TABLE V

Compound	Atomic charges (EHT) O_6	H_6	O_2	Atomic charges (CNDO 2) O_6	H_6	O_2	Activity Electroshock[a]	Activity Pentylenetetrazole[b]
5-Ethyl-5-phenylbarbituric acid	−1.311	0.332	−1.343				0.10[c]	5 0.21[c]
5,5-Diphenylhydantoin	−1.317	0.322	−1.341				0 0.4[c]	0 1.97[c]
5-Ethyl-5-phenylhydantoin	−1.326	0.322	−1.341	−0.371	0.150	−0.408	0.19[c]	5 2.11[d]
3,5,5-Trimethyloxazolidine-2,4-dione[e]	−1.327		−1.312	−0.337		−0.361	6.85[d]	5 1.75[d]
3,5-Dimethyl-5-ethyloxazolidine-2,4-dione[e]	−1.327		−1.313	−0.337		−0.360	2.55[d]	5 0.80[d]
5,5-Dimethyloxazolidine-2,4-dione	−1.327	0.323	−1.313	−0.343	0.161	−0.366		
5,5-Diethylbarbituric acid	−1.329	0.332	−1.342	−0.321	0.156	−0.368	1.01[b]	
3,3-Diphenylsuccinimide	−1.331	0.321	−1.353				0.18[g]	0 1.97[g]
5-Phenylhydantoin	−1.335	0.322	−1.341	−0.339	0.156	−0.384	0.90[c]	3 2.82[d]
3-Methyl-3-phenylsuccinimide	−1.340	0.321	−1.352	−0.364	0.159	−0.353	0.53[g]	5 0.34[g]
3-Ethyl-3-phenylsuccinimide	−1.340	0.321	−1.352				0.29[g]	5 0.32[g]
3-Phenylsuccinimide	−1.350	0.322	−1.353	−0.360	0.160	−0.355	1.70[g]	5 1.42[g]
Succinimide	−1.353	0.321	−1.353	−0.371	0.156	−0.371	>4.04[g]	0 5.05[g]
β-Methylglutarimide				−0.323	0.143	−0.323	Inactive[c]	
Glutarimide				−0.337	0.140	−0.337	Inactive[c]	
β,β-Dimethylglutarimide				−0.340	0.139	−0.340	Convulsant[c]	
β-Methyl-β-*n*-propylglutarimide				−0.342	0.142	−0.342	Dual action[c]	
β-Methyl-β-*n*-butylglutarimide				−0.354	0.139	−0.354	Anticonvulsant[c]	
β-Methyl-β-ethylglutarimide				−0.356	0.139	−0.356	Convulsant[c]	

[a–b] See corresponding footnotes in Table IV. [e] These compounds are demethylated at N metabolically (T. C. Butler, *J. Am. Pharm. Assoc.*, **44**, 367 (1955)). One of the demethylated compounds, 5,5-dimethyloxazolidine-2,4-dione, is included for comparison.

gether with activity data, in Table V. There is no correlation between the calculated atomic charges and observed activity, indicating that hydrogen-bonding ability, in terms of net atomic charges, is unrelated to the type or extent of activity. Indeed the charges on these atoms remain fairly constant, and it seems possible that their specific hydrogen-bonding ability is involved in both convulsant and anticonvulsant activity.

On this basis it is suggested that the CNS activity of the drugs studied may be due to a strong and specific hydrogen-bonding complex with a cellular substrate, where the type and extent of action depend on the position and size of substituent groups. Recent ir[9] and X-ray crystallography[10] studies demonstrated that a hydrogen-bonded complex is formed between a model substrate, 9-ethyladenine, and a number of barbiturates, including those studied here. It has been suggested subsequently[11] that the physiological activity of the barbiturates may be due to their disruption of the coenzyme, flavin-adenine dinucleotide. However the results of the calculations reported here, together with preliminary ir studies, indicate that the convulsant β-methyl-β-ethylglutarimide also associates with 9-ethyladenine. This cannot readily be explained by the coenzyme disruption hypothesis.

Acknowledgments.—I wish to express my gratitude to Professor A. S. Buchanan and Dr. R. D. Harcourt for many helpful discussions on this work. Financial support from a CPGA is gratefully acknowledged.

