments in this direction, however, were unsuccessful. Brookes and Walker (19) prepared several 3-methyl-4-alkyl sydnones (CIV) as likely antagonists of amino acids. In CIV the group R represents the α -side chain of some of the natural amino acids.



These sydnones, and the corresponding sydnone-imine derivatives, were inactive against various common bacteria. Similarly, 3,3'-pyridylsydnone gave negative results in tuberculosis, antibiotic, cancer, and chemotherapeutic assays (92).

Widely different types of biological activity, however, have been observed with other sydnones and sydnone imines. A series of substituted 3-phenylsydnones (CV) have been tested against the infections of bean and wheat leaf rust, and some exhibited marked activity (26). 3-Phenylsydnone inhibited the development of both infections. The presence of *o*- or *m*-chloro substituents increased the activity, while 3-*p*-chlorophenylsydnone was active against wheat leaf rust but not the bean infection. All other substituents studied, both in the 3-phenyl group and at the 4-position of the sydnone ring, destroyed the wheat leaf activity, but in some of the compounds high bean rust activity was retained. It is noteworthy that the precursors of 3-phenylsydnone, namely *N*-phenylglycine and *N*-nitroso-*N*-phenylglycine, which are potential hydrolysis products under biological conditions, were inactive toward both diseases.

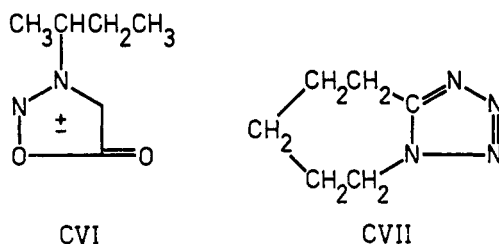
It is possible that the active sydnones function as antagonists of phenylalanine or glycine (26). The fact that compounds not possessing a 3-phenyl group are almost or completely inactive tends to support the former possibility, and the behavior of the phenylalanine analog (CIV, $\text{R} = \text{C}_7\text{H}_7$) in this biological system would be interesting.

A number of sydnones, again mostly substituted 3-phenyl derivatives, have ascaricidal activity and are claimed to be particularly effective against mites resistant to phosphorus-containing insecticides (75–77).

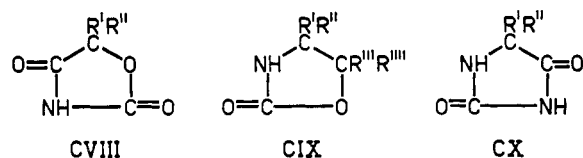
Sydnones appear to offer some promise in the search for anticancer agents. Daeniker and Druey (21) reported that 3,3'-ethylenedisynone possessed slight antitumor activity. Greco, Nyberg, and Cheng (39) screened a series of sydnones and sydnone imine salts and found that 3-*p*-methoxybenzylsydnone had specific activity against a particular mouse carcinoma. These authors also referred to the reported activity of 3-phenylsydnone itself.

In view of the fact that sydnones are dehydration products of *N*-nitroso- α -amino acids, it is interesting that many *N*-nitrosoamines, including *N*-nitrososarcosine ethyl ester, are carcinogenic, possibly owing to the formation of an active diazoalkane *in vivo* (27–29).

Certain sydnones behave as central nervous system stimulants. Thus 3-*sec*-butylsydnone (CVI) has an activity similar to that of pentamethylene tetrazole (Metrazol) (CVII) (62). Of a range of sydnones investigated the 3-*t*-octyl, $\text{CH}_3\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{CH}_3)_2$, deriv-



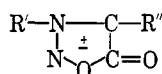
ative was the most active (CD_{50} 0.25 mmole/kg.), whereas 3- β -phenylethylsydnone was inert (61). A loose correlation was demonstrated between the central nervous system activity and the partition coefficient in a chloroform–water system. It is noteworthy that, whereas the sydnones act as stimulants, the structurally analogous heterocyclics, 2,4-oxazolidinediones (CVIII), 2-oxazolidinones (CIX), and hydantoins (CX), are anticonvulsants (62).



Finally, a wide range of sydnone imine salts and *N*-acyl derivatives possess analgesic and antipyretic activity (11–13).

