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Quantum Chemical Studies on Drug Action V: Involvement of Structure–Activity, Quantum Chemical, and Hydrophobicity Factors in Thrombocyte Uptake of 5-Hydroxytryptamine

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Abstract □ Inhibition of the uptake of 5-hydroxytryptamine (serotonin) in the thrombocyte by various tryptamine derivatives was investigated. The activity depended on the nature and position of the substituent. This activity was correlated with the total orbital energy and hydrophobicity factors. Other quantum parameters, such as the highest occupied molecular orbital energy and the lowest empty molecular orbital energy, failed to correlate. The possible involvement of two receptor sites that are sterically and electronically dissimilar is postulated because compounds fell into two distinct groups. The hydrophobicity factor was important in only one group of compounds, while the electronic factor was important in both.

Keyphrases □ 5-Hydroxytryptamine—uptake by thrombocytes correlated with structure–activity, quantum chemical, and hydrophobicity factors, effect of various tryptamine derivatives □ Thrombocytes—uptake of 5-hydroxytryptamine correlated with structure–activity, quantum chemical, and hydrophobicity factors, effect of various tryptamine derivatives □ Structure–activity factors—correlated with 5-hydroxytryptamine uptake by thrombocytes □ Quantum chemical factors—correlated with 5-hydroxytryptamine uptake by thrombocytes □ Hydrophobicity—correlated with 5-hydroxytryptamine uptake by thrombocytes □ Tryptamine—derivatives, effect on 5-hydroxytryptamine uptake by thrombocytes

In the past decade, quantum chemistry has been widely applied in pharmacology and medicinal chemistry, mainly to investigate drug activity. Even though the limitations of molecular orbital calculations have been recognized for many years, the various quantum parameters such as the highest occupied molecular orbital energy, the lowest empty molecular orbital energy, frontier electron density, and superdelocalizability have been correlated with observed activities (1, 2).

The highest occupied molecular orbital energy has been studied extensively because of its relation to the electron-donating ability. However, recent work (3) in molecular pharmacology has begun to show the inadequacy of the application of this concept without other physicochemical parameters. Molecular structure, hydrophobicity, and conformational details are also important determinants.

Quantum chemical data on about 50 derivatives of catechol, indole, imidazole, and lysergamide was reported previously (4, 5). This paper reports the effect of several structural analogs (Table I) of 5-hydroxytryptamine (serotonin) on its uptake by rabbit platelets. These data are further analyzed in terms of quantum chemical indexes and the hydrophobicity of these analogs.

EXPERIMENTAL

New Zealand albino male rabbits, approximately 6–12 months old, were used. The incubation experiments were carried out as follows. Blood was drawn from the rabbits by cardiac puncture. Enough edetate disodium solution (adjusted to pH 7.4 with sodium hydroxide) was added to give a final concentration of 1 mg of edetate/ml of blood. Platelet-rich plasma was obtained by centrifuging the blood at $50\times g$ for approximately 30 min. All operations were carried out using siliconized vessels at 2°.

Two milliliters of platelet-rich plasma was incubated with ^{3}H-5-hydroxytryptamine creatinine sulfate[1] (0.1 mmole = 2.5 mCi of ^{3}H-5-hydroxytryptamine) and appropriate amounts of an analog. The mixture was incubated at 37° for 30 min. Then the incubates were centrifuged at $500\times g$ to sediment the platelets. The sedimented platelet pellet was washed two times with 5 ml of saline.

The final platelet pellet was frozen overnight. The following morning, enough water was added to the platelet preparation to yield a 1.0-ml suspension. The turbidity of the platelets was measured[2] at 660 nm. The radioactivity of the platelet preparation was counted in a liquid scintillation spectrometer. The ratio of the radioactivity to the turbidity is a relative measure of the uptake of 5-hydroxytryptamine per unit volume of the platelet.

All analogs studied had either no activity or had inhibitory activity on the uptake of 5-hydroxytryptamine by the rabbit platelets. The ED_{50} (effective dose producing 50% inhibition) values of these drugs were determined by varying the concentration of the analog used over a wide range. A curve was plotted for each drug as shown in Fig. 1. The ED_{50} and/or ED_{25} (effective dose producing 25% inhibition) values for the analogs were obtained from these plots. The ED_{50} values are (I/S) ratios.

