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Review Article

Medicinal Chemistry of the Mesoionic Compounds

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CONTENTS

THE MESOIONIC COMPOUNDS possess structural features which have been of considerable interest to these laboratories as well as to other medicinal chemists. Their potential value as biologically active substances is found in their planar aromatic character, their relatively small size, the variation in electron density around the ring, and the possibility of selecting different patterns of electron density by selecting different mesoionic systems. Their highly charged, yet net neutral electrical character, and some of their chemical properties are also valuable assets in their potential usefulness as medicinal agents. Some biological studies have already been made or initiated with several mesoionic systems. It is, therefore, the purpose of this review to summarize the properties and the known biological activities of these systems and to discuss the relationships observed between the two.

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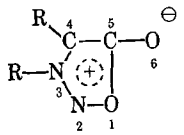
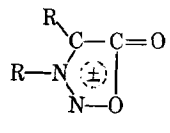
MESOIONIC COMPOUNDS

The term "mesoionic" was first suggested by Simpson (83) to describe a type of molecule which defied covalent representation. Schönberg (82) was the first to have recognized the existence of such compounds in his consideration of the reagent "nitron." The generality of this term became apparent when the structure of the sydnones (I) became known.



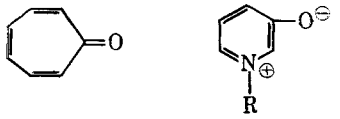
Ia



Ib

The definition of the term, given by Baker and Ollis (7) is as follows. (*a*) A five or six-membered heterocyclic aromatic ring which is not capable of being represented by a covalent structure. (*b*) All atoms of the ring furnish π-electrons to form a delocalized sextet. (*c*) The ring has a partial positive charge which is balanced by a corresponding negative charge on an exocyclic atom or group. (*d*) The ring must be planar or nearly so and must possess considerable resonance energy.

The definition precludes tropone (II) since a covalent representation is possible.



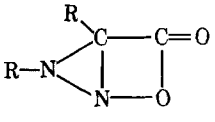
II III

Also the betaines (III) are not so classified since, in these cases, a high degree of charge fixation exists and the compound may be satisfactorily represented by the dipolar structure. Conventionally, mesoionic systems are depicted as in I*a* or I*b*. The atoms thus far encountered in rings have been carbon, oxygen, nitrogen, and sulfur. Bieber (12) has calculated that this combination of atoms could give possibly 288 five-membered mesoionic ring systems. The number of 5-membered rings actually synthesized to date is less than 20.

In this review, the authors will consider only those mesoionic ring systems for which any biological studies have been reported. The chemistry of mesoionic compounds has been reviewed by Baker and Ollis (7) and more recently by Ohta and Kato (75) in Japanese. Our objective is to discuss only the chemical and physical properties which may relate to, or may shed some light on, reported biological activity.

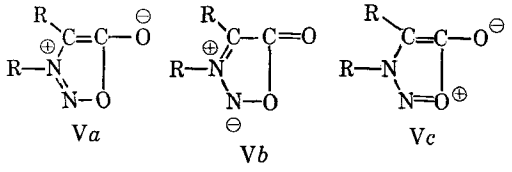
SYDNONES

Chemistry.—The first sydnone was prepared in 1935 by Earl and Mackney (33), who suggested structure IV for the product. Baker and Ollis

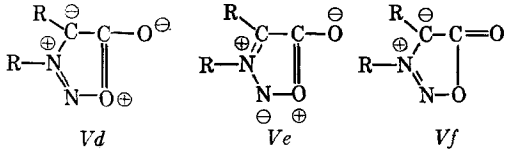


IV

(3) regarded this structure as unacceptable and proposed that the sydnones were resonance hybrids of numerous dipolar and tetrapolar forms (V).



Va *Vb* *Vc*



Vd *Ve* *Vf*

The proper evaluation of the contribution of the resonance forms to the structure is extremely difficult, pointing out an inherent defect in classical resonance or valence bond theory. The possibility that molecular orbital theory might be more illuminating as far as the sydnone electronic structure led Hill, Sutton, and Longuet-Higgins (50), Orgel, Cottrell, Dick, and Sutton (76), and later Bochvar and Bagaturyants (14) and Paoloni and Givmanini (99) to perform simple Hückel molecular orbital (MO) calculations. More recently, Kier and Roche (67) have performed MO calculations on the sydnones using the improved Hückel procedure known as the ω-technique, which takes into consideration some electron correlation. The parameters used were derived from ionization potentials and modified to give self-consistent values which would reproduce meaningful charge densities and relative energies (63, 64). From these values, the dipole moments of 3-phenyl- and 3-methylsydnone were calculated quite closely, and the ultraviolet absorption maxima were correlated with suitable MO calculated energies (67). The structures calculated are shown in Figs. 1 and 2.

Several observations can be made from these ground state structures.

(*a*) The exocyclic oxygen atom bears a high negative charge density. In comparison with the comparable oxygen atom of butyrolactone, the sydnone oxygen atom has a charge density higher by 0.15 of an electron. This indicates a more polarized carbonyl group, but the bond

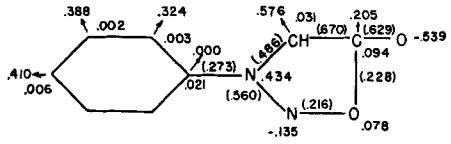


Fig. 1.—Molecular orbital calculated properties of 3-phenylsydnone from *Reference 67*. (The numbers in parentheses are bond orders, the numbers at the arrowheads are free valencies, and the other numbers are charge densities.)

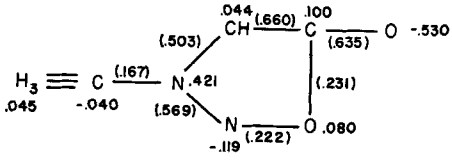


Fig. 2.—Molecular orbital calculated properties of 3-methylsydnone from *Reference 67*. (The numbers in parentheses are bond orders, and the remaining numbers are charge densities.)

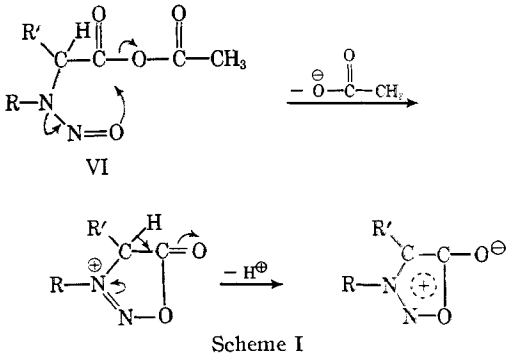
order suggests more double bond character than single bond character. This is consistent with X-ray diffraction bond length measurements by Bärnighausen, Jellinck, and Vos (8, 9), who found the C—O bond length to be 1.20 Å., close to a normal carbonyl bond length.

(*b*) The No. 3 nitrogen atom bears a high positive charge. The highest ring bond order is between the two ring carbon atoms while low bond orders exist between the ring O—N bond and the ring O—C bond. This suggests a significant contribution of canonical form V*a* to the structure of the sydnone, in a valence bond consideration.

(*c*) The sydnone ring is an electron-withdrawing substituent on the phenyl ring in 3-phenylsydnone, deactivating it at all positions. Inasmuch as ground state properties mirror excited state reactivities, this indicates that electrophilic substitution would be retarded on the benzene ring. This is borne out by experiment. Substitution reactions on 3-phenylsydnone invariably favor the 4-position of the sydnone ring (7).

The sydnones are derivatives of the 1,2,3-oxadiazole ring system, hence were named by Baker, Ollis, and Poole (4) as Ψ-5-keto-3-methyl-3,5-dihydro-1-oxa-2,3-diazole, using 3-methylsydnone as an example. The symbol Ψ reflects the uncertain electron distribution—hence, the inability to write formal covalent or single polar structures. As an alternative, Katritsky (59) has proposed a name based on a theoretical betaine representation; hence 3-methylsydnone becomes anhydro-5-hydroxy-3-phenyl-1-oxa-2,3-diazolinium hydroxide. In the opinion of the authors, the former name is superior since it does not attempt to invoke the use of a single canonical or polar form but is adaptable to a new electronic pattern in a heterocycle, one of uncertain electron distribution. Even within variously substituted sydnones, the electronic distribution would be quite variable depending on the substituents in the 3 and/or 4-position. *Chemical Abstracts* employs the use of the trivial name "sydnones" for these compounds, a name taken from the University of Sydney, where they were first made (33).

The original method of synthesis, described by Earl and Mackney (33), has not been significantly improved upon. It involves the treatment of an *N*-nitroso-α-amino acid with an anhydride such as acetic anhydride or trifluoroacetic anhydride (5). The latter reagent results in a completed reaction in seconds, while with acetic anhydride, standing for days may be necessary. Thionyl chloride (5) and phosgene (45) have also been used to close the ring. The possible substituents are alkyl or aryl but not hydrogen on the 3-position, and aryl, alkyl, or hydrogen on the 4-position. Baker, Ollis, and Poole proposed a mechanism for the formation, involving an intermediate mixed anhydride (VI) which they independently synthesized (5). (Scheme I.)



VI

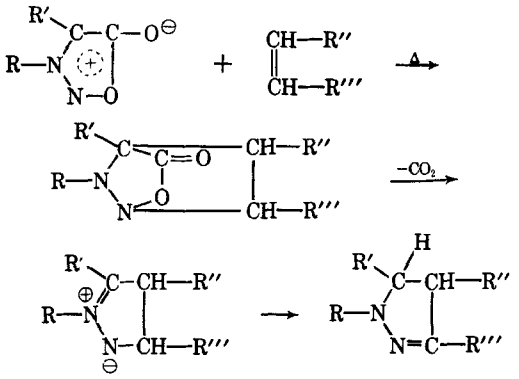
Scheme I

The chemistry of the sydnone ring has been studied extensively and reviewed recently by Nöel (72), Stewart (87), and Ohta and Kato (75). It is the authors' intention to discuss briefly only those reactions having any possible biological significance.