VIII. KNOWN SYDNONES AND SYDNONE IMINES

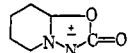
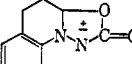
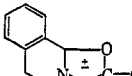
In Tables II–VII the sydnones are classified as alkyl including aralkyl (Table I), aryl (Table II), condensed ring (Table III), and binuclear (Table IV), while the

TABLE III
ARYL SYDNONES

R'	R''	M.p., °C.	Ref.	R'	R''	M.p., °C.	Ref.
3-C ₆ H ₅ N	HgCl	250-260	92	<i>p</i> -CH ₃ C ₆ H ₄	H	144-145	5
3-C ₆ H ₅ N	H	120.3-121.9	91, 92	C ₆ H ₅	CH ₃	98-99	34
		119-121	71			101-102	76
3,4-Cl ₂ C ₆ H ₃	H	145-147	76	CH ₃	C ₆ H ₅	131-132	31
<i>m</i> -BrC ₆ H ₄	H	152-153	31	<i>o</i> -CH ₃ OC ₆ H ₄	H	96.5-97.5	30
<i>p</i> -BrC ₆ H ₄	H	137.5-138.5	31	<i>m</i> -CH ₃ OC ₆ H ₄	H	136.5-137.5	30
C ₆ H ₅	Br	140	5	<i>p</i> -CH ₃ OC ₆ H ₄	H	125-126	30
		136-137	53	C ₆ H ₅	CONHNH ₂	303	55
		141	55	<i>p</i> -CH ₃ OC ₆ H ₄	SO ₃ H ^c	...	111
<i>m</i> -ClC ₆ H ₄	H	144.5-145.5	111	<i>p</i> -CH ₃ CO ₂ C ₆ H ₄	H	143-144	76
<i>p</i> -ClC ₆ H ₄	H	113	5	C ₆ H ₅	CO ₂ CH ₃	142	55
C ₆ H ₅	Cl	128.5	6			142.5-143	107
		127	31	CH ₂ CO ₂ H	C ₆ H ₅	200-201	84
C ₆ H ₅	I	164-165	69	C ₆ H ₅	HgOCOCH ₃	203.5-204.5	111
		154-155	70			201-202	69
C ₆ H ₅	HgCl	194-194.5	69	<i>p</i> -CH ₂ CONHC ₆ H ₄	H	251-253	76
<i>o</i> -NO ₂ C ₆ H ₄	H	147.5	30	<i>o</i> -C ₆ H ₄ C ₆ H ₄	H	69.5	42
<i>m</i> -NO ₂ C ₆ H ₄	H	139-140	30	C ₆ H ₅	C ₆ H ₅	75	42
<i>p</i> -NO ₂ C ₆ H ₄	H	184	5	<i>o</i> -CH ₃ C ₆ H ₄	CH ₃	72	42
		187-188	30	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃	166.5	42
C ₆ H ₅	NO ₂	150	43	<i>o</i> -C ₆ H ₄ OC ₆ H ₄	H	102	30
		142	6	<i>p</i> -C ₆ H ₄ OC ₆ H ₄	H	127-128	111
<i>m</i> -ClC ₆ H ₄	SO ₃ H ^a	...	111	<i>p</i> -C ₆ H ₄ OC ₆ H ₄	SO ₃ H ^d	...	111
C ₆ H ₅	H	134-134.5	34	2-CH ₃ O-5-(C ₂ H ₅ SO ₂)C ₆ H ₄	H	169-171	76
C ₆ H ₅	SO ₃ H ^b	...	111	2,6-(CH ₃) ₂ C ₆ H ₃	CH ₃	120.5-121	42
3-C ₆ H ₅ N	CH ₃	143	71	C ₆ H ₅	(CH ₃) ₂ COH	141-142	70
C ₆ H ₅	NH ₂ NH	134	70	β -C ₁₀ H ₇	H	159	30
C ₆ H ₅	COCl	133-134	63	3-C ₆ H ₅ N	C ₆ H ₅	118-20	71
C ₆ H ₅	CON ₂	102	55	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	114	6
<i>o</i> -(CO ₂ H)C ₆ H ₄	H	205-206	31	<i>p</i> -ClC ₆ H ₄	C ₆ H ₅	124	5
<i>p</i> -(CO ₂ H)C ₆ H ₄	H	248-249	31	C ₆ H ₅	<i>p</i> -ClC ₆ H ₄	129	6
C ₆ H ₅	CO ₂ H	193	55	<i>p</i> -(<i>p</i> '-ClC ₆ H ₄)OC ₆ H ₄	H	135-137	76
CH ₃	2,4-(NO ₂) ₂ C ₆ H ₃	170-171	82	C ₆ H ₅	C ₆ H ₅	184-185	5
C ₆ H ₅	CONH ₂	227	55			183-184	31
CH ₃	<i>p</i> -NO ₂ C ₆ H ₄	158-159	82			186-188	76
<i>o</i> -CH ₃ C ₆ H ₄	H	97-98	76	C ₆ H ₅	C ₆ H ₅ CH(OH)	134	70
		100	42	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	144.5-146	6
		96	44	<i>p</i> -CH ₃ C ₆ H ₄	C ₆ H ₅	151	5
<i>m</i> -CH ₃ C ₆ H ₄	H	79	42	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	156-157.5	6