The quantum parameters, the highest occupied molecular orbital energy, the lowest empty molecular orbital energy, the highest superdelocalizability, the total orbital energy[3] (calculated by summing the energies of the occupied orbitals and multiplying the sum by two to account for the double occupancy), and the π–π^* transition energy[4], were obtained using the Hückel method with the omega technique (6, 7) for the hyperconjugation model as described previously (3–5). The log P values, which measure the lipophilicity or the hydrophobicity, were calculated using the published values of Hansch *et al.* (8). The calculated quantum parameters, log P values, and experimental activities (ED_{50}) are listed in Table I.

[1] Amersham Searle.
[2] Beckman DU spectrophotometer.
[3] Total orbital energy is the same as the total π-electron energy.
[4] The π–π^* transition also has been referred to as "LEMO-HOMO" or $\Delta M\beta$.

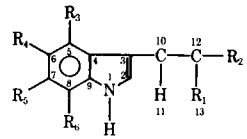

Table I—Structures and ED_{50}, log *P*, and Quantum Chemical Data for the Compounds Studied

Compound	R_1	R_2	R_3	R_4	R_5	R_6	HOMO β^{-1} [a]	LEMO β^{-1} [b]	HFED [c]	HSUP β [d]	TOE β^{-1} [e]	π–π^*	ED_{50}	log *P*
1	H_2	$N(C_2H_5)_2$	NH_2	H	H	H	0.318	−0.982	0.3198 at 2	2.0812 at R_3	42.480	1.300	7.5	2.27
2	H_2	$N(CH_3)_2$	NH_2	H	H	H	0.318	−0.982	0.3198 at 2	2.0812 at R_3	34.496	1.300	26.0	1.35
3	H_2	NH_2	NH_2	H	H	H	0.318	−0.982	0.3198 at 2	2.0812 at R_3	26.298	1.300	12.5	0.23
4	H_2	$N(C_2H_5)_2$	H	OH	H	OH	0.395	−0.969	0.4505 at 5	1.8962 at $N(R_2)$	48.620	1.364	84.0	2.83
5	H_2	$N(C_2H_5)_2$	H	OCH_3	H	OCH_3	0.392	−0.966	0.4554 at 5	1.8962 at $N(R_2)$	56.694	1.358	30.0	3.46
6	H_2	$N(C_2H_5)_2$	H	H	H	OH	0.423	−0.950	0.4378 at 3	1.8962 at $N(R_2)$	44.318	1.373	—	—
7	H_2	$N(C_2H_5)_2$	H	H	H	OCH_3	0.420	−0.947	0.4278 at 3	1.8967 at 15	48.356	1.367	18.0	3.48
8	H_2	NH_2	H	OH	OH	H	0.399	−0.962	0.464 at 2	1.948 at $N(R_2)$	32.422	1.361	22.5	0.72
9	H_2	NH_2	H	OH	H	OH	0.395	−0.969	0.4507 at 5	1.9482 at $N(R_2)$	32.426	1.364	48.5	0.12
10	H_2	NH_2	H	OCH_3	H	OCH_3	0.392	−0.966	0.4556 at −5	1.9485 at $N(R_2)$	40.510	1.358	9.5	1.42
11	H_2	$N(CH_3)_2$	H	OH	H	OH	0.395	−0.969	0.4505 at 5	1.8897 at $N(R_2)$	40.630	1.364	42.5	1.24
12	H_2	$N(CH_3)_2$	H	OCH_3	H	OCH_3	0.392	−0.966	0.4554 at 5	1.8897 at $N(R_2)$	48.704	1.358	9.3	2.54
13	H_2	$N(CH_3)_2$	H	H	H	OH	0.423	−0.950	0.4379 at 3	1.8897 at $N(R_2)$	36.330	1.373	46.0	1.91