An argument for the aromatic character of the sydnone ring is its stability and ability to undergo electrophilic substitution at the No. 4 carbon atom (7). Examples include halogenation (11) with chloride (5), bromine (4, 58), and iodine (71), mercuration (71), deuteration (95), nitration (45), acylation (98), formylation (90), and sulfonation (94). The 4-bromo derivative has been used as an intermediate to 3-phenyl-4-carboxysydnones (58) and 3-alkyl-4-carboxysydnones (62). Attempts to put electron-donating groups in the 4-position have been unsuccessful to date (58, 96).

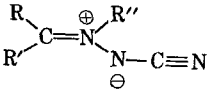
Baker, Ollis, and Poole (5) observed the unreactivity of the phenyl ring of 3-phenylsydnone to electrophilic substitution. This is predicted by the MO calculations of Kier and Roche (67) discussed earlier. On the other hand, it has been observed that a phenyl group in the 4-position of the sydnone is disposed to electrophilic attack, such as nitration (84).

An interesting reaction of the sydnones is their ability to add alkenes, alkynes, and nitriles to give pyrazole or pyrazoline derivatives with elimination of CO_2 (92, 54). Huisgen proposed Scheme II as the mechanism for the reaction (54). Huisgen (55) has compared this reaction of the



Scheme II

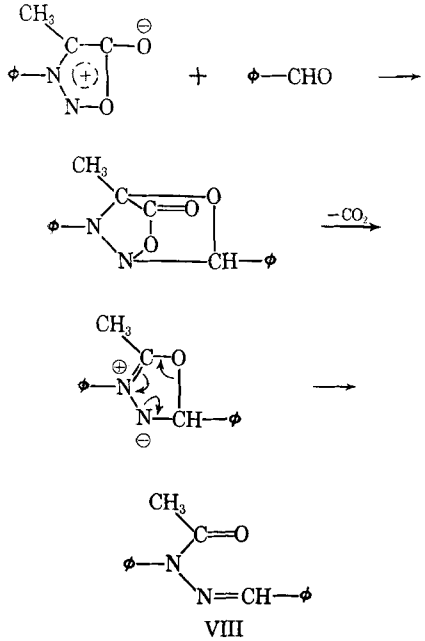
sydnones with the behavior of the azomethine imines (VII) which undergo similar addition reactions quite readily.



VII

The proposal has been made that resonance contributions (*Vb* and *Vf*) are more prominent in the ultimate structure of the sydnone than had been previously supposed (85). Addition 1,3 of a carbonyl group has also been observed (55), but a different sequence is followed to give an α-acyl hydrazine azomethine (VIII). (Scheme III.)

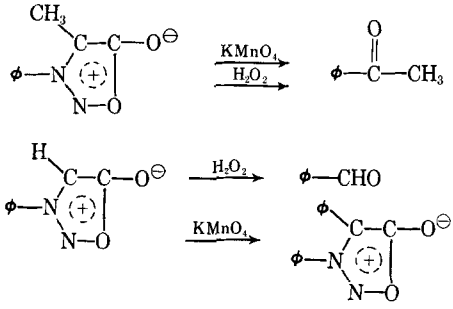
An extremely interesting reaction with an



VIII

Scheme III

as yet unresolved mechanism is the oxidation of sydnones. Hashimoto and Ohta (46) observed the products shown in Scheme IV.



Scheme IV

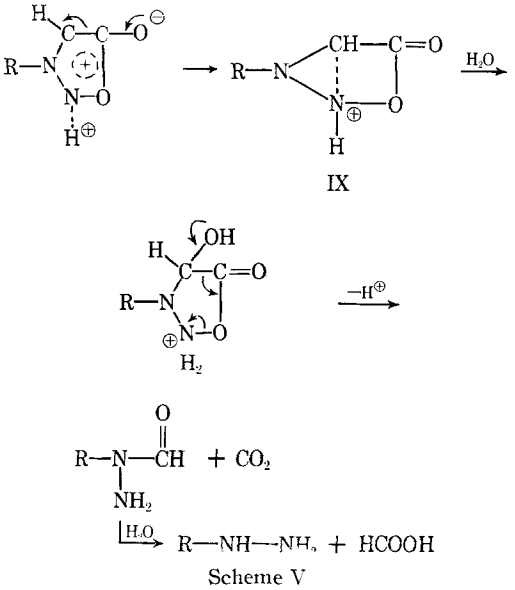
They suggested the formation of a phenyl radical from decomposition of the ring, followed by attack of the radical on an intact sydnone ring at position 4 to produce the products shown. Molecular orbital calculations show the value for the free valence at position 4 to be quite favorable for such a radical attack. (See Fig. 1.)

Acid hydrolysis of sydnones yield a substituted hydrazine, a carboxylic acid, and CO_2 (32, 33). Garrett (40) has studied the kinetics of this hydrolysis and found the order of decreasing rate in a series of 3-alkyl sydnones to be *tert*-butyl > isopropyl > methyl. He proposed, on the basis of his calculated entropies of activation, that the observed order was due to a decreasing negative charge on the ring due to a decreasing alkyl inductive effect. However, recent molecular orbital calculations (68) indicate that the alkyl groups cause insignificant perturbations in the electron distribution in the ring, an observation borne out by the fact that all of the 3-alkyl sydnones absorb at essentially the same wavelength (44, 60).

Garrett proposed a mechanism of acid hydrolysis (40) based on initial protonation of the nitrogen at position 2. This position was also predicted as the most energetically favorable position for protonation from molecular orbital calculations of protonation energies (68). The proposed mechanism of Garrett's further included the formation of an "incipient 2,4 bond or a quasidiazomethane" (IX). (Scheme V.)

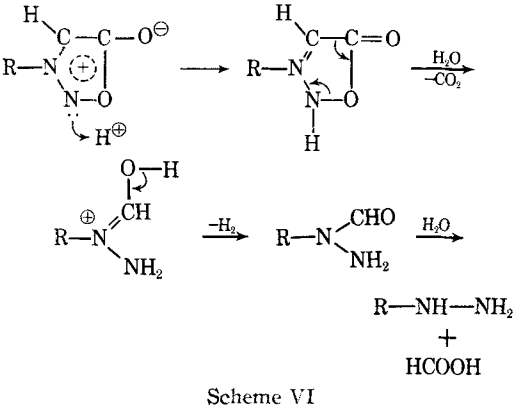
An alternate mechanism proposed by Garrett (40) involved the unlikely addition of H_2O across the 2,4 atoms, involving attack of $OH^{\ominus}$ at the N_2 position.

These two proposals seem unlikely on the basis of steric and electronic considerations. The quasidiazomethane ring structure was eliminated early in the sydnone studies (3). The attack by $OH^{\ominus}$ on the No. 2 nitrogen is predicted to



Scheme V

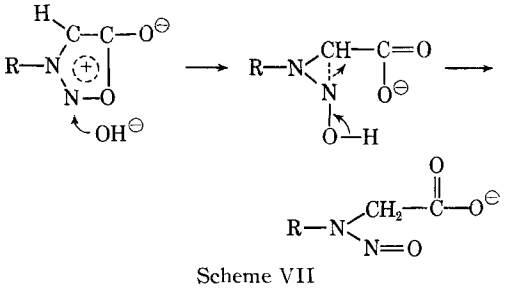
be, energetically, the least likely point of attack based on molecular orbital calculations of anion localization energies (68). A likely mechanism of acid hydrolysis would be Scheme VI (68), which is an expansion of the mechanism proposed by Baker and Ollis (7).



Scheme VI

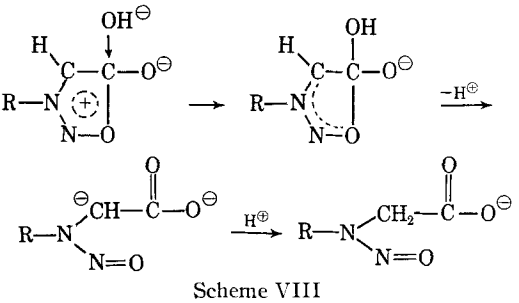
Acid hydrolysis of sydnone derivatives has become a general method for the synthesis of monoalkyl hydrazines that are difficult to obtain from more direct means (96).

Base-catalyzed hydrolysis of sydnones has been reported to regenerate the starting *N*-nitrosoaminoacid salt (32). Garrett (40) studied the kinetics of this reaction, and found the decreasing order of the rate of hydrolysis of 3-alkyl sydnones to be methyl > propyl > isopropyl > *tert*-butyl. The proposed mechanism of this hydrolysis (40) involved initial attack by OH⊖ on the No. 2 nitrogen, followed again by the formation of the intermediate "incipient 2,4 bond or quasidiazomethane." (Scheme VII.)



Scheme VII

This mechanism appears quite unlikely from the standpoint of valence bond reasoning. Furthermore, anion localization energies from molecular orbital calculations argue against this point of attack by OH⊖ (68). Energetically, the carbonyl carbon is the preferred point of attack by a reagent with a pair of electrons. Localization energies of the 3-alkyl sydnones predict the experimental order of hydrolytic rates and suggest the mechanism shown in Scheme VIII (68).

