8.5 g (0.08 mole) of Na_2CO_3, and 150 ml of absolute EtOH was refluxed for 2.5 hr. The hot supernatant solution was decanted from inorganic salts and concentrated. The oily residue was acidified by addition of 50 ml of 6 *N* HCl and to this mixture was added Et_2O; the solid which separated amounted to 17 g (29%), mp 108–112°, uv maxima (MeOH) at 260 mμ (ε 260) and 267 mμ (ε 171). The aqueous filtrate was concentrated to dryness and the residue was treated with MeOH and Et_2O to give a second solid which was devoid of uv absorption for phenyl, 18 g, mp 175–185°. A portion of the 17-g crop was recrystallized three times from EtOH–Et_2O to give pure **56**: mp 111–114°; nmr ($CDCl_3$), δ 8.9 (m, 2, $^+NH_2$), 7.36 (s, 5, C_6H_5), 4.63 (m, 1, *OH*), 3.80 (s, 2, $C_6H_5CH_2S$), 3.80 (m, 2, CH_2O), 3.00 (m, 5, SCH_2CH_2NCH), and 1.3 ppm (m, 13, $C_6H_{11}CH_2$).

[(2-Mercaptoethyl)amino]acetaldehyde Diethyl Acetal (8). Method E.—A solution of 80 g (0.62 mole) of aminoacetaldehyde diethyl acetal and 250 ml of toluene was dried by azeotropically distilling H_2O with the use of a Dean–Stark trap. To the refluxing solution was added slowly 31.5 g (0.21 mole) of ethyl 2-mercaptoethyl carbonate using techniques previously described.[4] The mixture was stirred and refluxed for 14 hr, and then distilled to give forerun of aminoacetaldehyde diethyl acetal, and 18.5 g (45%) of **8**, bp 74° (0.2 mm).

A solution of 5 g (0.026 mole) of **8** in dry Et_2O was treated with dry HCl to obtain 5 g (84%) of **9**, mp 95–97°.

2-{[(1,2,3,4,4a,9,10,10a-Octahydro-7-isopropyl-1,4a-dimethyl-1-phenanthryl)methyl]amino}ethanethiol Hydrochloride (43).—A reaction employing 45 g (0.16 mole) of commercial Rosin Amine D[22] and 8 g (0.05 mole) of ethyl 2-mercaptoethyl carbonate was carried out as described above for **8**. The toluene was evaporated and the residue was taken up in *ca.* 500 ml of EtOH. A solution of 9.9 g (0.026 mole) of lead acetate trihydrate in 50 ml of H_2O was added dropwise with stirring. Decantation of the solvent left a gummy solid which was crystallized from 65 ml of heptane to give 15 g of solid. Recrystallization from EtOH–H_2O gave 10 g of the lead salt (mp 112–116°) which was then dissolved in 500 ml of C_6H_6 and the solution was saturated with H_2S. The C_6H_6 solution was separated and concentrated, and the residue was dissolved in Et_2O. The HCl salt, formed by the addition of dry HCl, was recrystallized from EtOH–Et_2O to give 4.6 g (23%) of **43**, mp 243–246°.

2,2,2-Trifluoro-N-(2-mercaptoethyl)-N-octylacetamide.—To 70 g of trifluoroacetic anhydride was slowly added at *ca.* −50° with stirring 15 g (0.08 mole) of 2-(octylamino)ethanethiol.[23] The mixture was allowed to stir at 25° for 4 hr. Excess anhydride was removed at reduced pressure and a solution of the residue in MeOH was stored at 25° for 3.5 hr. The MeOH was evaporated and dilute $NaHCO_3$ was added to the residue. The slurry was extracted with Et_2O and the extract was washed successively with H_2O, saturated NaCl, dilute HCl, and again with saturated NaCl. The Et_2O solution was dried ($MgSO_4$) and concentrated to give 22 g of crude oil. Distillation resulted in 2 g of forerun and 15 g (66%) of product, bp 77–78° (0.05 mm).

Anal. ($C_{12}H_{22}F_3NOS$) C, H, N, SH.