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Molecular Orbital Calculations on a New Series of Substituted-Phenyl Choline Ethers

JAMES CROW,[1a] OTMAR WASSERMANN,[1b] AND WILLIAM C. HOLLAND[1c]

Department of Pharmacology and Toxicology, University of Mississippi School of Medicine, Jackson, Mississippi

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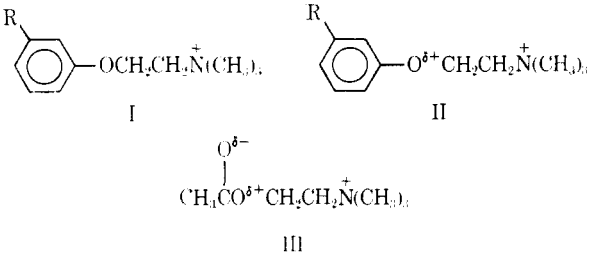
In addition to the onium head, it has been suggested that the electron density at some other points in the molecule of phenyl and substituted-phenyl choline ethers contribute to the intensity of nicotine-like activity. Simple Hückel molecular orbital calculations revealed that charge densities in the remainder of the molecule could not be correlated with pharmacologic activity. However, superdelocalizability at ring positions 2 and 6 and the energy of the highest occupied molecule orbital showed good parallelism with biologic activity. It was suggested that the aromatic ring may interact with the receptor by forming a charge-transfer complex.

The ganglionic stimulant action (nicotine-like action) of phenyl choline ethers (I) varies greatly with the substituent,[2] but the underlying mechanism of this activity remains obscure. In addition to the onium head, it has been postulated that the electron density at some other points in the molecule contributed to the intensity of nicotine-like activity.



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(2) (a) P. Hey, *Brit. J. Pharmacol.*, **7**, 117 (1952); (b) M. E. Coleman, A. S. Hume, and W. C. Holland, *J. Pharmacol. Exptl. Therap.*, **148**, 66 (1965).

Hey[2a] felt that the presence of a partial positive charge on the ether O (II) could explain his observations. On the other hand, Ormerod[3] and Sekul and Holland[4] suggested that a partial negative charge at an appropriate distance from the onium head was essential for nicotinic activity. This negative charge was assumed to be in a position analogous to the partial negative charge assigned to the carbonyl oxygen in acetylcholine (III).

In support of this latter conclusion is a molecular orbital study of the preferred conformation of nicotine by Kier.[5] He concluded from this study that two principal atoms necessary for nicotinic activity in the nicotine molecule are a positively charged nitrogen atom and a negatively charged atom about 4.85 Å removed. He further stated that its interaction with the receptor is similar to that of the carbonyl O of acetylcholine.

Molecular orbital calculations of Fukui, *et al.*,[6] on Hey's ethers showed no correlation between charge density on the ether oxygen and pharmacologic activity. However, they did find a good parallelism between the frontier electron density at the ether oxygen and superdelocalizability at the *ortho* ring positions and nicotinic activity.

Later Coleman, *et al.*,[2b] studied a new series of phenyl choline ethers exhibiting nicotinic activity. They attributed their findings to an inductomeric or polarizability effect of the substituent on the ring π electrons. They suggested that the partially negatively polarized rings provide a secondary binding feature in the molecule, presumably comparable to the easily polarized carbonyl oxygen of acetylcholine.

To further clarify the matter we have now completed molecular orbital calculations on the ethers prepared and assayed by Coleman, *et al.*[2b] These calculations are summarized and discussed in the present communication.

Methods

All the calculations were in the simple Hückel approximation.[7] In the simple Hückel method, relative values in a series of closely related molecules, such as the ones studied in this report, are more significant than absolute values. The method has been very successful in dealing with unsaturated systems. For this reason, we have not used the extended Hückel theory.[5] This latter procedure takes into consideration both σ and π electrons. It has had its greatest success in calculating the preferred conformations of hydrocarbons, both aliphatic and aromatic, as well as predicting conformational energies. These parameters would be of little value in the present study because the structures of the compounds examined are very similar.

The semiempirical parameters are those recommended by Krüger-Thiemer and Hansen.[8] Theirs is a recent and extensive collection of parameters and, in addition, they take into consideration the effects of the substituents on the aromatic carbon atom. The parameters used are given in Table I.