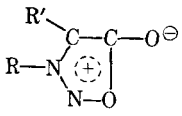


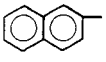
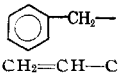
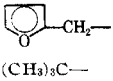
Scheme VIII

Physical Properties.—The assignments of carbonyl and carbon-hydrogen stretching frequencies in the infrared spectra of numerous sydnones have been made. A number of representative compounds are listed in Table I. The ν CO assignment of 1720–1770 cm.$^{-1}$ is consistent with the γ-lactone CO absorption at 1740 cm.$^{-1}$. The C—H absorption at 3190–3140 cm.$^{-1}$ is quite characteristic for this bond and has been used to detect the absence of a 4-substituent in sydnones (86).

The presence of an intense absorption band in the ultraviolet spectra of sydnones at 290–340 mμ ($\epsilon \sim$ 6000–8000) has been used as evidence of the aromatic character of the ring (7). Conjugation of the ring results in displacement to lower energy, *i.e.*, higher wavelength. Thus, 3-phenylsydnone absorbs at 310 mμ (44), 3-methyl-4-phenylsydnone at 317 mμ (86), and 3,4-diphenylsydnone at 340 mμ (35). (See Table II.) Kier and Roche (67) have calculated

TABLE I.—INFRARED ABSORPTION OF REPRESENTATIVE SYDNONES



R	R′	νCO (cm.⁻¹)	νCH (cm.⁻¹)	Ref.
$CH_3CH_2CH_2CH_2$—	H	1768	3185	(39)
—CH_2—CH_2— (bis)	H	1735	3190	(24)
	H	1766		(36)
	Br	1756		(39)
	H	1752		(36)
	H	1768	3140	(39)
CH_2=CH—CH_2—	H	1740		(60)
$(CH_3)_3C$—	H	1725		(60)
	H	1710		(60)
$(CH_3)_3C$—	CH_3	1735		(31)
CH_3CH_2—CH_2—	CH_3	1725		(31)
CH_3CH_2—CH(—CH_3)—	COOH	1690		(30)
	H		3150	(70)

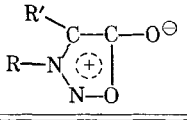
the energy levels by MO methods for 10 substituted sydnones with $\lambda_{max.}$ values ranging from 290 to 340 mμ. They have shown a correlation between the frequency maxima of the longest wavelength high intensity absorption and the energy difference between the highest filled and lowest empty MO's, characteristic of a $\pi \rightarrow \pi^*$ electronic transition.

The dipole moments of the sydnones are quite large compared to most organic compounds. Hill and Sutton (51, 52) and Earl, Leake, and LeFevre (34) studied a large number of sydnone moments and interpreted them. The moment is directed toward the exocyclic oxygen atom, and support was derived from these studies in the formulation of these compounds as mesoionic. An attempt to reproduce the dipole moment by calculation from MO charge densities led Orgel, Cottrell, Dick, and Sutton (76) to a total moment that was high by a factor of 1.6. Coulson (23) scaled the charge densities calculated by Hill, Sutton, and Longuet-Higgins (50) for phenylsydnone to conform to the experimental dipole moment. Calculations by Kier and Roche (67), using MO procedures and parameters previously described (63, 64), produced charge densities from which dipole moments for 3-methyl- and 3-phenylsydnone were calculated. These values corresponded quite closely to experimental values. (See Table III.)

Two studies on the proton magnetic resonance spectra of sydnones have appeared in the literature. Stewart and Danieli (85) observed an unexpectedly high field for the ring proton of several sydnone derivatives. They concluded that this occurrence was difficult to reconcile with the mesoionic formulation since the positive charge associated with the ring nitrogen adjacent to this position should markedly deshield this proton. A partially delocalized azomethineimine system was proposed in which some negative charge could be generated at the sydnone 4 carbon to contribute some diamagnetic shielding to the attached proton.

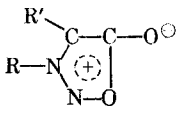
Lawson, Brey, and Kier (69) found essentially the same chemical shift for the sydnone ring proton. However, they concluded that this is a downfield shift from the normal resonances for olefinic hydrogens due either to the anisotropic effect of the aromatic sydnone ring, or to

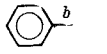
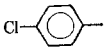
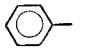
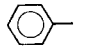
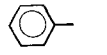
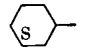
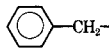
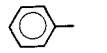
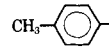
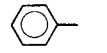
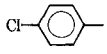
TABLE II.—ULTRAVIOLET ABSORPTION MAXIMA OF REPRESENTATIVE SYDNONES



R	R′	$\lambda_{max.}$ (EtOH)	ε	Ref.
CH_3	H	290	6600	(44)
$CH_3(CH_2)_3$—	H	289.5	6450	(44)
	H	310	5650	(44)
	H	312.5	4450	(44)
	H	310	4700	(44)
	H	300	6500	(44)
	CH_3CH_2—	307	6200	(44)
CH_3—		317	7700	(86)
$(CH_3)_3C$—	H	290	5900	(60)
$CH_3(CH_2)_3$—	CH_3—	295	6440	(31)
	H	315		(35)
		340		(35)
	CH_3—C(=O)—	324	6340	(43)

TABLE III.—DIPOLE MOMENTS OF REPRESENTATIVE SYDNONES



R	R′	Exptl. (μ Benzene, 25°)	Ref.
CH_3[a]	H	7.31 D	(67)
 [b]	H	6.48	(51)
CH_3	H	6.89	(51)
	H	5.01	(51)
	Cl	6.49	(51)
	Br	6.42	(51)
	CH_3	6.57	(51)
	H	6.7	(51)
	H	7.27	(51)
		6.55	(52)
		7.15	(52)
	NO_2	6.18	(52)
		4.61	(52)

[a] Calculated from MO charge densities (67), 7.06 D. [b] Calculated from MO charge densities (67), 6.47 D.

the electron withdrawing effect of the positive nitrogen. The resonance location of the ring proton is not sufficient evidence to support or discard theories concerning the aromaticity of the sydnone ring. (Table IV.)

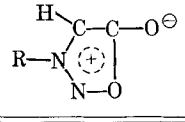
A further look at the chemical shifts of the hydrogens attached to the carbon α to the sydnone ring in 3-alkyl sydnones uncovered some interesting evidence dealing with the electronic structure of the sydnone ring (69). These protons show downfield shifts of about 1.8-2.1 τ units from their normal resonance positions in alkyl benzene derivatives and alkyl amines. The downfield shifts from their normal aliphatic positions are about 3.2 τ units. The strong deshielding of these protons has been interpreted (69) as being due to the combined effects of the ring current in the sydnone ring and the electronegativity of the positively charged 3 nitrogen of the sydnone nucleus which bears these substituents.

Another interesting phenomenon discovered by Lawson, Brey, and Kier (69) is the concentration dependency of the chemical shift of the sydnone ring proton in $CDCl_3$ solution. As the concentration of sydnone decreases in these solutions, the sydnone proton resonance shifts upfield. This has been attributed by these authors (69) to aggregation of the sydnone in concentrated solutions. The intermolecular interaction of sydnone rings will withdraw electron density and cause the proton to appear at comparably low field. As the concentration of solvent ($CDCl_3$) increases relative to that of the sydnone, hydrogen bonds could be formed presumably with the exocyclic oxygen atom, and thus bring about the break-up of the aggregates. The interaction of the sydnone with solvent would result in less electron withdrawal than sydnone–sydnone interaction; therefore, the ring hydrogen shifts upfield. This mechanism is supported by the fact that the solvent peak for sydnone concentrations of from 0–50% in $CHCl_3$ shifts from 2.74 to 2.25 τ. The indication here is that the solvent is forming hydrogen bonds with the solute.

There is also evidence that sydnone derivatives with larger side chains have their aggregates disrupted more easily than those derivatives with smaller side chains. This concentration effect is not nearly so pronounced in acetone solution due to the fact that the solvent cannot form the hydrogen bond necessary to cause the destruction of the sydnone aggregates.

The complexing ability of sydnones was first observed by Yamada and Kazima (93), who observed a carbonyl infrared absorption shift with iodine which was found to form a 1:1 complex with the sydnone, and the conclusion was drawn

TABLE IV.—PROTON MAGNETIC RESONANCE OF SYDNONES

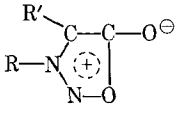


R	τ Sydnone	τ Alkyl αH	τ Alkyl αH on R-Benzene	τ Alkyl αH on R-NH_2	Ref.
CH_3—	3.62	5.90	7.70	7.80	(69)
CH_3—CH_2—	3.64	5.66	7.38	7.50	(69)
$(CH_3)_2CH$—	3.68	5.29		7.13	(69)
$(CH_3)_3C$—	3.72				(69)
	3.24	2.12		3.40	(69)
	3.22	2.30			(85)
	3.81	4.64			(85)
CH_3—(4-ϕ)		5.87			(85)

that the carbonyl oxygen was involved in the complex. Lawson, Brey, and Kier (69) observed a tendency to aggregate in solution with a series of 3-alkyl sydnones as was described in the NMR discussion. Gentile and Mao (41) studied metal halide complexes with a large number of sydnones and found complexation with strong Lewis acids such as $TiCl_4$, $SbCl_5$, $SnCl_4$, $FeCl_3$, $ZnCl_2$, and $TeCl_2$. They found that bonding occurred with the exocyclic oxygen in a 1:1 ratio in the solid state. These complexes dissociated completely in solution.