14	H_2	$N(CH_3)_2$	H	H	H	OCH_3	0.420	−0.947	0.4278 at 3	1.8897 at $N(R_2)$	40.364	1.367	—	—
15	H_2	NHC_2H_5	H	OCH_3	H	OCH_3	0.392	−0.966	0.4555 at 5	1.916 at $N(R_2)$	48.612	1.358	9.0	1.98
16	H_2	NHC_2H_5	H	H	H	OH	0.423	−0.950	0.4380 at 3	1.9160 at $N(R_2)$	36.232	1.373	6.0	1.81
17	H_2	NHC_2H_5	H	H	H	OCH_3	0.420	−0.947	0.4280 at 3	1.9160 at $N(R_2)$	40.272	1.367	9.0	2.46
18	H_2	NH_2	OH	H	H	H	0.376	−0.966	0.430 at 3	1.670 at 3	28.806	1.342	12.0	0.79
19	H_2	NH_2	H	H	OH	H	0.388	−0.948	0.489 at 3	1.680 at 3	28.796	1.336	19.0	0.79
20	H_2	NH_2	H	H	H	OH	0.423	−0.950	0.438 at 3	1.948 at $N(R_2)$	28.128	1.373	18.0	0.79
21	H_2	$NHCH_3$	H	OCH_3	H	OCH_3	0.392	−0.966	0.4555 at 5	1.9122 at $N(R_2)$	44.614	1.358	8.0	2.44
22	H_2	$NHCH_3$	H	OH	H	H	0.454	−0.914	0.5151 at 3	1.9122 at $N(R_2)$	32.230	1.368	1.9	1.35
23	H_2	$NHCH_3$	H	H	H	OCH_3	0.420	−0.947	0.4280 at 3	1.9122 at $N(R_2)$	36.278	1.367	3.5	2.00
24	NH_2	COOH	H	OH	OH	H	−0.320	−0.964	1.109 at 12	1.6051 at 2	39.452	0.644	—	—
25	NH_2	COOH	OH	H	H	H	−0.320	−0.955	1.1009 at 12	1.5422 at 2	34.846	0.635	—	—
26	NH_2	COOH	H	H	OH	H	−0.320	−0.937	1.1009 at 12	1.5515 at 2	34.832	0.617	—	—
27	NH_2	COOH	H	H	H	OH	−0.320	−0.952	1.1009 at 12	1.5187 at 3	34.842	0.632	—	—
28	H_2	$NHCH_3$	NH_2	H	H	H	0.318	−0.982	0.3198 at 2	2.0812 at R_3	30.410	1.300	35.4	0.79
29	H_2	NH_2	H	OCH_3	H	H	0.453	−0.913	0.514 at 3	1.948 at R_2	32.156	1.366	36.0	1.44
30	DL-α-Methyl-*m*-tyrosine						−0.084	−1.010	0.7078 at 10	1.0220 at 7	31.708	0.926	—	—
31	COOH	NH_2	H	OCH_3	H	H	−0.320	−0.915	1.1009 at 12	1.5134 at 3	38.868	0.595	—	—
32	L-3-Methylhistidine						−0.319	−1.077	1.1002 at 10	1.4602 at 3	29.243	0.758	—	—
33	COOH	NH_2	H	OH	H	H	−0.286	−0.893	1.064 at 12	1.4480 at 3	34.912	0.607	—	—
34	L-Histidine						−0.319	−1.113	1.1003 at 8	1.4478 at 3	25.203	0.794	—	—
35	DL-Norepinephrine						−0.316	−1.114	1.148 at 7	1.932 at NH_2	27.824	0.798	—	—
36	H_2	NH_2	H	CH_3	H	H	0.470	−0.896	0.521 at 3	1.948 at R_2	27.656	1.366	—	—
37	Spermine						0.681	−1.504	0.505 at —NH— and —NH—	1.947 at —NH_2, —NH—, —NH—, and NH_2	49.624	2.185	—	—
38	Histamine						0.519	−1.103	0.670 at 5	1.948 at —NH_2	18.492	1.622	—	—
39	COOH	NH_2	H	H	H	H	−0.286	−0.893	1.064 at 12	1.465 at 3	30.60	0.607	—	—
40	H_2	NH_2	H	H	H	H	0.444	−0.903	0.514 at 3	1.531 at 3	24.482	1.347	—	—

[a] Highest occupied molecular orbital energy. [b] Lowest empty molecular orbital energy. [c] Highest frontier electron density. [d] Highest superdelocalizability. [e] Total orbital energy.

