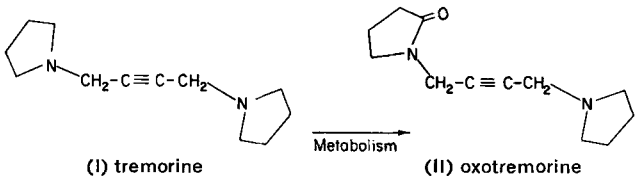
Molecular Orbital Conformation of Oxotremorine and a Comparison With the Muscarinic Pattern

LEMONT B. KIER

Abstract □ The conformational preference of oxotremorine has been calculated using extended Hückel molecular orbital theory. The molecule was found to be comparatively free in regard to the relationship of the two rings and the rotation of the lactone ring. The energy-permitted stereochemistry allows the quaternary nitrogen, the triple bond, and the carbonyl oxygen to assume the same relationship as previously calculated for the muscarinic pharmacophore, if the triple bond in oxotremorine is assumed to mimic the electronic character of the ether oxygen in the muscarinics.

Keyphrases □ Oxotremorine—molecular orbital conformation □ Molecular orbital conformation, oxotremorine—muscarinic activity □ Conformational molecular preference—oxotremorine

A current hypothesis on the peripheral and central actions of tremorine (I) and its metabolite oxotremorine (II) (Scheme I) is that the latter molecule is a muscarinic



Scheme I

agonist. The peripheral action of oxotremorine, studied by Cho *et al.* (1) leaves little doubt that this compound is a peripheral muscarinic agent equal in potency to acetylcholine. The effects can be blocked by pretreatment with anticholinergic drugs like methanthelinium or atropine bromides. In animals so pretreated, a tremor, ataxia, and spasticity still persist. Atropine sulfate blocks these effects and so it is presumed that the tremor effect is due to activation of muscarinic receptors in the central nervous system (*2*).

Studies by Lundgren and Malmberg (3) suggest that oxotremorine-induced tremors are not due to direct action in the CNS, but are due to the ability of the drug to induce an increased biosynthesis of acetylcholine in the CNS. Oxotremorine, however, fails to stimulate *in vitro* systems containing choline acetylase. It has been observed that there is a rise in acetylcholine level which roughly parallels the oxotremorine-induced

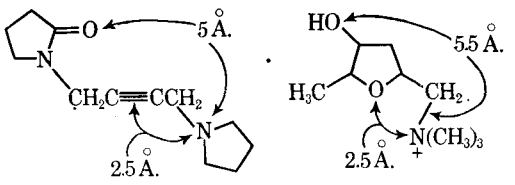


Figure 1—*Proposed steric relationship of essential features in oxotremorine and muscarine (6).*

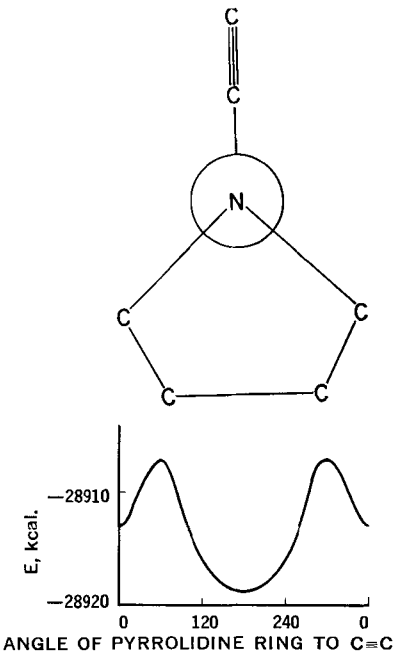


Figure 2—*Calculated relationship of pyrrolidine ring and triple bond in oxotremorine.*

tremor duration. Recent detailed studies by Cox and Potkanjak (4) on this comparative time course show a lack of parallel behavior between tremor manifestation and acetylcholine increase.

Since oxotremorine may be a CNS muscarinic agonist, it is of interest to contemplate how the structure of this molecule compares with known muscarinic agents. Cho *et al.* (1) have commented on the structural dissimilarity of oxotremorine to known muscarinic agents and suggested that oxotremorine was highly active owing to a process at the receptor related to Koshland's (5) induced-fit theory. However, Bebbington *et al.* (6) have compared molecular models of oxotremorine with muscarine and noted that the two could conceivably assume a common geometry, in which the same pattern of charged atoms would prevail. This required the invoking of the acetylenic bond as a negative site of binding in the oxotremorine molecule, mimicking the ether oxygen in muscarine. A plausible explanation for the possible direct receptor action of oxotremorine then centers on the ability of the molecule to assume a favorable conformation, mimicking the muscarinic pharmacophore, Fig. 1.