Biological Activity.—The earliest reported consideration of sydnones as biologically important agents was made by Brookes and Walker (17) in 1957 when they prepared several 3-methyl-4-alkyl sydnones as potential amino acid antagonists. Their compounds were tested against several microorganisms, including *Streptococcus haemolyticus*, *Staphylococcus aureus*, *B. coli*, *L. mesenteroides*, and filarial infections. No activity was observed. Davis, Becker, and Rogers (29) pursued the concept of the sydnones being analogs of amino acids. They tested a number of 3-substituted sydnones, mostly 3-aryl, against two fungal infections of plants. (See Table V.) The observed disease reduction appears not to be a function of where the phenyl ring substituent is, but rather what it is, in the case of controlling wheat rust. Specifically, the presence of chlorine at any position usually imparts activity to some extent. The same generalization can be made for the control of bean rust with the addition that 3-phenyl-4-substituted sydnones with no substituent on the phenyl ring also showed activity. Interestingly, the sydnones studied did not inhibit the fungal growth *in vitro*. This suggests that the sydnones perhaps function by increasing resistance to disease by a mechanism which renders the host tissue unfavorable to disease development. This is the role that the sydnones as possible amino acid antagonists might play (29).

Table V.—Activity of Sydnones Against Wheat and Bean Rust at 500 p.p.m. 3 Days After Inoculation[a]

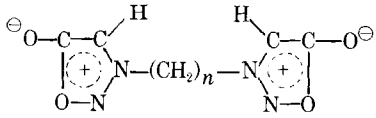


R	R′	Disease Reduction[b] Wheat Rust	Disease Reduction[b] Bean Rust
Phenyl	H	++	++++
o-Chlorophenyl	H	++++	+++
m-Chlorophenyl	H	+++	+++
p-Chlorophenyl	H	+++	—
2,4-Dichlorophenyl	H	+++	+++
3,4-Dichlorophenyl	H	+	—
p-Bromophenyl	H	—	+
p-Nitrophenyl	H	—	—
p-Tolyl	H	—	+
p-Methoxyphenyl	H	—	—
o-Ethylphenyl	H	—	++++
Phenyl	Methyl	—	+++
Phenyl	Nitro	—	
Phenyl	Chloro	+	++++
Phenyl	Bromo	—	++++
p-Chlorophenyl	Chloro	—	—
Methyl	H	—	+
Benzyl	H	—	—
Cyclohexyl	H	—	+

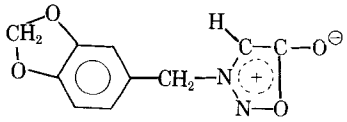
[a] Results taken from *Reference 29*. [b] ++++, 76–100% reduction, few lesions; +++, 76–100%, many lesions; ++, 51–75% reduction; +, 10–50% reduction.

Pütter and Wolfrom (78), in a series of patents, claimed ascaridal activity for a number of substituted 3-phenylsydnones. The claim was made that the compounds were particularly effective against mites resistant to phosphorus-containing insecticides. Tien and Hunsberger (90) synthesized *N*-(3-pyridyl)sydnone and subjected the compound to a general screen against tuberculosis, several bacteria, cancer, and other chemotherapy assays. The results reported were all negative.

A number of sydnones have been examined in the search for anticancer agents. Daeniker and Druey (24) synthesized a number of polymethylene-bis-sydnones, and reported some antitumor activity for the ethylene homolog.



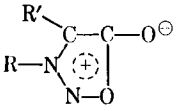
In a more recent antitumor study of sydnones and sydnonimines, Greco, Nyberg, and Cheng (42) reported activity against carcinoma 755 in mice with 3-(*p*-methoxybenzyl)sydnone. The same compound was inactive against sarcoma 180 and leukemia 1210 systems. An analog of this compound, 3-piperonylsydnone (X), was reported by Nyberg and Cheng (73) to be an active agent in preliminary antimalarial evaluation. At a dose of 10 mg./Kg. it was found to



X

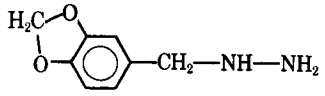
be active against *Plasmodium berghei* in mice. It was active either orally or subcutaneously and was found to be nontoxic at a dose of 500 mg./Kg. The acid and base hydrolysis products, piperonylhydrazine (XI) and *N*-nitroso-*N*-piperonylglycine (XII), respectively, were also tested and found to be inactive, suggesting that the intact ring is the active substance.

TABLE VI.—ALKYLSYDNONE PHYSICAL AND PHARMACOLOGICAL DATA[a]

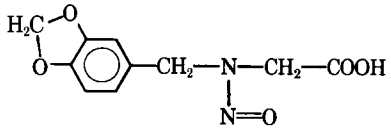


R	R′	$P_c\left(\frac{AMOH}{H_2O}\right)$	CD_{50}, mmole/Kg.	LD_{50}, mmole/Kg.
$(CH_3)_2CH$—	H	2.3	2.96	3.75
$CH_3(CH_2)_2$—	H	2.5	1.60	1.87
$(CH_3)_3C$—	H	4.9	0.87	1.30
$CH_3CH_2CH(CH_3)$—	H	6.4	1.13	1.55
$CH_3C(CH_3)_2CH_2C(CH_3)_2$—	H	8.0	0.25	0.31
	CH_3—	1.85	0.24	
CH_3CH_2—	CH_3—	2.05		
$CH_3(CH_2)_2$—	CH_3—	2.8	0.34	
$CH_3(CH_2)_3$—	CH_3—	2.9	0.13	
$CH_3(CH_2)_3$—	CH_3CH_2—	4.1	0.19	
$(CH_3)_3C$—	CH_3	6.7	0.71	

[a] Taken from *References 60* and *31*.



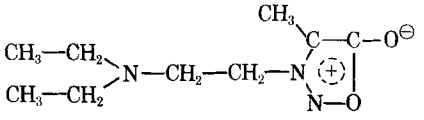
XI



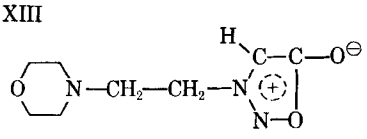
XII

A number of 3-alkyl sydnones were found by Kier and co-workers (61) to be potent central nervous stimulants. The 3-*sec*-butylsydnone was found to be a powerful respiratory stimulant in a heavily barbitalized dog. The stimulation appeared to be predominantly central, as there was little decrease of activity after vagotomy or denervation of the carotid sinus. The respiratory activity was superior to that produced by the same dose of pentylenetetrazol.[1] Kier and Dhawan (31, 60) studied the relationship between the partition coefficients of several mono and dialkyl substituted sydnones. It was observed that there was a correlation between partitioning into an oil phase and convulsive potency in the case of the 3-alkyl sydnones. (See Table VI.) In the case of the 3,4-dialkyl sydnones, the convulsive potency was found to be greater and independent of the partition coefficient. It is possible that in the case of the 3-alkyl sydnones, the absolute lipid solubility is sufficiently low so that the partition coefficient becomes a limiting factor concerning the amount of drug reaching the CNS. With the disubstituted sydnones, the absolute lipid solubility may be appreciably high so that in spite of a less favorable partition coefficient in some compounds, there is a sufficient concentration in the biolipid phase to permit an active level of sydnone to reach the site of action. Another explanation is that the intrinsic activity of the 3,4-dialkyl sydnones is significantly higher than that of the 3-alkyl sydnones, so that a less favorable partition coefficient would not mitigate against a high level of activity (31). The basic hydrolysis products of these sydnones did not elicit the same activity. Bruzzese and co-workers (18) synthesized a number of 3-aminoalkyl sydnones and noted essentially the same CNS stimulation previously observed (60), although a few were mild depressants. They also observed an analgesic action in most cases, particularly with the 3-diethylaminoethyl-4-methylsydnone (XIII) and 3-morpholinylethylsydnone (XIV). They also noted a hypoglycemic activity for several compounds. Bruzzese and his co-workers (19) hydrolyzed the 3-aminoalkyl sydnones to the corresponding hydrazines and subjected these products to the same tests. They found a dif-

[1] Marketed as Metrazole by Knoll Pharmaceutical Co., Orange, N. J.



XIII

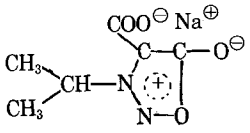


XIV

ferent pattern of activities from the sydnone precursors in most cases.

It is noteworthy that products of acid or base hydrolysis of sydnones failed to give the biological activities seen for the intact sydnone, suggesting that it is the ring itself, rather than an *in vivo* degradation product, which is the active species. This would tend to minimize the early suggestion of an amino acid antagonist (17, 29).

Fregly, Kier, and Dhawan (38) studied the diuretic and hypotensive properties of 3-*sec*-butylsydnone, 3-butyl-4-ethylsydnone, and 3-*iso*-propyl-4-sodium carboxylate sydnone (62) (XV). With comparable doses, 3-butyl-4-ethylsydnone was the most active with respect to urinary sodium output. (See Fig. 3.)



XV

The 3-*sec*-butylsydnone reduced rat blood pressure 5 to 10% over a 10 to 20 mg./Kg. dose range. The sydnone acid was inactive against blood pressure while the dialkyl sydnone was convulsive at low enough doses so that blood pressure measurements were interfered with.

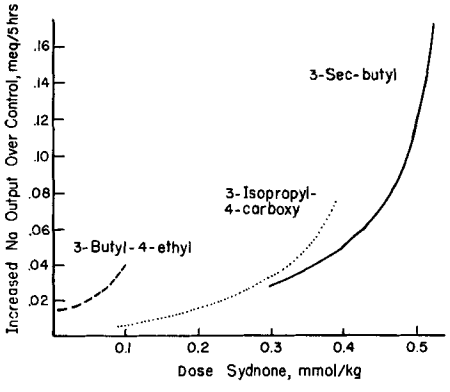


Fig. 3.—Comparison of urinary Na output by the three sydnones. (*Reference 33.*)

Oehme and co-workers (74) conducted an extensive pharmacological study of a large number of 3-phenylsydnones. They found that these compounds were significantly less toxic than the 3-alkyl sydnones (60) though the toxic manifestations were quite similar. (See Table VII and compare with Table VI.) They noted that at subtoxic doses in the rat a marked change occurred in the blood picture characterized by diminution of erythrocytes as well as formation of methemoglobin. They noted an analgesic effect $^1/_{30}$ of the effectiveness of morphine with the 3-(*o*-tolyl)- and the 3-(*m*-tolyl)sydnones.