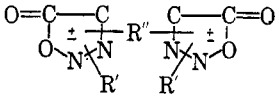
^a As Ba salt, m.p. 93°. ^b As Ba salt dihydrate, m.p. 85°. ^c As Ba salt. ^d As Ba salt tetrahydrate, m.p. 93°.

TABLE IV
CONDENSED RING SYDNONES

Sydnone	M.p., °C.	Ref.
1',2',3',4'-Tetrahydropyridino-1',2'-3,4-	104.5	42
		
3',4'-Dihydroquinolino-1',2'-3,4-	146	64
		
3',4'-Dihydroisoquinolino-2',1'-3,4-	166	64
		

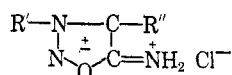
ACKNOWLEDGMENT.—The author is indebted to the Mathilda and Terence Kennedy Trust of the Weizmann Institute of Science, Rehovoth, Israel, for a Research Fellowship, during the tenure of which this review was commenced.

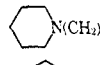
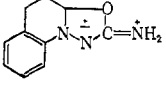

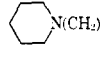
TABLE V
BINUCLEAR SYDNONES

R'	R''	M.p., °C.	Ref.
			
4-H	3,3'-(CH ₂) ₂	169	21
4-Br	3,3'-(CH ₂) ₂	163	21
4-Cl	3,3'-(CH ₂) ₂	120-130 ^a	21
4-H	3,3'-(CH ₂) ₄	170	21
4-CH ₃	3,3'-(CH ₂) ₂	182-183	21
4-H	3,3'-(<i>p</i> -C ₆ H ₄)	>360	104
4-H	3,3'-(CH ₂) ₆	114-115	21
4-Br	3,3'-(CH ₂) ₆	120-122	21
3-(CH ₂) ₂ CN	4,4'-CH ₂	206-207	85
3-(3'-C ₆ H ₄ N)	4,4'-Hg	255-258	92
3-C ₆ H ₅	4,4'-Hg	279-280	69
		274.5-275	111
3-C ₆ H ₅	4,4'-S	164-165	54
		163-164	70
3-C ₆ H ₅ CH ₂	4,4' direct connection	172.5-173.5	84
3-(<i>p</i> -C ₆ H ₄ OC ₆ H ₄)	4,4'-Hg	222.5-223.5	111

^a Explodes.