5-(Hydroxymethyl)-2-pyrrolidinone.—A solution of 147 g (1.0 mole) of L-glutamic acid in 400 ml of H_2O containing 10 g of charcoal and 1 ml of aqueous perrhennic acid (1.5 g of Re/ml) was hydrogenated for 5 days at 200° under H_2 at about 300 atm. The mixture was filtered and the filtrate was concentrated and distilled to give 55.5 g (48%) of 5-(hydroxymethyl)-2-pyrrolidinone as a viscous liquid: bp 153–160° (0.25 mm) [lit.[24] bp 185–187° (4 mm)]; nmr ($CDCl_3$), δ 7.5 (m, 1, *NH*), 4.6 (m, 1, *OH*), 3.6 (m, 3, $CHCH_2O$), and 2.1 ppm (m, 4, CH_2CH_2).

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Molecular Orbital Methods in the Study of Cholinesterase Inhibitors

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It has been suggested that the ability of 3-hydroxyphenyltrimethylammonium derivatives (3-HPTA) to inhibit acetylcholinesterase competitively depends on the strength of the hydrogen bond between the 3-hydroxy group of these derivatives and the esteratic site of AChE. However, the results of previous simple Hückel calculations did not appear to be related to the observed inhibition constants. Using very empirical molecular orbital (MO) methods, we have calculated some σ and π properties of these derivatives and have obtained a correlation which is consistent with a hydrogen-bonding interaction between the 3-hydroxy group of these compounds and the AChE receptor site.

In recent years there has been a pronounced trend toward the application of molecular orbital (MO) methods to questions of pharmacological interest. Successful correlations of drug activity with one or more of the indices derived by these procedures have been reported for hallucinogens[2] and other neurotropic drugs,[3] for batericides[4] and bacteriostats,[5] for antidiuretics,[6] and, most notably, for cholinergic substances.[7–13]

Interestingly, the inhibition potency of 3-hydroxyphenyltrimethylammonium (3-HPTA) derivatives

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toward AChE does not appear to be related to any of the usual MO indices[14] obtained from the results of simple Hückel calculations.[15,16] Since the behavior of σ electrons is neglected in the usual simple Hückel method, this observation could be interpreted as indicating the dominant role played by σ electrons in the interaction of 3-HPTA derivatives with AChE. Significantly, Wilson and Quan[17] noted that the introduction of a hydroxyl group in the 3 position of phenyltrimethylammonium improves binding to AChE by a factor of 120. Such a large effect, which is equivalent to a decrease of 2.9 kcal/mole in the free energy of binding, suggests that a hydrogen bond is involved.[17] From a MO standpoint, hydrogen bonding to or from the 3-hydroxy group should be most strongly dependent on its σ-MO properties, because the electron pair and the proton on oxygen are both part of the 3-HPTA σ system.

To assess the relative influence of σ- and π-MO properties on this enzyme–inhibitor interaction, we have used a very empirical MO method[18,19] to calculate certain σ and π properties of 3-HPTA derivatives. The use of the method in our particular application is justified only insofar as it has been shown to be adequate for the calculation of charge-related properties of organic molecules[18–20] and by the results that we have obtained. More sophisticated MO methods,[21–27] and a more extensive series of 3-HPTA derivatives, may provide further insight into the nature of this enzyme–inhibitor interaction, but the conclusions of such studies most probably would be in general agreement with those presented in this work.

Results and Discussion

The parameters used for the calculations in both this and a previous[14] study are presented in Table I. A comparison of the parameters to those suggested by Streitwieser[16] indicates that certain of the parameters used in the earlier work[14] may have been in error. The Coulomb integral for the methyl group seems to be too high, and the Coulomb integral for the hydroxy oxygen seems to be too low. In contrast, there is good agreement between the π parameters recommended[19] for the method used in this study and those suggested by Streitwieser. Although we have arbitrarily assigned a Coulomb integral of 0.1 to the carbon adjacent to the trimethylammonium group, to take into account the inductive influence of this group on the π system,[28] no attempt was made to include hyperconjugation due to the methyl groups. The results of our calculations which are pertinent to the following discussion are presented in Table II.[29]

TABLE I
Hückel π Parameters

This work[a]				Previous work[b]			
Atom	h_X	Bond	k_{CX}	Atom	h_X	Bond	k_{CX}
C	0.0	C–C	1.0	C	0.0	C–C	1.0
				CH_3	3.0	C–CH_3	0.7
O	2.0	C–O	0.9	OH	1.0	C–OH	1.0
				OCH_3	1.8	C–OCH_3	0.9
C(N+)	0.1			C(N+)	0.1		