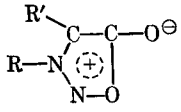
The sydnones studied were found not to have hypnotic effect themselves, but they did influence hexobarbital narcosis even in small doses. Particularly effective were the 3-(*o*,*m*, and *p*-tolyl)-sydnones, the 3-(*p*-methoxyphenyl)-, and the 3-phenyl-4-isopropylsydnones, which more than doubled the sleeping time. Substituents in the 4-position generally diminished this effect. They noted, in the case of the 3-(*m*-tolyl)sydnone, that the hexobarbital level in the rat brain, after sydnone pretreatment, was doubled. This suggested an interference with the microsomal decomposition process of the barbiturate as the cause of prolongation of the hexobarbital narcosis. This conclusion was reached when it was observed that 3-(*m*-tolyl)sydnone did not prolong sleeping time due to ethylbarbital, which is not metabolized by the rat.

In contrast to the convulsive activity found for the 3-alkyl sydnones (61), Oehme and co-workers (74) found considerable anticonvulsive activity for the 3-aryl sydnones. The 3-(*o*-tolyl)sydnones were the most active of the compounds tested. (See Table VII.) On isolated rat duodenum and guinea pig ileum, the sydnones studied had no effect. Finally, they observed that 3-methylsydnone did not inhibit glutamic acid decarboxylase. Furthermore, 3-methylsydnone and a number of 3-aryl sydnones did not inhibit monoamine oxidase, suggesting that conversion of the sydnones to the corresponding hydrazines is not involved.

In some recent work on four 3-phenyl-4-acyl sydnones (43), a modest hypotensive activity was noted when administered i. v. in dogs. There was quantitatively little differences between the compounds tested (acetyl, propionyl, isobutyryl, butyryl), the average blood pressure drop being about 10% at 10 mg./Kg. The action was of short duration.

It is evident that the 3-aryl sydnones generally

TABLE VII.—PHARMACOLOGY OF SYDNONES[a]



R	R′	LD_{50}, mmole/Kg.	ED_{50}, mg./Kg. Anticonvulsive: Electro-shock	Anticonvulsive: Pentylene-tetrazol	mm. Hg Rat, b.p. Lowering[b]
m-Tolyl	H	2.8	42	35	26
p-Tolyl	H	4.25	176	176	14
p-Tolyl	Isopropyl	2.8	218	218	21
p-Tolyl	Chloro	5.0	211	211	Lethal
p-Tolyl	Phenyl	—	—	252	11
p-Tolyl	Methyl	4.2	190	190	26
o-Tolyl	H	1.85	48	62	19
o-Tolyl	Nitro	3.3	221	221	14
m-Methoxyphenyl	H	5.0	80	140	15
p-Methoxyphenyl	H	2.4	192	192	8
o-Methoxyphenyl	H	5.0	165	192	16
p-Ethoxyphenyl	H	5.0	205	140	11
Phenyl	Phenyl	5.0	238	238	3
p-Chlorophenyl	Phenyl	2.8	273	273	24
Methyl	H	5.0	100	100	4
Phenyl	Methyl	2.9	140	176	10
Phenyl	Isopropyl	1.7	102	204	9
p-Carboxyphenyl	H	5.0	206	206	8
m-Tolyl	Methyl	2.4	190	95	15
m-Tolyl	Isobutyl	2.5	232	232	11

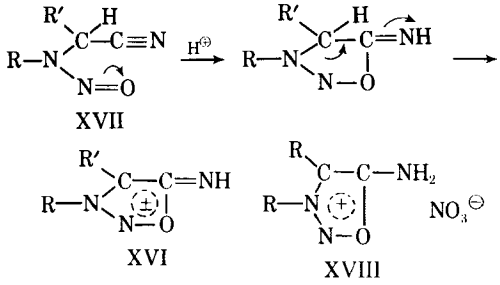
[a] From *Reference 74*. [b] 0.025 mmole/Kg.

exert a depressant type of CNS response while the 3-alkyl sydnones exert a convulsive response. This dichotomy of action is not unlike barbiturates and hydantoins, depending on the presence of or absence of certain substituents on the nitrogen atoms of these compounds. This analogy has been noted and commented upon (61). A glance at the ground state electronic structures of 3-phenyl- and 3-methylsydnones (see Figs. 1 and 2) reveals some differences in the charge density patterns around the rings of these two modifications. These differences are possibly involved in determining the type of CNS action elicited.

SYDNONIMINES

Chemistry and Physical Properties.—Brookes and Walker (17) first reported the synthesis of a sydnonimine (XVI) from the reaction of an *N*-methyl-*N*-nitroso-α-amino-nitrile (XVII) with nitric acid. (Scheme IX.) The salt in this case was the nitrate (XVIII). The sydnonimines have also been reported to be formed with hydrogen chloride (25, 57, 91) and dilute hydrochloric acid (25). The free sydnonimine (XVI) does not exist and removal of the acid causes ring opening (17).

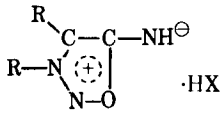
The structure of sydnonimine salts has not been settled. Structure XVIII is usually used to represent the imine salt; however, the infrared



XVII XVI XVIII

Scheme IX

spectrum of this compound shows absorption at 1588–1606 cm.$^{-1}$ and 1671–1770 cm.$^{-1}$, which Yashunskii (97, 98) ascribes to a $=\overset{\oplus}{N}H_2$ and a C=N group, respectively. This raises the possibility that a better representation for a sydnonimine salt may be structure XIX with a closely associated molecule of acid. Ohta and Kato (26) point out that structure XVIII does not give the usual amino group reactions such as diazotization or alkylation; hence, this structure



XIX

may not be an adequate model for the sydnonimine salt. Other derivatives of the imine salt can be formed such as the *N*-nitroso (57), *N*-nitro

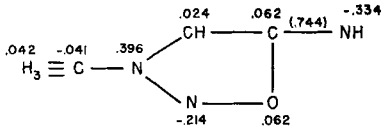
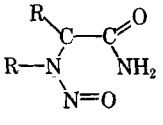


Fig. 4.—Molecular orbital calculated properties of 3-methylsydnonimine from *Reference 67*. (Number in parenthesis is a bond order. The remaining numbers are charge densities.)

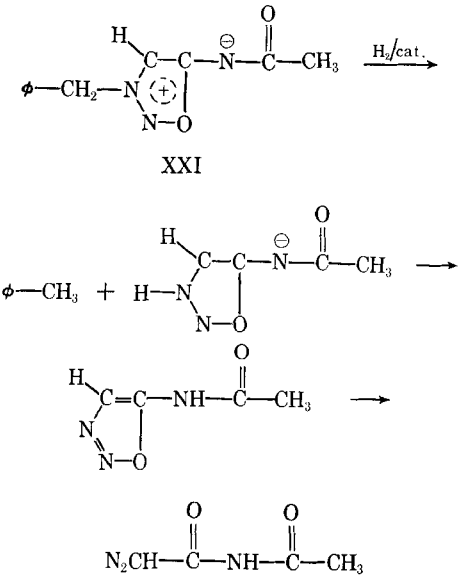
(17), *N*-acyl (57), *N*-phenyl-carbamoyl (26), and *N*-benzene-sulfonyl (27). The aromatic nature of the ring is illustrated by the fact that the 3-phenyl-*N*-acetyl-sydnonimine can be brominated and mercurated in the 4-position. Also, the NMR spectrum of the proton at position 4 supports ring aromaticity (26).

A molecular orbital treatment (68) (Fig. 4) lends support to structure XIX as being more truly representative of the sydnonimine structure. The exocyclic NH group bears a distinct negative charge density, while the C—NH bond is decidedly more of a double bond than the C—NH bond depicted in structural representation XVIII. The trisubstituted ring nitrogen bears a high positive charge density, though it is lower than the corresponding atom in methylsydnone.

Sydnonimines, unlike sydnones, are stable to acid (26). In alkali they suffer ring opening to give the nitrosoamides (XX). Prolonged exposure to hot concentrated acid cleaves the ring (25) but does not give a hydrazine derivative, in contrast to the behavior of the sydnones. Catalytic hydrogenation of sydnonimines and derivatives gives aliphatic amides with the exception of the 3-benzyl-*N*-acetylsydnonimine (XXI) which debenzylates to give α-diazoacetylacetamide (XXII) (28). Ohta (75) reported the same product from the treatment of the hydrochloride salt with acetic anhydride. (Scheme X.)



XX



XXI

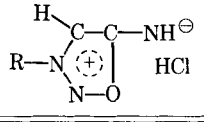
XXII

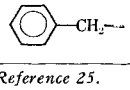
Scheme X

The ultraviolet absorption of the sydnonimines closely resembles that of the sydnones. The alkyl derivatives absorb at about 290 mμ (ε ~ 8500), while the aryl derivatives are shifted to lower energy, *i.e.*, 306 mμ (ε ~8100) for 3-phenylsydnonimine HCl, and 323 mμ (ε ~ 8700) for 3,4-diphenylsydnonimine HCl (25). Molecular orbital calculations on 3-methylsydnonimine (68) predict an absorption maxima, using the correlation equation of Kier and Roche (68), of 300 mμ in fair agreement with the experimental value.