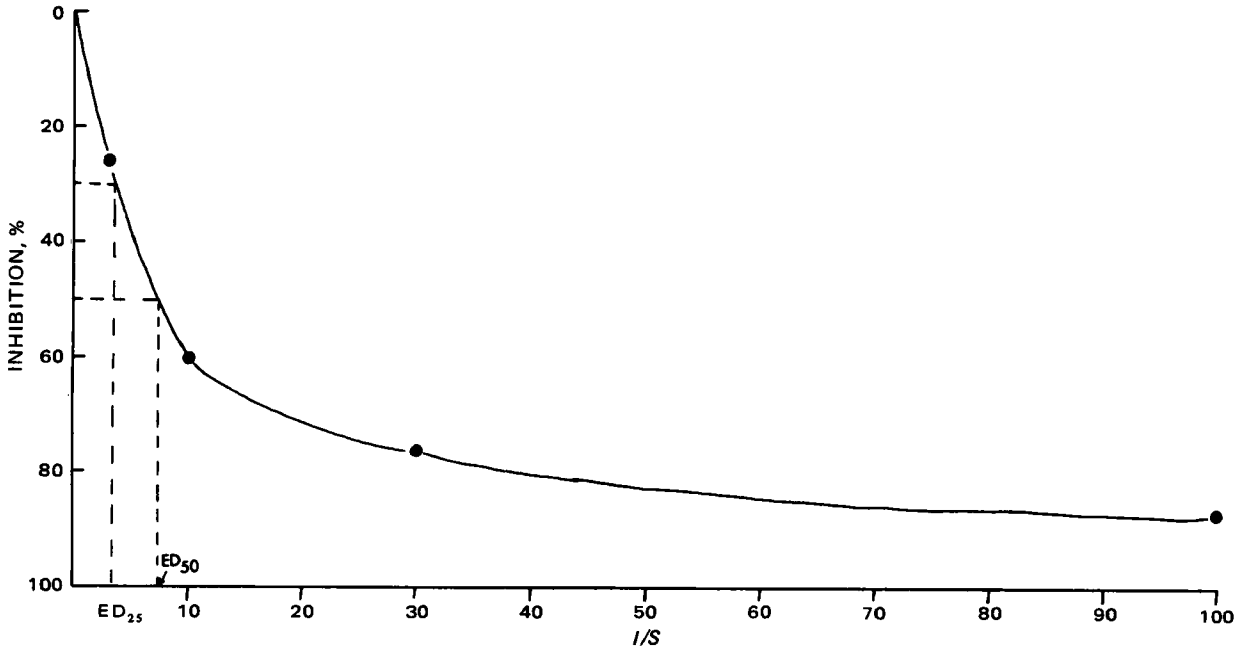

Figure 1—*Plot of percent inhibition* versus *the* I/S *ratio (*I = *concentration of inhibitor, and* S = *concentration of substrate). The* ED_{50} *and* ED_{25} *values are shown by the dotted lines. Only the* ED_{50} *values were calculated in the present investigation (Table I).*

RESULTS

The highest occupied molecular orbital energy, lowest empty molecular orbital energy, highest superdelocalizability, π–π^* transition energy, and highest frontier electron density did not correlate with the observed activity (ED_{50}). But the total orbital energy did correlate with the activity. Figure 2 shows the plot of log ED_{50} *versus* the total orbital energy. The data distinctly separated into upper and lower groups. Moreover, a linear relationship was observed between the points within each group and the total orbital energy, which might be attributed to the similar behavior of the compounds in each group.