Parameters for σ Framework[18–20]

	Bond						
	C–H	O–H	C–C	C–N[+]	C_{ar}–C_{ar}	C–O	C_{ar}–O
ϵ_{rs}	1.00	0.45	1.00	1.33	1.00	0.95	0.95
γ_{rs}	0.3	0.3	0.1	0.1	0.1	0.1	0.1
γ_{ss}	0.4	0.4	0.1	0.1	0.1	0.1	0.1
δ_r^0	0.07	0.40	0.07	0.07	0.12	0.07	0.12
δ_s^0	0.00	0.00	0.07	0.31	0.12	0.40	0.40

The biological activities for a congeneric series of compounds, when compared to a number of possible physical variables, are often observed to bear no relation to any one of the variables taken independent of the others. In these cases, as Hansch has shown,[30] an appropriate linear combination of the independent variables may be necessary in order to make a correlation evident. Accordingly, in our attempts to relate the inhibition potencies ($pK_I = -\log K_I$) of the 3-HPTA derivatives to their calculated MO properties, multiple regression techniques were employed whenever possible. Since some question exists with regard to π parameter choice in the earlier work,[14] similar multiple regression equations were derived, when possible, using the data reported in the early work. The multiple regression equations obtained are presented together for comparison.

It must be noted that the method used for the calculation of the σ charges[18,19] prevents all of the charges from being considered simultaneously as independent variables in a multiple regression analysis. The σ charges are obtained following solution of sets of simultaneous equations, rather than, as for the π charges, from an orbital coefficient associated with independent MO's. The calculated σ charges are therefore strongly interrelated, and their improper use in a multiple regression analysis could result in an interaction between the terms of the model equation which subsequently would afford a meaningless correlation.[31]

In a preliminary analysis of the data, equations were selected that contained either the net π charge, Q^π, the nucleophilic π superdelocalizability, $S^{(N)}$,[32] or the electrophilic π superdelocalizability, $S^{(E)}$,[32] as independent variables. None of the equations selected correlated the data, but the equations containing terms associated with positions 1 and 3 (Table II) did

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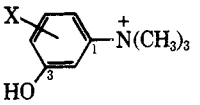
Table II
Inhibition Constants (pK_I), Acidity Constants (pK_a), and Calculated MO Quantities for Some 3-HPTA Derivatives



X	pK_a[a]	pK_I[a]	σ and π charges on positions[b] C1	C3	O of 3-OH	Superdelocalizabilities[c,d] C1	C3	O of 3-OH
4-CH_3	8.2	8.995	−0.039	0.034	0.075	0.835	0.805	1.063
			(0.055)	(0.116)	(−0.446)	(0.825)	(0.795)	(0.061)
6-CH_3	8.3	7.954	−0.041	0.035	0.075	0.835	0.805	1.062
			(0.053)	(0.119)	(−0.446)	(0.825)	(0.795)	(0.061)
5-CH_3	8.2	7.792	−0.037	0.037	0.075	0.830	0.799	1.061
			(0.055)	(0.119)	(−0.446)	(0.830)	(0.799)	(0.061)
6-OCH_3	8.6	7.716	−0.178	0.035	0.074	1.946	0.839	1.069
			(0.064)	(0.119)	(−0.446)	(1.254)	(0.839)	(0.070)
H	8.1	7.491	−0.037	0.037	0.075	0.830	0.799	1.061
			(0.056)	(0.119)	(−0.446)	(0.830)	(0.799)	(0.061)
4-OCH_3	8.0	6.068	−0.069	−0.001	0.071	0.950	0.939	1.094
			(0.056)	(0.127)	(−0.445)	(0.766)	(0.756)	(0.057)

[a] Data of ref 17. [b] σ charges in parentheses below π charges. [c] As defined in ref 32. [d] $S^{(N)}$ in parentheses below $S^{(E)}$.

seem to warrant further consideration. The respective equations (1–6) which were subsequently obtained are given below. Despite the poor fits