In a previous study, the author calculated the conformations of three potent muscarinic agents using a molecular orbital theory in which overlap integrals and nonbonded interactions are treated for all valence

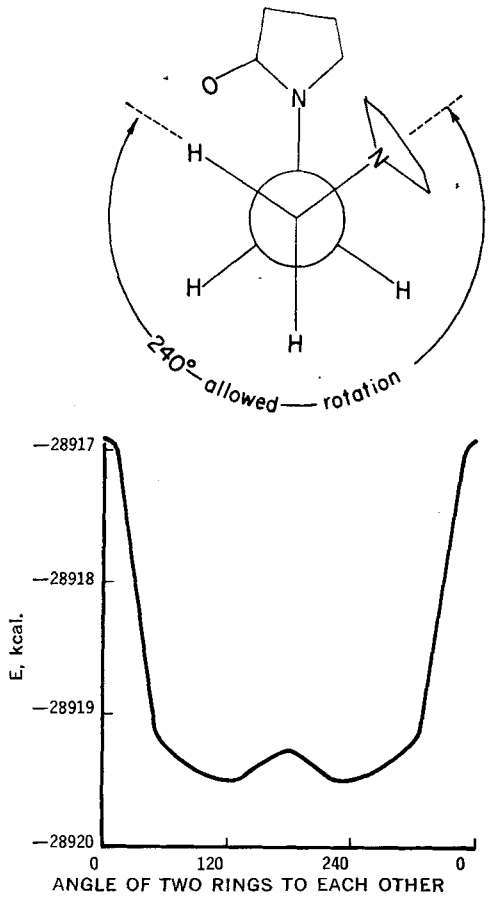


Figure 3—*Calculated relationship of the two rings in oxotremorine.*

electrons (7). The method, known as extended Hückel theory, generates a total energy as a function of geometry; hence, conformation preference can be assessed by energy minimization (8). A common pattern of charged atoms or groups was calculated for acetylcholine, muscarine, and muscarone. The author has predicted that this pattern is a reasonable working model of the muscarinic pharmacophore.

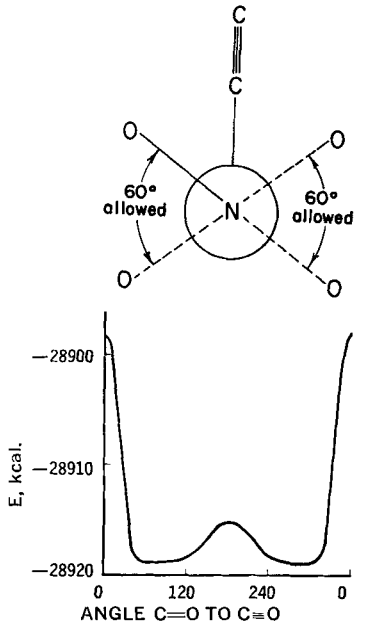


Figure 4—*Calculated relationship of the lactone ring and the triple bond in oxotremorine.*

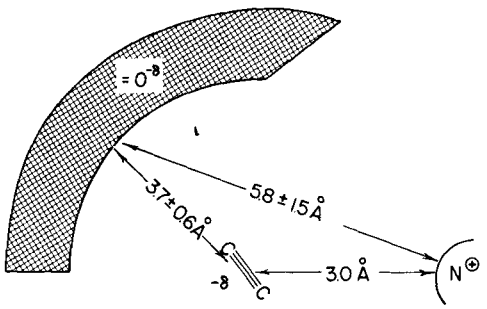


Figure 5—*Calculated energy-permitted relationship of essential features in oxotremorine. Shaded area shows region which oxygen atom may occupy relative to the other molecular features.*

In the present study, the author undertook molecular orbital calculations on the oxotremorine molecule, to determine its preferred conformation and to see whether a pattern of charged atoms or groups corresponded to the previously calculated muscarinic pharmacophore.

EXPERIMENTAL

The molecule was calculated as the protonated salt. Standard bond lengths and angles were used according to Pople and Gordon (9). The Coulomb integrals and Slater exponents were those previously employed by Hoffmann (8) and the author (7). In comparing the energy *versus* geometry profiles, the preferred conformation was taken to be the geometry of lowest energy. All geometries within 1 kcal. or less of this energy minimum were considered to be equally preferred.

RESULTS AND DISCUSSION

The results of the calculations show that the molecule can exist in a variety of preferred structures. The two rings exhibit considerable independence with respect to their conformational preferences. When the distance between any two first-row atoms on opposite rings exceeds 4 Å., the two rings are not influential in respect to their preferred conformations. We have justified the assumption that distant atoms do not influence conformation in a recent quantum mechanical discussion (10). This assumption has been used by others (11).