The calculations were made using an IBM system 360 Model 40 at the Missisippi Research and Development Center, Jackson, Miss. All calculations were done in double-precision arithmetic with input values having three significant figures. An IBM PL/I program was employed.

The following indices were calculated for each atom, with the exception of methylated onium head: free valence, net charge and superdelocalizability, and the energies of the highest filled (HOMO) and the lowest empty molecular orbital (LEMO).

The nicotine-like activities of the ethers employed were taken from the data of Coleman, *et al.*[2b] These activities were obtained from dose-response curves and are expressed as relative ones on a molar basis with phenyl choline ether set equal to one. Values greater than 1 represent enhanced nicotine-like activity.

TABLE I
SEMIEMPIRICAL PARAMETERS USED IN THE HÜCKEL CALCULATIONS

Bond or atom	Coulomb integral	Resonance integral	No. of electrons
C (aromatic)	$h_C = 0.0$	$k_{C-C} = 1.0$	1
C–N (amino)	$h_N = 1.5$	$k_{C-N} = 1.0$	2
	$h_C = 0.0$		
C–N (aromatic)	$h_N = 0.4$	$k_{C-N} = 1.0$	1
	$h_C = 0.0$		
C–O (ether)	$h_O = 2.0$	$k_{C-O} = 0.8$	2
	$h_C = 0.0$		
C–F	$h_F = 3.0$	$k_{C-F} = 0.7$	2
	$h_C = 0.2$		
C–Cl	$h_{Cl} = 2.0$	$k_{C-Cl} = 0.4$	2
	$h_C = 0.15$		
C–Br	$h_{Br} = 0.9$	$k_{C-Br} = 0.3$	2
	$h_C = 0.1$		
C–I	$h_I = 0.5$	$k_{C-I} = 0.2$	2
	$h_C = 0.05$		
C–NO_2 (–N^+)	$h_{N^+} = 0.6$	$k_{C-N} = 1.0$	1
	$h_C = 0.0$		
C–NO_2 (–O^-)	$h_{O^-} = 1.6$	$k_{N^+-O} = 1.0$	1

Results

Molecular orbital calculations were made for a series of *meta*-substituted-phenyl choline ethers; their structures and relative nicotine-like activities are given in Table I. Since no correlation between free valence, π charge density, and LEMO were noted, these indices will not be considered.

In our calculations, superdelocalizability at ring positions 2 and 6 and the energy of the highest occupied molecular orbital showed parallelism with pharmacologic activity. Superdelocalizability is a measure of the ability of atoms in a molecule to form a weak π bond with an appropriate group in the receptor. The energy of the highest occupied molecular orbital is a relative measure of the ability of an electron in the highest occupied orbital of a compound to be transferred to an acceptor molecule. In such studies molecular orbital energies are represented in β units (β is the resonance integral). The smaller the coefficient of β, the greater is the electron-donating property of the molecule within a series of closely related compounds.

In Table II, we have also included assays on pyridyl choline ether and pyridylethyltrimethylammonium. Here again the correlation between nicotine-like stimulant action and the energy of highest occupied molecular orbital (HOMO) is reasonably good.

Discussion

In proposing a mechanism of binding one can consider a number of possible interactions between the ethers and the receptor. It is now well known that onium head is essential for nicotine-like activity. The remaining part of the molecule contributes to binding at a nearby site to

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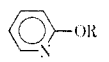
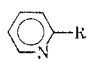
(8) E. Krüger-Thiemer and R. Hansen, *Arzneimittel-Forsch.*, **16**, 1453 (1966).

TABLE II

RELATIVE NICOTINE-LIKE ACTIVITY SUPERDELOCALIZABILITY AT RING POSITIONS 2 AND 6 AND THE ENERGY OF THE HIGHEST OCCUPIED MOLECULAR ORBITAL OF PHENYL AND *meta*-SUBSTITUTED-PHENYL CHOLINE ETHERS

