or equal to an 85% deparasitation, while piperazine under the same conditions displays only 60–70% activity.

Single Dose. As with the multiple doses, only substances showing activity equal to or higher than 85% were retained. These comprised the adducts prepared from 4-methyl-, 3-methoxy-, 3-chloro-, and 3-methyl-6-nitrophenol, di-*tert*-butyl-3,5-pyrocatechol, resorcine, 2-methylresorcine and di-*tert*-4,6-resorcine, and hydroquinone and di-*tert*-2,5-hydroquinone.

A study is currently underway in regard to the active dose limits and possible side effects. Preliminary results suggest that the di-*tert*-butylphenols **41** and **44** will show promise in this respect, despite the fact that they contain less than 30% piperazine.

Structure–Activity Relationships. Although at the start of this investigation we were attracted by the possibility of a relationship between biological activity and the strength of the hydrogen bond linking the phenol to piperazine, no clear correlation seems to emerge from the results reported here.

Experimental Section

Melting points were determined on a Reichert microscope and are uncorrected. The method used for activity determinations was described in an earlier paper.[1] Ir spectroscopic measurements were performed on a Perkin-Elmer 457 instrument for potassium bromide disks (0.5 mm). Wavelengths are given within ±3 cm^{-1} after calibration of the band at 3027.1 of polystyrene.

Method of Synthesis. To 1 mol of phenol dissolved in toluene, a corresponding quantity of piperazine was added. Either a spontaneous crystallization occurred immediately or the mixture was heated to the boiling point and left to cool, whereupon crystallization took place. In the rare cases where crystallization did not then occur, the solvent was evaporated and the residue crystallized from the appropriate solvent.

Acknowledgment. We thank Mr. F. Collomb, Director General of CHRYSA, for the generous gift of phenols leading to adducts **9–14**.

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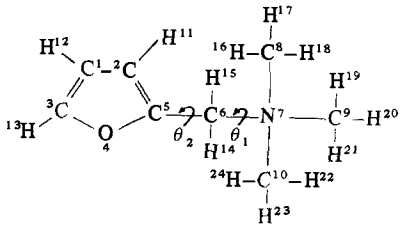
A Note on Molecular Orbital Calculations of Furfuryltrimethylammonium

James W. Crow

Department of Pharmacology, University of Kansas Medical Center, Kansas City, Kansas 66103. *Received July 24, 1972*

Furfuryltrimethylammonium (I, FTA), a potent muscarinic, exhibits, in general, the pharmacological characteristics of methacholine but has been especially effective in the treatment of urinary retention due to its direct action on the bladder.[1]

If a muscarinic agonist is to produce its activity *via* direct interaction with the muscarine receptor, it is reasonable that the stereochemistry of its active centers approximates that of other muscarine-like agonists.[2-4] Kier,[3] using EHT-MO, has described the preferred conformation of ACh,



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muscarone, and muscarine. Three active centers were predicted for any muscarine-like compound—a quaternary N, -O-, and C=O or COH. It is interesting to note the presence of two of these centers in FTA (quaternary N and the -O-) but an apparent lack of Kier's third site. To clarify this matter we completed a molecular orbital study on FTA using Hoffmann's extended Hückel theory.[5]

Methods. Hoffmann's extended Hückel theory[5] (EHT) was employed in this study. The two required programs were supplied by the University of Indiana's Quantum Chemistry Program Exchange. Bond angles and bond lengths are of standard magnitude. The planarity of the furan ring, however, produces slightly modified molecular parameters.[6]

Other EHT parameters, which include a choice of K, Slater exponents, and 2 s and 2 p Coulomb integrals, are chosen consistent with Kier.[3] The FTA system shows two torsion angles: θ_1 = C(8)-N(7)-C(6)-C(5) and θ_2 = N(7)-C(6)-C(5)-C(2). As in previous studies,[2-4] the 3-methyl groups attached to the quaternary N are held in a staggered conformation. N(7)-C(6)-C(5)-C(2) is varied from 0 to 180° in increments of 30°. Due to the molecular symmetry the second 180° rotation would yield duplicate results.

The computations were made on the IBM 370 Model 165. All calculations were performed in double precision and PL/I and FORTRAN IV were the programming languages used.

Results

One conformation was determined to be the minimum energy state, N(7)-C(6)-C(5)-C(2) = 90°, with a 1.3 eV energy barrier (Figure 1). It should be stated that the potential well is overestimated in EHT but the energy barrier

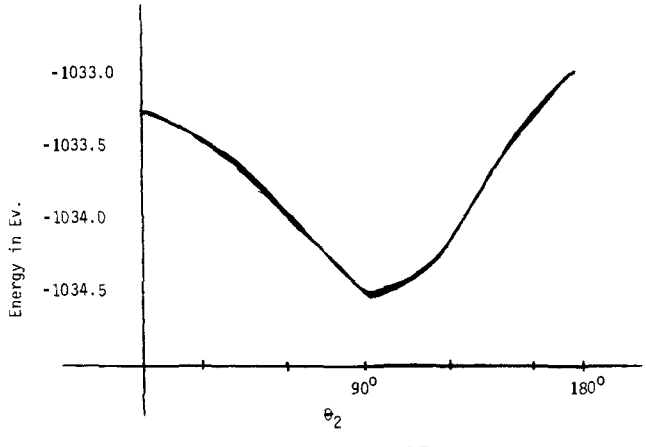


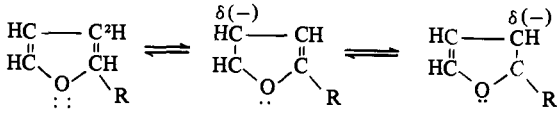
Figure 1. Total energy *vs.* conformation of FTA.