A least-squares analysis of Fig. 2 yields the following equations. For the upper group:

$$\log ED_{50} = 0.1399 + 3.415 \times 10^{-2} \text{ total orbital energy} \qquad \begin{matrix} n & r & s \\ 12 & 0.832 & 0.141 \end{matrix} \qquad \text{(Eq. 1)}$$

For the lower group:

$$\log ED_{50} = -0.7982 + 3.947 \times 10^{-2} \text{ total orbital energy} \qquad \begin{matrix} n & r & s \\ 11 & 0.884 & 0.148 \end{matrix} \qquad \text{(Eq. 2)}$$

In addition, the log ED_{50} was correlated with the log (total orbital energy). The least-squares equation for the upper group is:

$$\log ED_{50} = -2.952 + 2.908 \log (\text{total orbital energy}) \qquad \begin{matrix} n & r & s \\ 12 & 0.851 & 0.134 \end{matrix} \qquad \text{(Eq. 3)}$$

For the lower group, it is:

$$\log ED_{50} = -5.539 + 3.954 \log (\text{total orbital energy}) \qquad \begin{matrix} n & r & s \\ 11 & 0.893 & 0.142 \end{matrix} \qquad \text{(Eq. 4)}$$

From the calculated correlation coefficients, it appears that the log–log plot yields a slightly better correlation. In any event, both methods lead to a separation of the data into two distinct groups.

Figure 3 shows the plot of the activity *versus* the log P or the hydrophobicity of the derivatives tested. Surprisingly, the data again separated into two distinct groups. And the compounds fell into the same groups as in the total orbital energy correlation (Fig. 2). Therefore, the separation is apparently not artificial. The least-squares equations for the lipophilicity relationship are as follow. For the upper group:

$$\log ED_{50} = 1.215 + 0.223 \log P \qquad \begin{matrix} n & r & s \\ 12 & 0.650 & 0.190 \end{matrix} \qquad \text{(Eq. 5)}$$

For the lower group:

$$\log ED_{50} = 7.899 \times 10^{-2} + 0.361 \log P \qquad \begin{matrix} n & r & s \\ 11 & 0.801 & 0.189 \end{matrix} \qquad \text{(Eq. 6)}$$

The poor correlation of the upper group may indicate that the hydrophobicity of these compounds plays a minor role in the drug activity mechanism. On the other hand, the hydrophobicity might be significant for the lower group of compounds as shown by the degree of correlation.

The experimental activity was further analyzed in terms of both total orbital energy and log P to assess the degree of electronic and hydrophobic interactions. Multiple regression analysis (9) of these data produced the following equations. For the upper group:

$$\log ED_{50} = \underset{(\pm 0.038)}{-3.581} + \underset{(\pm 0.939)}{3.363} \log (\text{total orbital energy}) - \underset{(\pm 0.094)}{0.0554} \log P \qquad \begin{matrix} n & r & s \\ 12 & 0.856 & 0.132 \end{matrix} \qquad \text{(Eq. 7)}$$

For the lower group:

$$\log ED_{50} = \underset{(\pm 0.033)}{-3.275} + \underset{(\pm 0.842)}{2.324} \log (\text{total orbital energy}) + \underset{(\pm 0.092)}{0.226} \log P \qquad \begin{matrix} n & r & s \\ 11 & 0.938 & 0.109 \end{matrix} \qquad \text{(Eq. 8)}$$

The numbers in the parentheses represent the standard error of the estimate for the respective coefficients. Thus, by comparing Eqs. 3 and 4 with Eqs. 7 and 8, respectively, it is clear that the inclusion of the hydrophobicity factor does not lead to an improvement for the upper group of compounds. However, a slight improvement is observed for the lower group of compounds, reconfirming that the hydrophobicity makes a lesser contribution to the activity of the upper group.

DISCUSSION

From the observed experimental activities (Table I), it is seen that both the side chain and ring substituents are important in deciding the inhibitory activity on the uptake of 5-hydroxytryptamine. If the side-chain substituents are bulky, for example, $R_2 = N(C_2H_5)_2$, the activity decreases. The higher the ED_{50} value, the lower is the inhibitory activity.