	Rel nicotine-like act., *M* basis[b]			Superdelocalizability ring position		
Structure[a]	1	2	3	2	6	HOMO
C_6H_5OR	1.0	1.0	1.0	0.9751	0.9751	0.7692
m-IC_6H_4OR	5.4 ± 0.5	5.4 ± 0.4	6.3 ± 0.3	0.9947	0.9928	0.4812
m-BrC_6H_4OR	2.9 ± 0.2	3.5 ± 0.4	3.2 ± 0.3	0.9869	0.9837	0.7393
m-ClC_6H_4OR	1.6 ± 0.2	1.8 ± 0.2	2.4 ± 0.3	0.9779	0.9742	0.7671
m-FC_6H_4OR	1.1 ± 0.1	1.5 ± 0.2	1.5 ± 0.2	0.9746	0.9706	0.7685
m-$H_2NC_6H_4OR$	3.3 ± 0.3	3.7 ± 0.4	3.7 ± 0.4	1.2800	1.2781	0.5322
m-$O_2NC_6H_4OR$	0.4 ± 0.08	0.7 ± 0.1	0.4 ± 0.07	0.9483	0.9228	0.7738
			0.5 ± 0.05			0.8040
			0.2 ± 0.01			0.9467

[a] R = $(CH_2)_2N(CH_3)_3^+Br^-$. [b] Coleman, *et al.*[29] 1: blood pressure of dog, 2: blood pressure of cat, 3: cat superior cervical ganglion (nictitating membrane).

increase or decrease the intensity of activity. If such be the case, what is the nature of the intermolecular forces involved? The ether could sterically approximate the receptor, be bound by electrostatic attraction, form H bonds, enter into complex formation, or act as an electron donor or acceptor. While steric factors are frequently important, they cannot explain the observed difference in activity of these compounds since they have a constant spatial disposition. The lack of correlation with π-charge distribution speaks against electrostatic interaction. Furthermore, if an electron-transfer mechanism is involved, the negative correlation with the energy of the lowest empty molecular orbital indicates that the ethers do not act *via* electron acceptance. Thus, despite the crudeness of the theoretical data discussed here, the close relationship between HOMO and superdelocalizability of atoms at the 2 and 6 ring positions and nicotine-like activity suggests that aromatic ring interacts with a secondary group(s) in the receptor by formation of a charge-transfer complex.

Comparison of Parameters Currently Used in the Study of Structure–Activity Relationships[1]

A. LEO, CORWIN HANSCH, AND C. CHURCH

Department of Chemistry, Pomona College, Claremont, California 91711

Received May 1, 1969

The reactivities of a large group of miscellaneous molecules, as measured in four different biological systems, were correlated using the following parameters: octanol–water partition coefficient, polarizability, molar attraction constant, parachor, adjusted parachor, and molecular weight. Three of the systems show a linear dependence upon these parameters and the fourth requires the addition of a squared term. Regression analysis shows that log P (octanol–water) correlates a greater percentage of the biological activity of the 70 compounds than the other parameters studied. Other reasons for the perferred use of log P are also given.

Ever since the work of Meyer and Overton at the turn of the century, efforts have been made to find suitable physicochemical parameters with which one could correlate the difference in biological activity of the members of a set of congeners.[2,3] These studies have usually found the best correlations in biochemical or pharmacological examples where "nonspecific toxicity" was being considered. In fact, the best definition of "nonspecific toxicity" might well be high correlation with a single physical constant such as an oil–water partition coefficient. While partition coefficients[4,5] have been the favorite parameter, others have also been studied. However, almost no comparisons have been made of the various parameters on the same biological data. At this stage of development it is quite important to have some idea of the relative merits of the different kinds of constants. In this report we are most interested in comparing octanol–water partition coefficients with other physical constants. A large number of systems have now been analyzed using log P or π from this system.[2,3,5]

In selecting sets of biological data, a number of criteria have guided our choice. We have looked for sets of data in the simplest systems where past experience has indicated that nonspecific toxicity appeared to follow lipophilic character of the drugs. We also chose data where a good variety of structural change was present in the set of congeners. As Meyer and Hemmi pointed out,[4] there is little to be gained by comparing homologous series. We also chose sets with relatively large numbers of drugs having a good spread in activity. The parameters we have selected for comparison with log P (octanol–water) are polarizability,

(1) This work was supported by Grant CA 11110 from the National Institutes of Health.

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(3) C. Hansch, *ibid., 1967*, 348 (1968).

(4) K. H. Meyer and H. Hemmi, *Biochem. Z.*, **277**, 39 (1935).

(5) C. Hansch in "Medicinal Chemistry," Vol. I, E. J. Ariëns, Ed., Academic Press, Inc., New York, N. Y., in press.