The NMR spectra of sydnonimines (25) exhibits a low field singlet for the proton on C-4. (See Table VIII.) The position of this peak is very strong evidence of π-electron delocalization in this sytem. The induced ring current causes a magnetic anisotropic shift of the proton to lower field than benzene protons. It is further interesting to note the very large downfield shift of the C-4 proton in the 3-phenyl derivative. This may be due to a combined anisotropic effect of the two aromatic rings. The magnitude of the downfield shift for the ring proton in the 3-alkyl sydnonimines also appears to be greater by more than 1 τ than the corresponding chemical shift in 3-alkyl sydnones.

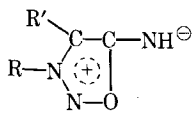
TABLE VIII.—CHEMICAL SHIFT OF SYDNONIMINES[a]

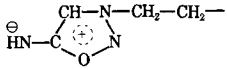
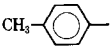
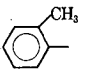


R	τ Ring H
CH_3	2.45
	1.97
	2.55

[a] From *Reference 25*.

TABLE IX.—PHARMACOLOGY OF SYDNONIMINES[a]



R	R′	LD_{50}, mmole/Kg.	Rat Blood Pressure Lowering, mm. Hg
$CH_3CH_2CH_2CH_2$—	H	0.54	13
			1
$CH_3CH_2CH_2CH_2$—	H	1.30	4
	H	1.23	8
	H	0.86	28
	H	1.50	13
		1.35	12
	H	2.38	22

[a] From *Reference 74*.

Biological Activity.—Interest in the potential biological activity of sydnonimines stems from the first reported testing of salts of 3-methyl-4-isopropyl and 3-methyl-4-isobutylsydnonimines (17). They showed no activity in experimental filarial infections. Daeniker and Druey (26) and subsequent patents (10) described the analgesic, antipyretic, anti-inflammatory, antiallergenic, and hypotensive effect of sydnonimines, with the 3-benzylsydnonimine salt being particularly active. Greco, Nyberg, and Cheng (42) synthesized a number of 3-alkyl sydnonimine salts for anticancer screening and reported no activity.

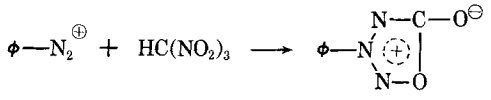
Oehme and co-workers (74) made a detailed pharmacological study of a number of sydnonimine salts. They found the sydnonimine salts studied to be more toxic than a series of sydnones studied at the same time. (See Table IX and compare with Table VII.) Deaths occurred with marked convulsions. The analgesic effects were not significant. The sydnonimines have no hypnotic effect themselves but a number of them did potentiate hexobarbital sleeping time. (See Table IX.) The compounds unsubstituted at position 4 were the most active, a situation comparable to the sydnones. The sydnonimines had no effect as anticonvulsants against pentylenetetrazol or electroshock at 0.1–0.4 mmole/Kg.

The sydnonimines tested by Oehme (74) showed spasmolytic effects in the rat duodenum and the guinea pig ileum. They noted a decrease in acetylcholine and histamine-induced contractions. They also noted a decrease in barium-induced spasms, with 3,4-diphenyl- and 3-*p*-tolyl-4-phenylsydnonimine salts. The strength of the effect corresponded to that of papaverine. The sydnonimines were hypotensive only in high doses, the effect not being pronounced (74). They did not inhibit the enzyme glutaminic acid decarboxylase *in vitro*.

There appear to be some fundamental differences in the activities of the sydnonimines and the sydnones. While the sydnones appear to act more by central mechanisms, the sydnonimines act more strongly on isolated organs.

PSEUDOÖXATRIAZOLES

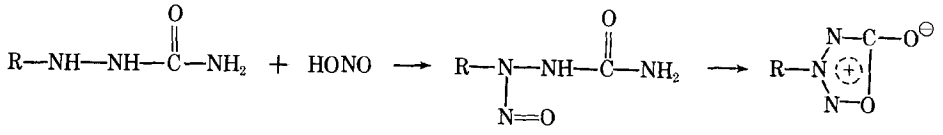
Chemistry and Physical Properties.—The Ψ-oxatriazoles (XXIII) are a group of mesoionic compounds formed by replacing a ring carbon atom in the sydnone with a nitrogen. The nitrogen atom donates one electron to the 6 π-electron sextet, hence the two classes of heterocycles are isoconjugate. Quilico (79) and Ponzio (77) reported the synthesis of this ring system when they observed the reaction of phenyldiazonium salt with nitroform. (Scheme XI.)



XXIII

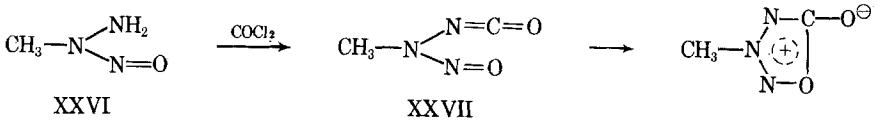
Scheme XI

They prepared the phenyl and *p*-nitrophenyl derivatives. Boyer and Cantor (15) reported the synthesis of the first alkyl-Ψ-oxatriazole using the appropriately substituted semicarbazide (XXIV) as the starting material. Boyer and Cantor proposed as the intermediate in the nitrosation step, the *N*-nitrososemicarbazide (XXV) a proposal subsequently confirmed by Boyer and Hernandez (16), who isolated the intermediate nitrososemicarbazide at low temperature. (Scheme XII.) Hashimoto and Ohta (49) reported the synthesis of methyl pseudoöxatriazole from the reaction of phosgene on *N*-nitroso-*N*-methylhydrazine (XXVI). They proposed an isocyanate intermediate (XXVII) although the carbamylchloride (XXVIII) is a possibility. (Scheme XIII.) Farrar (37) has prepared the phenyl derivatives by reacting potassium diazomethanedisulfonate (XXIX) with phenyldiazonium salt to form potassium hydrazono-

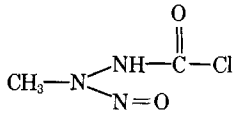


XXIV XXV

Scheme XII



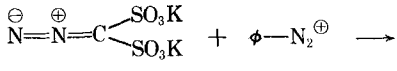
XXVI XXVII



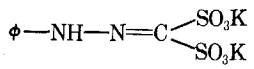
XXVIII

Scheme XIII

methanedisulfonate (XXX). (Scheme XIV.) Reaction of this compound with nitrous acid gave phenyl-Ψ-oxatriazole.



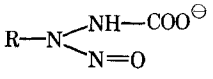
XXIX



XXX

Scheme XIV

Practically nothing is known about the chemistry of this mesoionic heterocycle. Boyer and Hernandez (16) noted that cyclohexyl-Ψ-oxatriazole resisted dilute acid, but with 80% sulfuric acid at 75° gave cyclohexanol, CO_2, and NH_3. The Ψ-oxatriazoles are considerably less stable in base (68) yielding a base-soluble product which gives a positive nitroso test. A likely structure for this compound is XXXI. This would be analogous to the base hydrolysis product of the sydnones.



XXXI

Molecular orbital calculations (68) give the ground state charge densities and bond orders shown in Fig. 5. Using the localization energy technique (81) the predicted point of protonation is the No. 2 nitrogen atom. It is interesting to note that the charge density of the Ψ-oxatriazole exocyclic oxygen is lower than that calculated for the corresponding atom of 3-methylsydnone. By contrast, the No. 3 nitrogen atom of methyl-Ψ-oxatriazole is substantially higher in positive charge then the corresponding atom of 3-methylsydnone.

Using the correlation equation derived from sydnones by Kier and Roche (67) relating U. V. absorption frequency with the MO calculated energy difference between the highest filled and lowest empty molecular orbitals (corresponding to a $\pi \rightarrow \pi^*$ spectral transition), the calculated $\lambda_{max.}$ for methyl-Ψ-oxatriazole is found to be 264 mμ, which agrees very closely with the experimental value of 260 mμ (68). The calculated value for phenyl-Ψ-oxatriazole is 277 mμ, which is very close to the experimental value of 275 mμ (37).

The infrared absorption band due to the carbonyl group lies between 1780 and 1800 cm.$^{-1}$. The ultraviolet absorption maximum is at 260 mμ ($\epsilon \sim 9000$) for alkyl derivatives and at 275 mμ ($\epsilon \sim 13{,}500$) phenyl (37).

Biological Activity.—Kier (65, 66) studied a number of alkyl substituted Ψ-oxatriazoles in the hope of finding an enhanced hypotensive activity previously noted for the isoconjugate sydnones (38). The compounds studied (see Table X) were free from toxicity at doses of 200 mg./Kg. in mice. Doses of 20 mg./Kg. i. v. in anesthetized dogs gave very prompt depressor effects in each case. The more potent hypo-

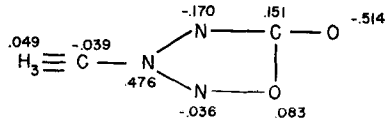
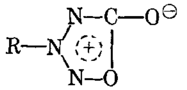


Fig. 5.—Molecular orbital calculations for methyl Ψ-oxatriazole from *Reference 68*, showing charge densities.