A further decrease in inhibitory activity occurs when two hydroxyl groups are substituted on the ring. That is, two hydroxyl groups are more effective in reducing the activity than a single hydroxyl, a single methoxy, or two methoxy groups. The activity also varies according to the position of the hydroxyl groups. For example, the ED_{50} values

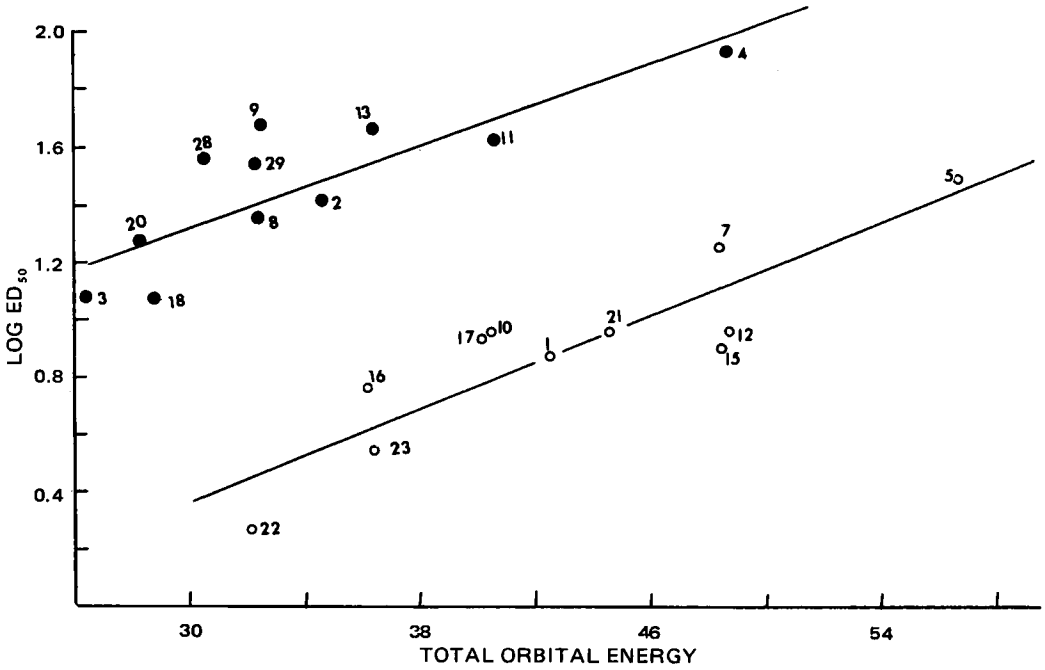

Figure 2—*Plot of log ED_{50}* versus *the total orbital energy. The numbers on the graph correspond to the compound numbers in Table I. The straight lines are the least-squares lines (Eqs. 1 and 2).*

of 6-hydroxytryptamine (Compound 19), 7-hydroxytryptamine (Compound 20), 5,6-dihydroxytryptamine (Compound 8), and 5,7-dihydroxytryptamine (Compound 9) are 19.0, 18.0, 22.5, and 48.5, respectively.

Various molecular orbital studies indicated extended (10) or folded (11) or extended and folded (12, 13) conformations to be the stable forms for 5-hydroxytryptamine. A recent empirical method study (14) also predicted two preferred (the most stable form) conformations (extended and folded, which are sterically different) for 5-hydroxytryptamine. These two stable conformations were also predicted by an NMR solution study (15). In the empirical study (14), it was suggested that these two stable conformations might correspond to two 5-hydroxytryptamine receptor sites. In the present study, the separation of compounds into two distinct groups (Figs. 2 and 3) may be a clear indication that two receptor sites of a sterically and electronically dissimilar nature are involved. Thus, one group of compounds might inhibit 5-hydroxytryptamine on the same site, so the correlation between them is possible.

It is generally accepted that anti-5-hydroxytryptamine activity is the result of the blocking of 5-hydroxytryptamine by a drug molecule at 5-hydroxytryptamine receptor sites. The drug molecule may bind to the receptor site(s) blocking the complexing of 5-hydroxytryptamine. However, this kind of drug–receptor binding may not be the only process that ultimately leads to inhibition.