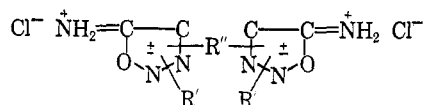
TABLE VI
SYDNONE IMINE HYDROCHLORIDES



R'	R''	M.p., °C.	Ref.	R'	R''	M.p., °C.	Ref.
CH ₃	H	158	39	<i>p</i> -CH ₃ OC ₆ H ₄	H	191-193	13
		155	22				
C ₂ H ₅	H	142-143	39		H	162-163	101
CH ₃	CH ₃	183	22				
<i>n</i> -C ₃ H ₇	H	138-139	39			211-212	13
<i>i</i> -C ₃ H ₇	H	141.5-142	102				
		146-147	39				
		150	22				
<i>n</i> -C ₄ H ₉	H	148	39	C ₆ H ₅ (CH ₂) ₂	H	155-158	22
		145-146	22	C ₆ H ₅ (CH ₂)CH	H	80	11
CH ₃	<i>i</i> -C ₃ H ₇	185	19			70-71	22
(CH ₃) ₂ N(CH ₂) ₂	H	165-166	101	C ₆ H ₅ CH ₂	CH ₃	135	22
CH ₃	<i>i</i> -C ₄ H ₉	165	19	3,4-(CH ₃) ₂ C ₆ H ₃	H	182	22
<i>n</i> -C ₄ H ₉	CH ₃	152.5-153	94			181-182	13
(CH ₃) ₂ N(CH ₂) ₃	H	170-171	101	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃	227-229	13
<i>p</i> -ClC ₆ H ₄	H	192	13			228	22
		190	22				
C ₆ H ₅	H	184	57		H	196	22
<i>p</i> -HOC ₆ H ₄	H	200	22				
cyclo-C ₆ H ₁₁	H	154-155	102		H	156-157	101
		159-160	22				
(C ₂ H ₅) ₂ N(CH ₂) ₂	H	151	101	<i>n</i> -C ₃ H ₁₇	H	159-160	22
<i>p</i> -ClC ₆ H ₄ CH ₂	H	136-137	22	C ₆ H ₅	<i>n</i> -C ₃ H ₇	140	22
2-CH ₃ -5-ClC ₆ H ₃	H	170-172	13	C ₆ H ₅ CH ₂ (CH ₃)CH	CH ₃	163-164	94
3-Cl-2-CH ₃ OC ₆ H ₃	H	170-172	22	<i>n</i> -C ₄ H ₉	C ₆ H ₅	145	22
C ₆ H ₅ CH ₂	H	111.5-112	106	C ₆ H ₅	C ₆ H ₅	205	57
		124-125	11, 22	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -ClC ₆ H ₄	188	22
<i>o</i> -CH ₃ C ₆ H ₄	H	147-148	13, 22			187-188	13
<i>m</i> -CH ₃ C ₆ H ₄	H	189-191	13			122-124	22
		194-196	22			121-123	11
<i>p</i> -CH ₃ C ₆ H ₄	H	194-195	13	C ₆ H ₅ CH ₂	C ₆ H ₅	197-198	13
		191-193	22	<i>p</i> -CH ₃ C ₆ H ₄	C ₆ H ₅	198	22
C ₆ H ₅	CH ₃	214	57	<i>p</i> -CH ₃ C ₆ H ₄	3,4-(CH ₃ O) ₂ C ₆ H ₃ ^a	137	22
<i>o</i> -CH ₃ OC ₆ H ₄	H	155-156	22			135-137	13
		192-193	13				
<i>m</i> -CH ₃ OC ₆ H ₄	H	182-184	22				
		180-182	13				

^a Hemihydrate.

TABLE VII
BINUCLEAR SYDNONE IMINE HYDROCHLORIDES



R'	R''	M.p., °C.	Ref.
4-H	3,3'-(CH ₂) ₂	197-198	22
		189.5-190	112
4-H	3,3'-(CH ₂) ₃	194.5	112
4-H	3,3'-(CH ₂) ₄	183	112
4-CH ₃	3,3'-(CH ₂) ₂	177.5-178 ^a	103
4-H	3,3'-(CH ₂) ₂ O(CH ₂) ₂	174.5-175	112
4-H	3,3'-(CH ₂) ₆	167.5	112
4-H	3,3'-(<i>m</i> -C ₆ H ₄)	145-148	11
4-H	3,3'-(<i>p</i> -C ₆ H ₄)	>300 ^b	104
4-H	3,3'-(CH ₂) ₆	194-195	22
		191-191.5	112
4-H	3,3'-(<i>p</i> -CH ₂ C ₆ H ₄ CH ₂)	150-152	22

^a Picrate. ^b Dihydrate.

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