Mesoionic Ψ-Oxatriazoles as Hypotensive Agents

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A number of alkyl substituted mesoionic Ψ-oxatriazoles were investigated as hypotensive agents. They were found to produce rapid, deep, and sustained hypotension with no observable side effects. The potency followed a reverse order of mesomeric contribution of the alkyl substituents. Molecular orbital calculations revealed a large positive character on the N_3 and, in comparison with the corresponding 3-alkylsydnone and 4-acylsydnone nitrogen atom, appears to correlate with hypotensive potency.

Over the past several years studies in this laboratory on the mesoionic sydnones (I) have revealed a marked pharmacological activity in the form of CNS stimulation (1–3). In addition it was found that the sydnones possess a moderate diuretic and hypotensive property (4). Unfortunately, this hypotensive activity manifested itself at a dose level very close to the convulsive dose level, so that useful information concerning structure–activity relationships, mechanism of action, and the development of a potentially useful drug was denied.

With these problems in mind, the authors have studied a modified sydnone structure in the hope of finding a greater hypotensive activity and a reduced convulsive activity. The approach, in this study, was to consider a change in the ring which would not alter the over-all mesoionic character, *i.e.*, it was decided to study an isoconjugate heterocycle. An example of such a ring system is the mesoionic pseudooxatriazole (II). This compound is identical to the sydnone ring except for the replacement of the No. 4 carbon atom of the sydnone with a nitrogen atom.

The pseudooxatriazoles have been known since 1933, when Ponzio (5) prepared the phenyl derivatives by treating a phenyl diazonium salt (III), with nitroform (IV). More recently, Boyer and Canter (6) have prepared alkyl Ψ-oxatriazoles from the action of nitrous acid (V) on the appropriate semicarbazide (VI). Hashimoto and Ohta (7) have prepared the methyl derivative from the action of carbonyl chloride (VII) on *N*-nitroso-*N*-methylhydrazine (VIII). The most recent contribution to the synthesis of these compounds has been by Farrar (8), who synthesized the phenyl derivative from potassium diazomethane-disulfonate (IX), and a benzenediazonium salt (III) followed by treatment with nitrous acid. The Ψ-oxatriazoles studied in this work were previously described (9). The authors have confined their study to a few simple alkyl substituted Ψ-oxatriazoles in order to minimize partition coefficient effects and yet to study the electronic effect of substituents on the ring (Scheme I.)

In order to examine the electronic alterations produced in the ring by replacement of the —CH— of the sydnone with an —N— in the Ψ-oxatriazoles, the electronic structure was calculated using molecular orbital methods previously described for the sydnones (10). The ground state structure is shown in Fig. 1 for methyl Ψ-oxatriazole. The calculations have been tested by the use of the equation derived for the sydnones (10) relating the U.V. absorption maximum with the energy difference between the highest filled and lowest vacant molecular orbital (characteristic of an approximation of a $\pi \rightarrow \pi^*$ transition). From the authors' calculations of methyl Ψ-oxatriazole a value of 264 mμ for the predicted transition was obtained, which is quite close to the experimental value of 260 mμ obtained in a methanol solution. Thus, it was felt that the calculations have some validity in reproducing the electronic structure of the Ψ-oxatriazoles.

A comparison between the electronic structures of methyl Ψ-oxatriazole and 3-methyl sydnone (Fig. 1) is illuminating. The exocyclic oxygen of methyl Ψ-oxatriazole has a lower charge density while the No. 3 nitrogen atom has a substantially more positive character.

The two flanking nitrogen atoms both have charge densities in the negative range, while the —CH— flanking the No. 3 nitrogen of the sydnones is positive in character.

EXPERIMENTAL

In mice, the six Ψ-oxatriazoles under study, methyl, ethyl, isopropyl, 3-pentyl, *sec*-butyl, and *tert*-butyl, in doses of 200 mg./Kg. i.p. caused no apparent signs of toxicity. Doses of 600–800 mg./Kg. were required to produce death.

Administration of the liquid compounds in doses of 20 mg./Kg. i.v. in anesthetized dogs produced a prompt depressor effect in all cases. After the initial fall in blood pressure, there was, characteristically a small short-lived rise followed by a long period of hypotension which lasted for several hours in the case of the more potent compounds (Table I). During this period of hypotension, the animals remained normal with regard to respiration, EKG pattern, and gross and general appearance. The heart rate showed no important changes, being sometimes slightly increased or slightly decreased, although usually unaltered. The hypotensive effect ranged from approximately a 10% decrease for methyl Ψ-oxatriazole to over a 40% decrease for the *tert*-butyl Ψ-oxatriazole. There was a tendency to longer duration of effect with the more potent compounds (Table I). Hypotensive activity was also found in the spinal cat which indicates that in the cat the action is not centrally mediated. Pretreatment in dogs with atropine (1–2 mg./Kg.) or pyribenzamine (5 mg./Kg.) did not block the hypotensive effects, indicating that cholinergic effects or histamine release are unlikely causes of the hypotensive effects. Pressor responses in the dog to DMPP (25 mcg./Kg.) and epinephrine or norepinephrine (2–4 mcg./Kg.) were not reduced by the Ψ-oxatriazoles, indicating that ganglionic or α-receptor blockade are also unlikely causes.