Previous work

$$pK_I = \underset{(-0.48)}{-23.10Q^{\pi}_1} + \underset{(0.85)}{55.10Q^{\pi}_3} + 3.86 \quad (F = 0.55, r = 0.52) \quad (1)$$

$$pK_I = \underset{(2.34)}{80.44S^{(N)}_1} - \underset{(-2.00)}{109.3S^{(N)}_3} + 23.21 \quad (F = 3.13, r = 0.82) \quad (2)$$

$$pK_I = \underset{(0.35)}{6.90S^{(E)}_1} - \underset{(-0.63)}{10.88S^{(E)}_3} + 10.49 \quad (F = 0.60, r = 0.53) \quad (3)$$

This work

$$pK_I = \underset{(0.36)}{2.09Q^{\pi}_1} + \underset{(2.31)}{59.98Q^{\pi}_3} + 6.33 \quad (F = 2.76, r = 0.80) \quad (4)$$

$$pK_I = \underset{(-1.72)}{-6.06S^{(N)}_1} + \underset{(2.24)}{54.02S^{(N)}_3} - 30.01 \quad (F = 2.59, r = 0.79) \quad (5)$$

$$pK_I = \underset{(0.26)}{0.18S^{(E)}_1} - \underset{(-2.52)}{14.31S^{(E)}_3} + 19.37 \quad (F = 3.19, r = 0.82) \quad (6)$$

indicated by the tests of significance,[33] it should be noted that, in general, improved correlations are obtained using the π–MO quantities calculated in this study.

On the basis of the t test for the first term in each of equations 1–6, this term was deleted and a least-squares analysis was used to obtain the best straight line for each of the remaining independent variables. For comparison, the total of the σ and π net charges Q^T at position 3 was similarly treated. The resulting equations (7–13) are given below. The tests of significance for eq 11–13 show no improvement over those

Previous work

$$pK_I = 27.07Q^{\pi}_3 + 6.45 \quad (F = 1.07, r = 0.46) \quad (7)$$

$$pK_I = 13.29S^{(N)}_3 - 1.99 \quad (F = 0.36, r = 0.29) \quad (8)$$

$$pK_I = -5.07S^{(E)}_3 + 11.92 \quad (F = 1.38, r = 0.50) \quad (9)$$

This work

$$pK_I = 59.19Q^{T}_3 - 1.18 \quad (F = 4.34, r = 0.72) \quad (10)$$

$$pK_I = 50.27Q^{\pi}_3 + 6.18 \quad (F = 6.89, r = 0.79) \quad (11)$$

$$pK_I = 18.62S^{(N)}_3 - 7.18 \quad (F = 1.49, r = 0.52) \quad (12)$$

$$pK_I = -14.05S^{(E)}_3 + 19.34 \quad (F = 8.23, r = 0.82) \quad (13)$$

for eq 4–6. In one instance, however, lower tests of significance are obtained (compare eq 5 and eq 12), which suggests that with a larger number of 3-HPTA derivatives the pK_I might be found to be dependent on both $S^{(N)}_1$ and $S^{(N)}_3$. If this is the case, the contribution of $S^{(N)}_1$ could be ascribed to the interaction of the trimethylammonium group with the anionic site of AChE, while the contribution of $S^{(N)}_3$ could indicate the concurrent participation of the 3 position in a second interaction.

To gain an indication of the possible nature of the species interacting with positions 1 and 3, a model equation was used that contained as independent variables Q^{π}, $S^{(N)}$, and $S^{(E)}$.[34] Multiple regression analysis yielded eq 14 and 15. The apparently

$$pK_I = \underset{(2.35)}{38.63Q^{\pi}_1} + \underset{(2.34)}{11.88S^{(N)}_1} - 0.29 \quad (F = 2.85, r = 0.81) \quad (14)$$

$$pK_I = \underset{(-4.16)}{-1307.00Q^{\pi}_3} + \underset{(4.19)}{229.37S^{(N)}_3} - \underset{(-4.35)}{296.37S^{(E)}_3} + 109.66 \quad (F = 19.16, r = 0.98) \quad (15)$$

equivalent contributions of Q^{π}_1 and $S^{(N)}_1$ in eq 14 suggests that position 1 is interacting with a negatively charged group of the AChE receptor. This group seems to interact with the π charge at position 1 and apparently further interacts by polarizing the π cloud

(33) The F test indicates the significance of the equation; the multiple correlation coefficient r indicates the "goodness of fit;" and the t test (value in parenthesis found below each variable) indicates the contribution of each term to the correlation obtained.