Snyder (1) utilized the concept of structural resemblance to understand biological activities such as hallucinogenic activity. He tried to explain, with the help of this concept, the hallucinogenic activities of various indolealkylamine and amphetamine derivatives. He proposed that the latter derivatives achieve a conformation similar to a portion of the lysergic acid diethylamide (lysergide) molecule in order

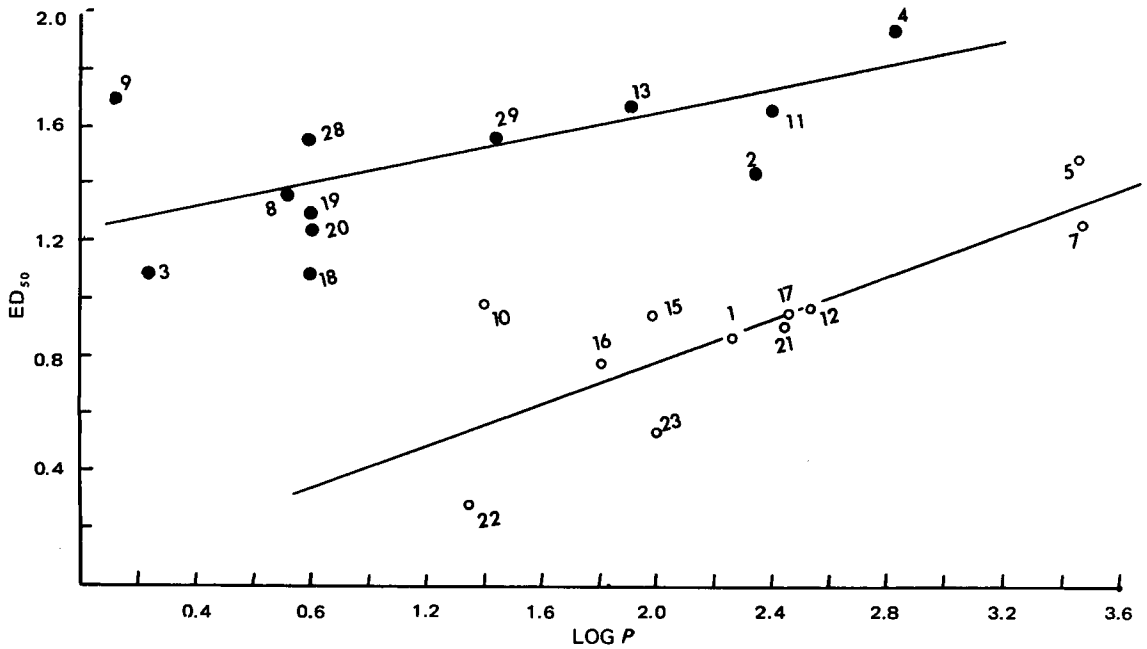

Figure 3—*Plot of log ED_{50}* versus *log* P. *The numbers on the graph correspond to the numbers in Table I. The straight lines are the least-squares lines (Eqs. 5 and 6).*

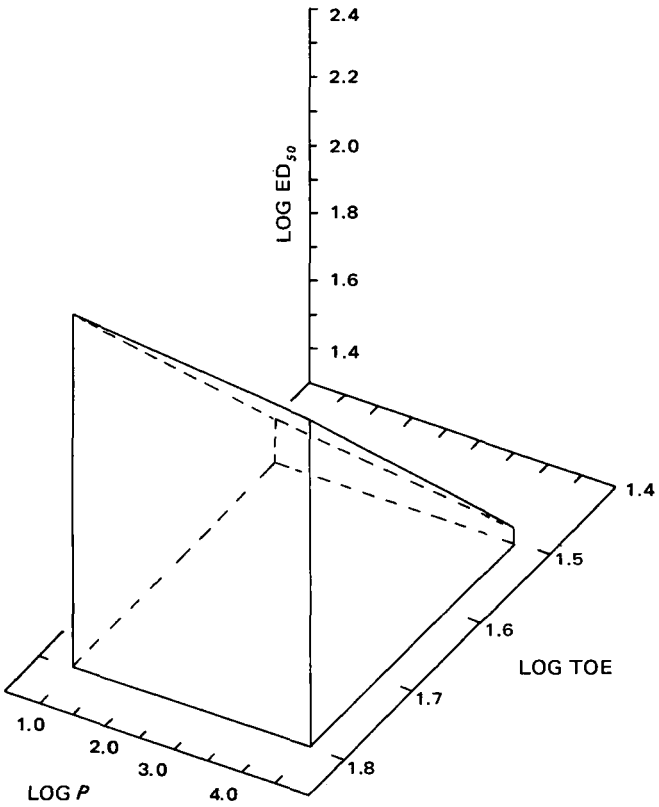

Figure 4—*Structure–activity surface generated by Eq. 7. (TOE = total orbital energy.)*