Table I. Interatomic Distances in the FTA System Determined from EHT Calculations

d (1,4)	2.2 Å
d (1,7)	4.5 Å
d (4,7)	3.2 Å
d (4,2)	2.2 Å
d (7,2)	2.4 Å

is correctly placed in the rotational diagram.[5] The interatomic distances are represented in Table I.

By applying the data to a series of similar pharmacologically active agents, two active sites are determined: the quaternary N and the -O- with the interatomic distances similar to corresponding centers of ACh, muscarone, and muscarine (2.8 ± 0.6 Å). The third active center in the FTA system may be demonstrated by noting only the order of charge distributions in EHT calculations. The EHT calculations reveal the largest negative charge, excluding the -O-, to be located on atoms C(1) and C(2). Likewise, the contributing resonance forms of the FTA structure II suggest a



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negative charge to be situated at these same sites. It will be our purpose to correlate spatially this most negative carbon atom with the third center proposed by Kier.

An interatomic distance of 4.9-5.4 Å has been reported between the quaternary N and the C=O or the -OH of ACh, muscarone, and muscarine and 3.0 Å between the -O- and this third center in these systems.[3]

Similar active centers are reported in studies using conformationally restricted analogs of muscarinic agents—the dioxolanes. According to Garrison[7] and May,[8] 4.6 Å separate the N and one of the ether oxygens and 3.6 Å the N and the other -O- center. In further support of this hypothesis, Beckett[9] studied series of muscarine analogs using stereoselectivity in the reactions of cholinesterase and cholinergic receptors. He postulated distances of 4-7 Å and approximately 3 Å separating an anionic cavity and two positively charged points in the muscarinic receptor, corresponding to the quaternary N, the -O-, and C=O. Recently Baker, *et al.*,[10] described the conformation of the 3-methyl derivative of FTA using X-ray data. The distances separating the -O- and the quaternary N and C(1) and the quaternary N in this highly active muscarinic system are extremely close to those calculated of the unsubstituted compound using EHT. No attempt was made by these authors to designate C(1) as a third active center. It should be noted that a correlation here would yield evidence in favor of a three-centered muscarinic receptor.

Our molecular orbital results in Table I show good spatial correlation between centers N(7), O(4), and the most negative, ring carbon C(1) in FTA and the N, -O-, and C=O (-OH) of ACh, muscarine, and muscarone. Even better agreement is seen in the 1,3-dioxolane analogs and the 3-methyl-FTA derivative supporting both the concept of a three-centered muscarinic pharmacophore and the validity of describing biologically active agents *via* molecular orbital treatments. Our computational results suggest that a "three-centered receptor" is most important in the early stages of drug-receptor interaction.

Acknowledgments. This project was supported in part by Kansas University Medical Center, Endowment Grant No. 72-2428.

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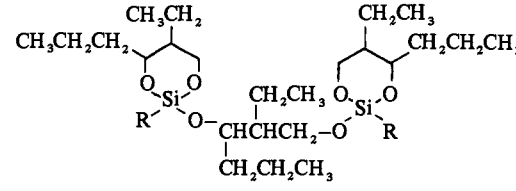
Silyl Ether Precursor-Type Insect Repellents[1]

Daniel D. Garner and Lorrin R. Garson*

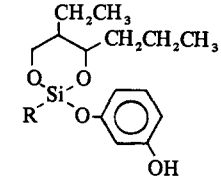
Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee Medical Units, Memphis, Tennessee 38103.
Received December 27, 1972

As an extension to our continued interest in the development of insect repellents with prolonged activity, we have synthesized compounds incorporating an insect-repellent component and one capable of anchoring to the skin. The novel entities, called "precursor molecules," may themselves be effective repellents; however, it is the gradual breakdown of the latter which is expected to provide perdurable repellency through sustained release of the repellent component. The rationale of this approach has previously been discussed in detail.[2,3] The reported[4] insectifugal activity of several heterocyclic silicon compounds **1-4** which incorporate the



1, R = CH_3
2, R = $CH_3CH_2CH_2$
3, R = $CH_3CH_2CH_2CH_2CH_2$
4, R = C_6H_5

standard insect repellent 2-ethyl-1,3-hexanediol (Rutgers 612) in their structures prompted us to include this repellent into a precursor molecule through silyl ether linkages with resorcinol. Compounds **5-7** are designed to bind to the skin *via* the phenolic moiety and gradually release the repellent diol through hydrolysis of the silyl ether linkages subsequent to dermal application. There is considerable evidence to suggest that these silyl ethers would be readily



5, R = CH_3
6, R = CH_3CH_2
7, R = $CH_3CH_2CH_2CH_2$

susceptible to hydrolysis and that steric factors (*i.e.*, nature of the R group) play a predominant role in the rates of hydrolysis.[5a,6-8] Therefore, by varying the size of the R group, the rate of cleavage could conceivably be controlled to afford the optimal release of repellent diol **8**. Due to the tendency of silanetriols to undergo polymerization,[5b,6,7] **9** (and also the corresponding silanetriols of **6** and **7**) should