(34) Theoretical justification for equations of this form will be presented in a later paper.

at this position. In contrast, position 3 appears to be undergoing a polarization interaction with an electrophile (see below) as indicated by the favorable contributions of $S^{(E)}{}_3$ and $Q^{\pi}{}_3$ in eq 15.

A comparison of eq 5 and 12 previously suggested that $S^{(N)}{}_3$ makes a contribution to the binding of 3-HPTA derivatives with AChE. Based on eq 14 and 15, however, it seems more suitable to interpret the contribution of $S^{(N)}{}_3$ in eq 5 as reflecting the ability of the π-electron pair on the 3-hydroxy oxygen to conjugate with position 3.

Equations similar to eq 14 and 15 were used to assess the contribution made by the 3-hydroxy group in the inhibition of AChE. Multiple regression analysis gave the highly satisfactory correlations shown in eq 16–18. A comparison of the tests of significance

$$\begin{matrix} pK_I = & -6561Q^{\pi}{}_o & - & 806S^{(E)}{}_o & + & 164S^{(N)}{}_o & + & 1347 \\ & (-2.88) & & (-3.10) & & (2.46) & & \end{matrix}$$
$$(F = 9.67,\ r = 0.99) \quad (16)$$

$$\begin{matrix} pK_I = & -4007Q^{\sigma}{}_o & + & 54S^{(E)}{}_o & - & 47S^{(N)}{}_o & - & 1835 \\ & (-6.09) & & (-2.73) & & (-2.09) & & \end{matrix}$$
$$(F = 38.60,\ r = 0.99) \quad (17)$$

$$\begin{matrix} pK_I = & -2695Q^{T}{}_o & - & 289S^{(E)}{}_o & + & 34S^{(N)}{}_o & - & 686 \\ & (-7.96) & & (-9.81) & & (2.10) & & \end{matrix}$$
$$(F = 65.05,\ r = 0.99) \quad (18)$$

(F test and t test) makes it readily apparent that the σ charge on oxygen controls the interaction of the 3-hydroxy group with the AChE receptor. Of particular note is the contribution of $S^{(N)}{}_o$ in eq 18, for although the magnitude of its coefficient is small, the t test indicates that its contribution is at least as significant as $Q^{T}{}_o$.

The good correlation obtained with eq 18 makes it possible to estimate the relative importance of $S^{(E)}{}_3$ (eq 15) in the interaction. The t test on $S^{(N)}{}_o$ in eq 18 indicates this term is of lesser importance; hence, it was deleted and replaced by $S^{(E)}{}_3$ to yield eq 19. The

$$\begin{matrix} pK_I = & -2925Q^{T}{}_o & - & 581S^{(E)}{}_o & + & 62S^{(E)}{}_3 & - & 509 \\ & (-7.21) & & (-3.59) & & (1.88) & & \end{matrix}$$
$$(F = 55.89,\ r = 0.99) \quad (19)$$

t test indicates the contribution of $S^{(E)}{}_3$ is minor. Therefore, the simplest equation which correlates the data is given by eq 20.

$$\begin{matrix} pK_I = & -2571Q^{T}{}_o & - & 283S^{(E)}{}_o & - & 645 \\ & (-5.27) & & (-6.58) & & & \end{matrix}$$
$$(F = 44.44,\ r = 0.98) \quad (20)$$

Conclusions.—Equations 1–15, although they fit the data poorly, seem to be suitable for qualitative indications of the nature of the interactions between 3-HPTA derivatives and AChE. Position 1 is indicated as interacting with a negative group on AChE, and, in light of the correlations provided by eq 18–20, position 3 is correctly indicated as interacting with an electrophilic species. On the basis of these equations, however, it is not possible to make a quantitative statement regarding the relative magnitudes of the interactions or whether the interactions are attractive or repulsive in nature. A more extensive series of compounds might make such a quantitative assessment possible.

The good correlations given by eq 18–20 are more amenable to a quantitative interpretation. For this purpose, it is convenient to describe the interactions suggested by these equations in terms of a proposal first offered by Debye.[35] According to Debye, a bonding interaction which is primarily electrostatic in origin may be given, to higher orders of approximation, by a power series expansion: the first term is Coulomb's law and the second term contains the atomic polarizabilities of the bonding atoms. Thus, the first term of eq 18–20 may be considered as representing a charge–charge interaction between the 3-hydroxy oxygen and an atom of the AChE receptor, while the following terms may be considered as representing the charge–polarizability interactions accompanying the formation of an ionic bond. Since the dependent variable pK_I is a measure of free energy, each of the terms in eq 18–20 represents contributions to the free energy of binding and may be interpreted accordingly.