The pyrrolidine ring is symmetrically disposed relative to the triple bond, Fig. 2. The two rings can assume any conformation except that which eclipses their methylene connecting groups, Fig. 3. The lactone ring can assume two zones of conformational preference to within 60° of coplanarity with the acetylenic bond, Fig. 4. The distance separating the pyrrolidine protonated nitrogen from the center of the triple bond is 3.0 Å. The distance between the carbonyl oxygen and the protonated nitrogen ranges from 4.3–7.2

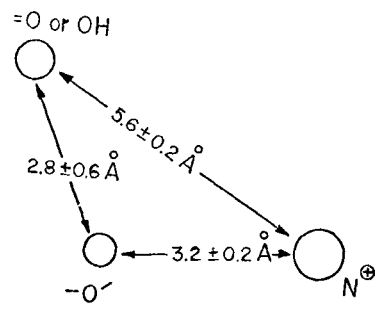


Figure 6—*Calculated muscarinic pharmacophore based on conformations calculated for acetylcholine, muscarine, and muscarone (7).*

Å., owing to the variation possible in conformational preference. The carbonyl oxygen distance from the center of the triple bond ranges from 3.1–4.2 Å.

An allowed pattern of atoms can thus be drawn for oxotremorine, Fig. 5. This calculated energy-allowed pattern clearly mirrors the muscarinic pattern, previously proposed, Fig. 6.

It can be concluded that oxotremorine can assume a muscarinic pharmacophore, within its structure, on the basis of theoretical calculations of its preferred conformations. Although conclusive pharmacological evidence that would brand oxotremorine as a central muscarinic agonist is still lacking, these studies implicate the feasibility of this mechanism.

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Antiradiation Compounds XIII: 1-(Dithioacetic Acid)-Pyridinium Betaines

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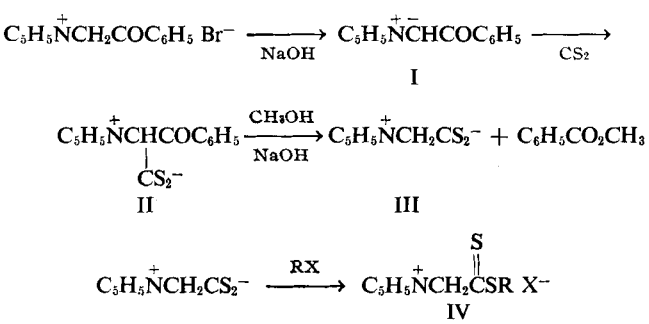
Abstract □ Active mono-*S*-alkyl esters prepared from 1-(dithioacetic acid)-pyridinium betaine (III) were found to be sufficiently stable for screening as radiation-protective agents, and *e*-withdrawing substituents in the pyridine ring gave stable betaines. Reaction of the methyl ester of III with phenacyl bromide and alkali resulted in *S*-alkylation to give a ketene mercaptal betaine (VIII). Both the allyl and *p*-nitrobenzyl esters of 1-(dithioacetic acid)-pyridinium halides were radiation-protective in mice, and betaines with substituents in the pyridine ring were radiation-protective in a bacterial test.

Keyphrases □ Antiradiation compounds—synthesis □ 1-(Dithioacetic acid)-pyridinium betaines—synthesis □ Pharmacological screening—antiradiation compounds □ IR spectrophotometry—structure

Amino and guanidino zwitterions containing the thiosulfate (1), phosphorothioate (2), and trithiocarbonate (3) groups, as well as other zwitterionic structures (4) which contain the β-mercaptoethylamine moiety have shown appreciable radiation-protective abilities in mice. α-Acetamidinium thiosulfate zwitterions (5) have also shown good radiation-protective properties. It appeared likely, therefore, that other zwitterions containing, or giving rise to, a thiolate anion should be radiation-protective. Dithioacetic acid pyridinium betaines, obtained from the reaction of carbon disulfide and pyridinium ylids, appeared to have the necessary structural requirements for protective activity in a charged nitrogen and a thiolate anion, and were therefore investigated for possible radiation-protective properties.

Pyridinium betaines are compounds, termed by Kröhnke (6), which contain a negatively charged carbon, oxygen, or sulfur adjacent to, or at greater distance from, the positively charged nitrogen; the term ylid is now generally used where the charges are on adjacent atoms. When phenacylpyridinium bromide is treated with alkali, a red solution of the ylid (I) results. Reaction with carbon disulfide gives the α-dithiocarboxylate zwitterion (II) which decomposes to the dithioacetic acid betaine (III) in methanolic alkali (6). This compound, although unstable, can be isolated, and remains stable long enough for derivatives to be prepared. Conversion to the active allyl and *p*-nitrobenzyl esters (IV) was carried out, and compounds of sufficient stability for antiradiation screening were obtained.



Reaction of the dithioacetic acid betaine (III) with bromoethylamine hydrobromide did not give the desired ester; also, no reaction with phenyl halides or