TABLE X.—BLOOD PRESSURE EFFECT OF Ψ-OXATRIAZOLES AT VARIOUS INTERVALS IN ANESTHETIZED DOGS[a]



R (20 mg./Kg.)	T + 10 sec.	T + 5 min.	T + 10 min.	T + 15 min.	T + 30 min.	T + 60 min.
	% of Blood Pressure After Injection					
CH_3	81	91	92	90		
CH_3—CH_2—	80	88	88	84		
$(CH_3)_2CH$—	66	75	70		69	76
CH_3—CH_2 \ CH— / CH_3—CH_2	69	72	68		75	67
CH_3—CH_2 \ CH— / CH_3	43	64	54		59	64
CH_3 | CH_3—C— | CH_3	46	66	57		47	43

[a] From *Reference 66.*

tensive compounds exhibited prolonged activity, in some cases lasting several hours. Other signs such as respiration, EKG pattern, heart rate, and gross and general appearance remained normal during this period of hypotension. The hypotensive effect ranged from approximately a 10% drop in blood pressure for methyl-Ψ-oxatriazole to about a 40% decrease for *tert*-butyl-Ψ-oxatriazole. Hypotensive activity was observed in the spinal cat, indicating that activity in the cat is not centrally mediated. Pretreatment in dogs with atropine or tripelennamine did not block the hypotensive effects, indicating that cholinergic effects or histamine release are unlikely causes of the hypotensive effects. Pressure responses in the dog to DMPP and epinephrine or norepinephrine were not reduced by the Ψ-oxatriazoles, indicating that ganglionic or α receptor blockade are also unlikely causes. On isolated rabbit ileum and rat ileum or uterus, the Ψ-oxtriazoles produced a prompt inhibition of smooth muscle activity in low concentrations. The hypotensive activity of these compounds may well be due to the relaxation of smooth muscle at the periphery. The order of potency found by Kier (66) was *tert*-butyl > *sec*-butyl ≅ 3-pentyl ≅ isopropyl > ethyl > methyl. This is in the order of increasing mesomeric contribution to the ring, suggesting that a minimization of π electron contribution enhances hypotensive activity.

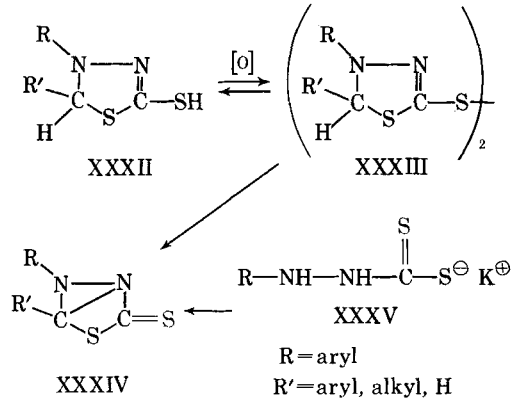
A comparison of three groups of mesoionic compounds which have shown hypotensive activity—namely, the Ψ-oxatriazoles (66), the 4-acyl sydnones (43), and the alkyl sydnones (38)—revealed the decreasing order of hypotensive potency as Ψ-oxatriazoles > 4-acyl sydnones > 3-alkyl sydnones. A comparison of the π-charge densities of the No. 3 nitrogen atom of each series reveals a decreasing positive charge, +.476, +.448, +.421, respectively. Thus, the involvement of this portion of the ring as a cationic moiety with a receptor was suggested (66). It is interesting to note that the calculated charge density of the No. 3 nitrogen of phenyl-Ψ-oxatriazole is +.484 (68) which, if the previous correlation holds, should lead to the prediction that it is a more potent hypotensive agent than the alkyl Ψ-oxatriazoles. No tests have been reported on this compound.

MESOIONIC 1,3,4-THIADIAZOLES

Chemistry and Physical Properties.—In 1895, Busch (20) noted that a thiadiazolinethiol (XXXII), oxidized to its disulfide (XXXIII), underwent a disproportionation to give the original compound (XXXII) plus a new compound postulated as XXXIV. Busch later synthesized the same compound by reaction of the potassium salt of an aryldithiocarbazinic acid (XXXV) with an acid chloride (21). (Scheme XV.) In this latter procedure, the compound in which R′ = H was made by using ethyl

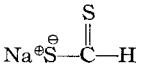
CH_3—CH_2—O—CH=NH·HCl

XXXVI



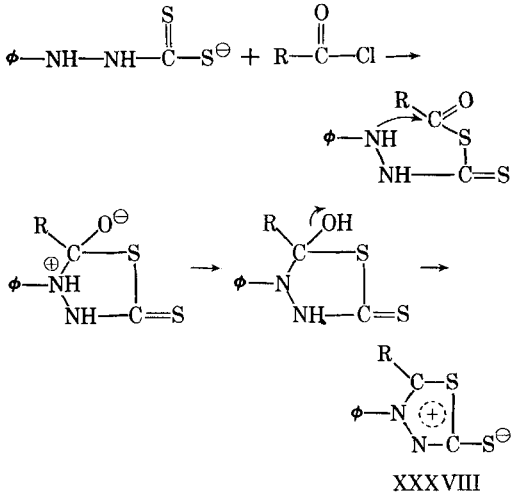
Scheme XV

formamidate hydrochloride (XXXVI) as the reagent (22). A more recent synthesis of this compound utilizes sodium dithioformate (XXXVII) with XXXV (6). The mechanism



XXXVII

of the reaction forming the mesoionic thiadiazoles is unknown. Baker (6) suggested a mixed anhydride as an intermediate. Stewart and Kier (89) proposed a mechanism employing this mixed anhydride intermediate. (Scheme XVI.)



XXXVIII

Scheme XVI

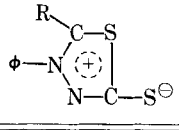
In 1938, Schönberg (82) suggested that the compound (XXXIV), synthesized by Busch, would be better represented by a hybrid structure involving several charged forms. These are now known to be a member of the mesoionic family of aromatic heterocycles and are conventionally represented as XXXVIII.

The question of proper nomenclature is still unsettled. According to Katritzky (59) these compounds would be named anhydro - 4,5-disubstituted - 2 - thio - 1 - thia - 3,4 - diazolinium thiol, and according to Baker (6), Ψ - 4,5 - disubstituted - 2,4 - dihydro - 2 - thio - 1 - thia - 3,4 - diazole. As a matter of expediency, we have referred to these compounds as mesoionic 1,3,4-thiadiazoles in print or as "pseudothiadiazoles" in conversation.

These compounds are high melting, yellow to orange solids. They are not dethionated by HgO in boiling benzene but at elevated temperatures and pressures the diphenyl derivative decomposes to several products including *N*-, *N*′-dibenzophenylhydrazine (22). With HgO in boiling ethanol, the ring cleaves to give a dithiocarbazinic acid (XXXV) (22). Oxidation with potassium permanganate results in the formation of benzanilide from the diphenyl compound. In hot base, the ring opens to reform the dithiocarbazinic acid salt (XXXV).

The diphenyl and the 4-phenyl-5-methyl compounds have dipole moments of 8.8 D in benzene (56) characteristic of mesoionic compounds. Stewart and Kier (89) reported an absorption band at 1325–1355 cm.$^{-1}$ for a number of mesoionic thiadiazoles, which they assigned to the thiocarbonyl group. (See Table XI.) In the same study they reported a U. V. absorption maximum of high molar absorptivity at about

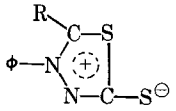
Table XI.—Mesoionic 1,3,4-Thiadiazole I.R. and U. V. Absorption[a]

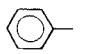
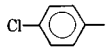
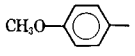
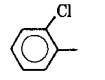


R	ν (C—S⊖) cm.$^{-1}$	λmax.	ε
H	1335	380	1800
CH_3—	1335	353	3000
CH_3CH_2—	1345	356	3100
$(CH_3)_2CH$—	1355	358	3400
$CH_3(CH_2)_2$—	1345	358	3400
$(CH_3)_3C$—	1355	357	3700
CH_3—$(CH_3)_3$—	1345	358	3400
$CH_3(CH_2)_4$—	1345	358	3400
	1335	405	4600
Cl— 	1325	410	5000
CH_3—O— 	1335	403	4400
	1325	396	3700

[a] From *Reference 89*.

TABLE XII.—ANTIBACTERIAL TESTING OF MESOIONIC 1,3,4-THIADIAZOLES[a]



R	Sensitivity to *S. aureus*[b]	Microorganisms *D. pneumoniae*[b]	Hypotensive Effect	Pulse Rate Decrease	Pulse Pressure Increase
H—	++	—	—		
CH_3	++++	+++	+		
CH_3CH_2—	++++	+++	—		
$(CH_3)_2CH$—	++++	+++	+		+
CH_3—$(CH_2)_2$—	++++	+++	—		
$(CH_3)_3C$—	+	+	+	+	+
CH_3—$(CH_2)_3$—	+	+	+	+	+
CH_3—$(CH_2)_4$—	0	0	—		
	+	+	+		
	+	+			+
	+	+	+		
	0	0	—		
Control	0	0			
Penicillin G	++++	++++			

[a] From *References 88, 89.* [b] +, relative radius of inhibition zone on agar plates. The compound was placed on the paper disk by evaporation of a DSMO solution.

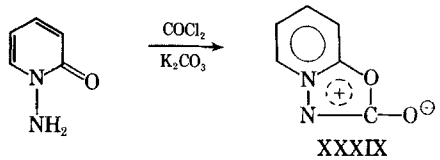
358 mμ for the 4-phenyl-5-alkylthiadiazoles and an absorption at about 400 mμ for the diaryl derivatives. (See Table XI.) It is interesting to note that the presence of an *ortho* substituent on the 5-phenyl group (4-phenyl-5-*o*-chlorophenylthiadiazole) must provide sufficient steric bulk to twist the ring out of coplanarity with the mesoionic ring, thereby isolating the two from maximal conjugation. This results in a shift of the $\lambda_{max.}$ to higher energy (lower wavelength). (See Table XI.)

Biological Activity.—Kier and Stewart (88, 89) tested a series of 4-phenyl-5-substituted mesoionic thiadiazoles against Gram-positive *Staphylococcus aureus*, *Diplococcus pneumoniae*, and Gram-negative *Escherichia coli*. Activity was observed with the 5-methyl, 5-ethyl, 5-isopropyl, and 5-propyl derivatives. Compounds with longer chains or greater bulk in this position had lower activity. The compounds were not active against the Gram-negative *E. coli*.