A comparison of eq 16–18 reveals the σ-charge on oxygen makes the most important contribution to the free energy of binding. The negative sign associated with this term indicates an attractive interaction. A minor, but important, contribution to the free energy of binding results from the polarization of the π cloud on the 3-hydroxy oxygen by an electrophilic species (indicated by $S^{(E)}{}_o$). It seems reasonable to assume that the same electrophilic species that polarizes the π cloud on oxygen is also interacting with the σ charge on oxygen. Following Wilson and Quan,[17] if the electrophilic species is identified as a proton or as a proton donor, the indicated interaction has the characteristics expected of a hydrogen bond. The bond which is formed appears to be slightly destabilized by repulsions (indicated by the positive signs of $S^{(E)}{}_3$ and $S^{(N)}{}_o$ in eq 18 and 19). The repulsions could be due to the interaction of the electrophilic species in the bond with the π cloud at position 3 and to the interaction of an electronegative atom (possibly also bonded to the electrophilic species) associated with the AChE receptor with the π cloud on oxygen. For the compounds considered, the repulsive interactions are of relatively little importance. Therefore, the bonding interaction leading to inhibition of AChE is sufficiently described by eq 20.

A hydrogen-bond distance is usually in the range of 2.5–2.7 A.[36] The interpretation which has been given for the terms in eq 16–18, if reasonable, should allow an estimate of the bond distance between the 3-hydroxy oxygen and the AChE receptor atom. For this purpose, eq 20 should be sufficient. Expressing the free energy of binding ΔG° by

$$\Delta G^{\circ}/RT = pK_I = aQ^{T}{}_o + bS^{(E)}{}_o + c \quad (21)$$

a charge–charge interaction would require that

$$a = Q_r e^2/RT\epsilon_{ro}D_{ro} \quad (22)$$

while a charge–polarizability or charge–induced dipole interaction would require[37] that

$$b = Q_r e^2 k/RT\epsilon_{ro}D_{ro}{}^4 \quad (23)$$

In eq 22 and 23, Q_r is the net charge of the electrophilic species interacting with the net charge $Q^{T}{}_o$, D_{ro} is the

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distance separating the charges, ϵ_{ro} is the effective dielectric between the charges, e is the electrostatic unit of charge, and RT has its usual significance. The quantity k in eq 23 is included as a parameter defining the relation between electronic polarizability α[35] and the π superdelocalizability $S^{(E)}$. That is, it is assumed that

$$\alpha = kS^{(E)} \quad (24)$$

The ratio of the coefficients of eq 20, according to equations 21–23, is given by

$$a/b = 2571/283 = D_{ro}^3 \quad (25)$$

in which it is assumed that k is equal to 1. The bond distance is therefore

$$D_{ro} = 2.08 \text{ Å} \quad (26)$$

which is of the same order of magnitude as could be assigned to a hydrogen bond. Thus, despite the crude nature of the MO calculations on which eq 20 is based, the *relative* magnitudes of the coefficients in this equation are not unreasonable from a physical standpoint. The *absolute* magnitudes of the coefficients, however, may be greatly in error.

It should be noted that the correlation provided by eq 20 gives no indication of whether the 3-hydroxy group is functioning as a proton donor or a proton acceptor. Either mode of bonding is consistent with the correlation obtained. This work, however, provides substantiating evidence for the dominant mode of interaction of 3-HPTA derivatives with AChE and indicates a method whereby hydrogen-bonding interactions may be investigated in biological systems.