When the compounds were tested on an isolated rabbit ileum and rat ileum or uterus maintained in a muscle bath, they produced a prompt inhibition of the smooth muscle activity in concentrations of 1–5 μl./ml.

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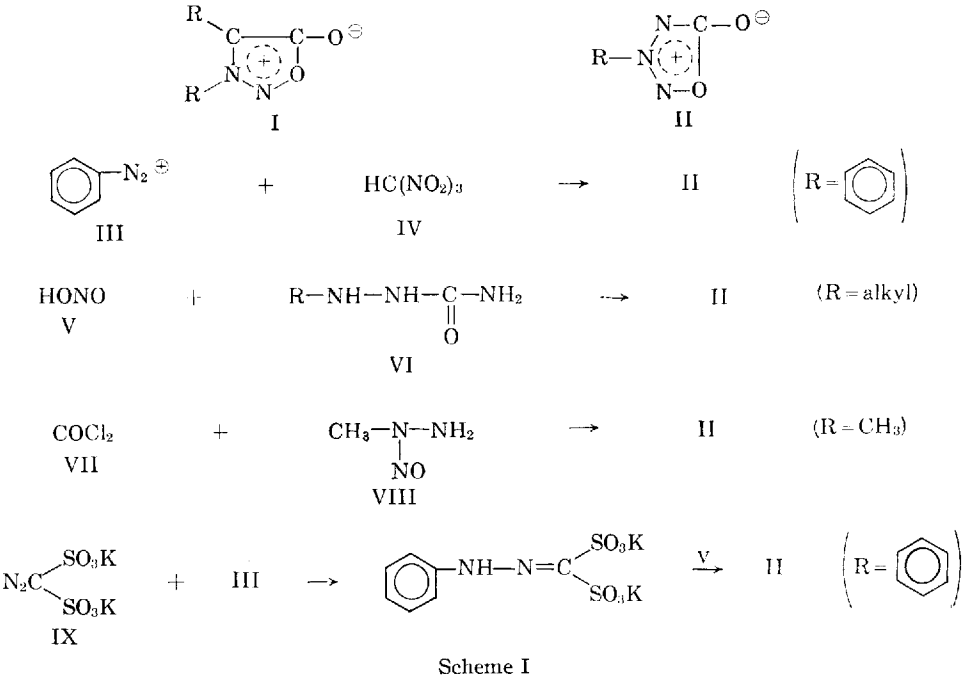

Scheme I

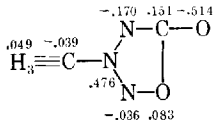

Fig. 1.—Electronic structure of methyl Ψ-oxatriazole from molecular orbital calculations.

TABLE I.—BLOOD PRESSURE FALL AT VARIOUS INTERVALS IN ANESTHETIZED DOGS

Ψ-Oxatriazole, 20 mg./Kg.	Blood Pressure Fall in % of Normal					
	T + 10 sec.	T + 5 min.	T + 10 min.	T + 15 min.	T + 30 min.	T + 60 min.
Methyl	19	9	8	10		
Ethyl	20	12	12	16		
Isopropyl	34	25	30		21	24
3-Pentyl	31	28	32		36	33
sec-Butyl	57	36	46		41	36
tert-Butyl	54	34	43		53	57

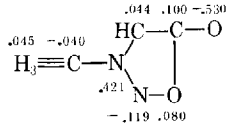

Fig. 2.—Electronic structure of methyl sydnone. (From *Reference 10.*)

The Ψ-oxatriazoles then, in doses that produce no obvious toxic effects, produce in dogs prompt, prolonged hypotensive effects which may well be due to the relaxation of smooth muscle at the periphery.

DISCUSSION

From Table I it is evident that the decreasing order of potency at the dose level studied is *tert*-butyl > *sec*-butyl ≧ 3-pentyl ≧ isopropyl > ethyl > methyl. This is in the increasing order of mesomeric contribution of the alkyl group to the aromatic ring. A minimum mesomeric contribution to ring then appears to improve the hypotensive potency.

An examination of the electronic structure of methyl Ψ-oxatriazole in Fig. 2 reveals that a major portion of the positive character of the ring resides on the trisubstituted nitrogen atom. The possible significance of the positive character of the ring, and especially the positive character of the trisubstituted nitrogen atom is revealed in a comparison of the Ψ-oxatriazoles, the 3-phenyl-4-acylsydnones, and the alkylsydnones. Greco and Kier (11) have shown that the 3-phenyl-4-acylsydnones possess a moderate hypotensive potency, while the alkylsydnones show less hypotensive activity (4). The order of potency and the corresponding charge densities of the trisubstituted nitrogen atoms for these three series of compounds are:

Ψ-oxatriazoles	>	3-phenyl-4-acylsydnones	>	3-alkylsydnones
q_n = +.476		q_n = +.448		q_n = +.421

This trend suggests an important role for the trisubstituted nitrogen atom as a partial cationic moiety in the interaction of the compound with a receptor. If this correlation is correct, the prediction follows that the as yet untested phenyl-Ψ-oxatriazole with a trisubstituted nitrogen charge density of +.484 should be a more potent hypotensive agent than the compounds reported.

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