In other pharmacological tests, Stewart (88) observed that the LD_{50} exceeded 500 mg./Kg. i. p. in mice with each of the compounds in Table XII. The 5-alkyl compounds produced moderate convulsions in rats at higher doses. In anesthetized dogs, a number of compounds produced a fairly rapid lowering of blood pressure with a varying effect on the pulse rate. (See Table XII.) A direct cardiac effect or a peripheral vasodilation was assumed to be implied by the increase in pulse pressure with the 5-*p*-chlorophenyl compound as well as the production of extra systoles with the onset of the hypotensive effect.

ISOSYDNONES

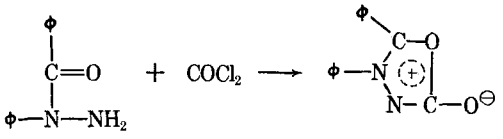
Chemistry and Physical Properties.—A modification of the sydnone ring, in which the lactone moiety is reversed, has been referred to as an isosydnone (XXXIX) (1). Hashimoto and Ohta (48) have named these Ψ-2,4-dihydro-4,5-disubstituted 2-keto-1-oxa-3,4-diazoles, while *Chemical Abstracts* indexed the compounds as 5-hydroxy-2,3-disubstituted-1,3,4-oxadiazolium hydroxide inner salts. This ring system was first reported by Hoegerle (53), who synthesized a number of bicyclic isosydnones (XXXIX). (Scheme XVII.) Using this



XXXIX

Scheme XVII

same method, Hashimoto and Ohta synthesized the first monocyclic isosydnone (48) (XL) from an α-acylhydrazine (XLI). (Scheme XVIII.)

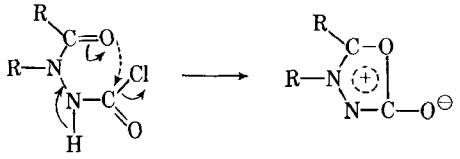


XLI XL

Scheme XVIII

The same authors attempted the synthesis of 4-methyl-5-phenylisosydnone but were not able to isolate enough of their products to fully characterize it. Ainsworth (1) succeeded in synthesizing and characterizing the 4-methyl-5-phenyl compound using phosgene in dioxane. Two 4,5-dialkyl isosydnones were first reported by Roche and Kier (80) using essentially the same synthesis, thus establishing the stability of a completely nonaromatic substituted isosydnone.

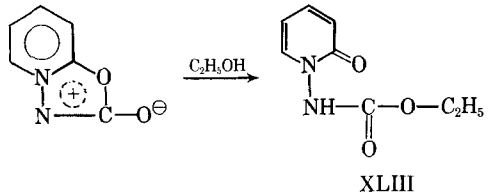
Ainsworth (1) has suggested the mechanism of formation starting with chloracylation of the hydrazine (XLII) followed by ring closure.



XLII

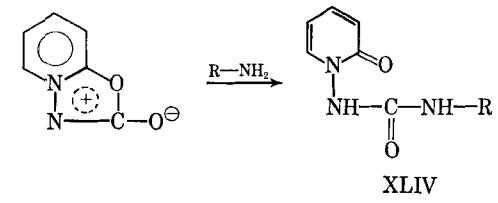
Scheme XIX

(Scheme XIX.) Hoegerle (53) noted that the ring was unstable when warmed in ethanol, yielding the substituted ethylurethane (XLIII). (Scheme XX.) Similarly, he noted the formation of the substituted urea XLIV, upon warming with NH_3 or an aliphatic amine. (Scheme XXI.) This behavior was confirmed by Hashimoto and Ohta (48) in the monocyclic isosydnone. Hashimoto and Ohta (48) observed that the product of acid hydrolysis of diphenylisosydnone was the starting material *N*-benzoyl-*N*-phenylhydrazine. They proposed a mechanism for the reaction. (Scheme XXII.) They observed that alkaline hydrolysis of the same compound led to phenylhydrazine and benzoic acid. They proposed the intermediate *N*-carboxy-*N'*-benzoyl-*N'*-phenylhydrazine (XLV) in the reaction.



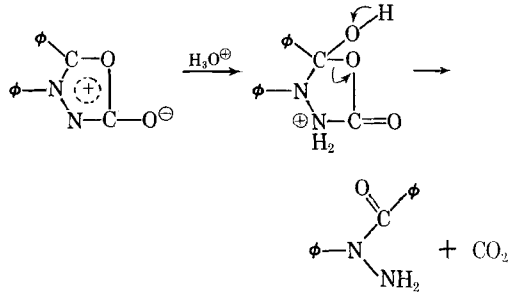
XLIII

Scheme XX

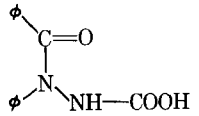


XLIV

Scheme XXI



Scheme XXII



XLV

The isosydnones possess high dipole moments, characteristic of the high charge separations found in mesoionic compounds. Ainsworth (1) reported a dipole moment of 7.58 ± 0.06 D for 4-methyl-5-phenylisosydnone in benzene at 25°. Bishop (13) in Ollis' laboratory reported dipole moment values for several aryl isosydnones, all at least 1 D higher than similarly substituted sydnones.

The infrared spectrum revealed a band at 1750–1760 cm.$^{-1}$ (1, 47, 53) which undoubtedly is due to the exocyclic C—O group. This is quite close to the typical value for the same group in the sydnones. The ultraviolet absorption maximum occurs (1, 53) at 290–325 mμ with high molar absorptivity. This is probably due to the isosydnone ring and is again comparable to the sydnone ring absorption.

Molecular orbital calculations using the methods described by Kier and Roche (67) give some insight into the electronic structure of the isosydnones. (See Fig. 6 for the calculation of 4-methyl-5-phenylisosydnone.) The charge den-

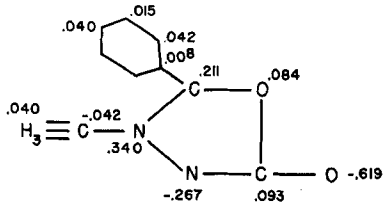


Fig. 6.—Molecular orbital calculation of 4-methyl-5-phenylisosydnone from *Reference 68*. (The numbers refer to charge densities.)

sity on the exocyclic oxygen atom is almost 0.1 electron higher than on the corresponding atom of the sydnone. This higher charge density indicates a higher calculated dipole moment than for sydnones, a prediction confirmed by the value of Ainsworth (1) of 7.58 D for 4-methyl-5-phenylisosydnone. The positive charge on the trisubstituted ring nitrogen is substantially lower than that of the sydnones, while the No. 5 ring carbon bears a much higher positive charge than the similarly placed ring carbon atom of the sydnone. Using the correlation equation derived from sydnones by Kier and Roche (67) relating U. V. absorption frequency with the energy difference between the highest filled and lowest vacant molecular orbital (corresponding to a $\pi \rightarrow \pi^*$ spectral transition), the calculated $\lambda_{max.}$ for 4-methyl-5-phenylisosydnone is found to be 296 mμ which corresponds very well to Ainsworth's experimental value of 294 mμ (1).

Biological Activity.—Interest in the isosydnones arose because of their isomeric relationship with the sydnones. In some preliminary studies Ainsworth reported (2) that 4-methyl-5-phenylisosydnone was inactive in an antibiotic screen at 25 mcg./ml. against 19 organisms representing animal pathogens, saprophytes, and bacterial and fungal plant pathogens. It was also inactive in entomology screening at 500 p.p.m. In a mouse behavior screening test, the pattern of activity suggested that the compound may be a cholinergic agent. The 4,5-diphenylisosydnone was found to give the same results against microorganisms.

SUMMARY

Much remains to be explored concerning the biological activity of mesoionic compounds. The work done to date clearly indicates significant activity and a potential as useful medicinal agents in several compounds. That the mesoionic compounds possess marked activity is not surprising, in the view of the authors. These ring systems are composed of delocalized π electrons which have been appreciably perturbed by the cores from which they arise. This perturbation is sufficient to deny the use of conventional, classical structural representations, and leads to the definition and depiction of a new class of heterocycle, the mesoionics. This perturbation results in a common structural feature found in the systems just reviewed and in many other mesoionic systems, that is, an oppositely charged dipolar segment at the extrema of a four-atom chain.

$$\overset{+\delta}{\text{—N—X—Y—}}\overset{-\delta}{\text{O}}$$

The extent of these partial charges is not obvious from classical resonance considerations, but emerges only after molecular orbital treatments, pointing out the tremendous value and utility of this technique to the medicinal chemist.

This charged four-atom segment is the hallmark of many pharmacologically active classes of drugs. Its significance perhaps lies in its ability to electrostatically interact with two complementary partially charged positions on a receptor macromolecule such as a protein helix.

A second structural feature of the mesoionic systems which suggests potential value is the fact that, although the molecules are internally charged and possess high dipole moments, they are over-all electrically neutral, therefore soluble to a much greater extent in nonpolar or lipoid solvents. Thus, *in vivo*, we have the capability of crossing lipoid barriers with a molecule which internally is appreciably ionic. This circumvents the problem found with quaternary salts and molecules rich in polar groups such as carbohydrates, which are usually constrained in their action to a water compartment, being generally unable to pass through a lipoid barrier.

Finally, the mesoionic rings are comparatively small in size, about 16 Å.^{2} for methylsydnone, and are planar, thus eliminating conformational problems and permitting the relatively close approach of all ring atoms to a receptor surface.

As the chemistry and electronic structures of more of these ring systems are studied and elucidated, more obvious relationships between these properties and their biological activities will be revealed, and the direction of future research on these compounds will be indicated.

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