N-*sec*- and N-*t*-Alkyl Derivatives of Methoxamine and Related Compounds[1]

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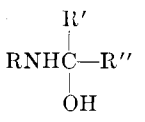
A number of N-*sec*- and N-*t*-alkyl derivatives derived from or related to methoxamine [*erythro*-α-(2,5-dimethoxyphenyl)-β-aminopropanol] have been prepared. Some of these compounds exhibited the physiological properties of "β-blockers" and antiarrhythmic agents. Several had a marked tendency to lower the blood levels of glucose and free fatty acids. *In vivo* N-*sec*-alkyl compounds were found to be degraded metabolically to the parent methoxamine (among other products) but the N-*t*-alkyl system was stable as regards this degradation. The *sec*-alkyl derivatives were prepared mainly by reductive alkylation of methoxamine, *t*-alkyl compounds from the appropriate amine and bromo ketone followed by reduction. When reductive alkylation created a third point of asymmetry, the physiologically inferior enantiomeric pair D-alkylamino-(−)-methoxamine–L-alkylamino-(+)-methoxamine was formed preferentially. Some conclusions are possible as to the spatial requirements of "receptor" sites.

Methoxamine [*erythro*-α-(2,5-dimethoxyphenyl)-β-aminopropanol] has been regarded pharmacologically as a pure α-adrenergic stimulant. Interest having been expressed as to the fashion in which this property would be altered by, *e.g.*, N-isopropyl substitution, a considerable number of such derivatives were prepared by reductive alkylation of methoxamine base in the presence of available aliphatic ketones, cycloalkanones, and aromatic aldehydes.

In these reactions, the aromatic aldehydes probably form Schiff's bases but the ketones presumably give only alkylolamines



by an equilibrium reaction. When methoxamine base was allowed to stand overnight in the presence of excess acetone before reduction, about one-third of the calculated amount of hydrogen was absorbed rapidly and the remaining two-thirds quite slowly. As might be expected, reactions with the other aliphatic ketones were much slower, presumably corresponding largely to slower formation of alkylolamine (and less favorable equilibria in that step).

The reductions with aromatic aldehydes proceeded rapidly and in good yield. There was no evidence for formation of tertiary amines which had seemed possible *a priori*. Data on the compounds of these types are presented in Tables I and II. No physiological properties of serious interest were found among the benzylamino and cycloalkylamino derivatives.

The compound first prepared, N-isopropylmethoxamine (I), was first regarded as a β-adrenergic blocker. Further investigation revealed more complicated behavior and interest centered on two properties. The first of these was the ability to restore normal sinus rhythm to hearts in which this had been disturbed by a number of stimuli (*cf.* ref, 1b, 1c, and especially 1h).

This antiarrhythmic activity was manifested by a number of the higher analogs of isopropylmethoxamine

(1) This paper reports part of a joint investigation carried out in collaboration with the Pharmacology Department of these laboratories. Detailed discussions of the pharmacological findings will be published separately. Preliminary reports that have appeared are (a) S. Norton and F. Soroko, *Fed. Proc.*, **21**, 417 (1962); (b) C. H. Ellis and S. Norton, 22nd International Congress of Physiological Sciences, Leiden, 1962; *Excerpta Med., Intern. Congr. Ser.*, **48**, 1205 (1962); (c) C. H. Ellis and S. Gross, *Fed. Proc.*, **22**, 247 (1963); (d) R. A. Salvador, K. I. Colville, L. A. Lindsay, and J. J. Burns, *ibid.*, **22**, 508 (1963); (e) K. I. Colville, L. A. Lindsay, R. A. Salvador, and J. J. Burns, *ibid.*, **23**, 542 (1964); (f) R. A. Salvador, K. I. Colville, S. A. April, and J. J. Burns, *J. Pharmacol. Exp. Ther.*, **144**, 172 (1964); (g) J. J. Burns, K. I. Colville, L. A. Lindsay, and R. A. Salvador, *ibid.*, **144**, 163 (1964); (h) C. H. Ellis, *Arch. Int. Pharmacodyn. Ther.*, **150**, 144 (1964); (i) J. J. Burns, K. I. Colville, L. A. Lindsay, S. A. April, and R. A. Salvador, *Pharmacologist*, **6**, 186 (1964); (j) J. J. Burns and L. Lemberger, *Fed. Proc.*, **24**, 298 (1965); R. A. Salvador and S. A. April, *ibid.*, **24**, 298 (1965); (k) K. I. Colville, L. A. Lindsay, and J. J. Burns, *Pharmacologist*, **7**, 178 (1965); (l) R. A. Salvador, S. A. April, and L. Lemberger, *ibid.*, **8**, 181 (1966); (m) R. A. Salvador, S. A. April, and L. Lemberger, *Fed. Proc.*, **25**, 500 (1966).