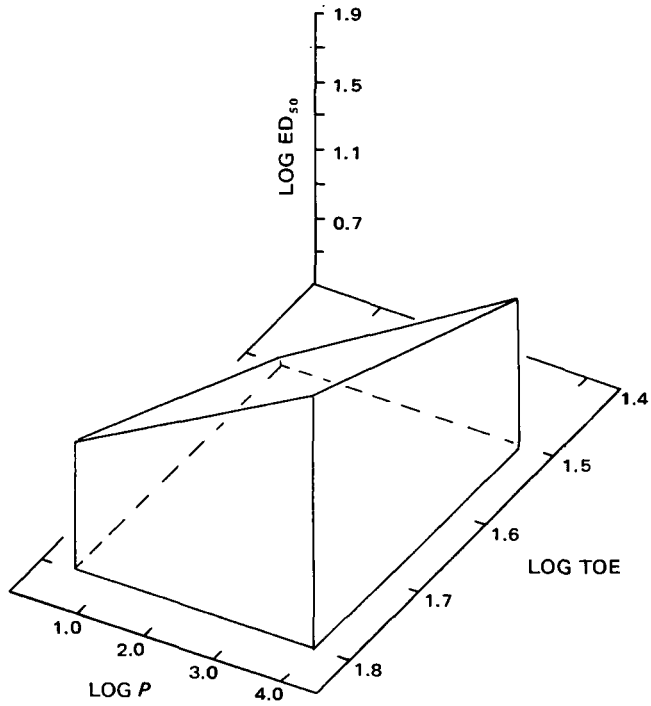

Figure 5—*Structure–activity surface generated by Eq. 8. (TOE = total orbital energy.)*

to elicit the hallucinogenic response. This hypothesis was supported by X-ray work (16).

The same idea also can be extended to the inhibitory activity of the tryptamine derivatives studied here. Furthermore, the conformational resemblance of a molecule can be related to its observed activity. Under biological conditions, the interaction of 5-hydroxytryptamine with the receptor site(s) may not occur in only the previously mentioned preferred conformations. Moreover, the minimum energy conformations, as determined by X-ray (16) and other methods (10–14), may not necessarily be the conformations at the receptor site (17). However, due to a lack of knowledge about the receptor site conformations, it is postulated that the two preferred conformations of 5-hydroxytryptamine are responsible for its action.

Evidence for an electronic dissimilarity of the previously mentioned two receptor sites may be obtained as follows. Cammarata (18) applied the Arrhenius equation to biological activity:

$$\log A = -\Delta E/2.303RT + c \qquad \text{(Eq. 9)}$$

where R is the gas constant, T is the absolute temperature, ΔE is the change in energy, and c is a constant. In Eq. 9, A reflects an equilibrium or a rate constant for the formation of a drug–receptor complex. The ΔE can be assumed to be the sum of the various contributions (18), such as:

$$\Delta E = \Delta E^e + \Delta E^d + \Delta E^s + \Delta E^p \qquad \text{(Eq. 10)}$$

where ΔE^e, ΔE^d, ΔE^s, and ΔE^p are the changes in electronic, solvation, steric, and conformational energies, respectively. More generally, Eq. 10 can be written as:

$$\Delta E = a_1 \Delta E^e + a_2 \Delta E^d + a_3 \Delta E^s + a_4 \Delta E^p \qquad \text{(Eq. 11)}$$

where a_1, a_2, a_3, and a_4 are coefficients. By substituting Eq. 11 into Eq. 9, the following equation is obtained:

$$\log A = -\frac{1}{2.303RT}(a_1 \Delta E^e + a_2 \Delta E^d + a_3 \Delta E^s + a_4 \Delta E^p) + c \qquad \text{(Eq. 12)}$$

Since the observed activity was correlated with the total orbital energy, ΔE^e can be represented by the total orbital energy. Thus, the final activity relationship takes the form:

$$\log A = -(2.303RT)^{-1}(a_1\beta)\,(\text{total orbital energy}) + (a_2' \Delta E^d + a_3' \Delta E^s + a_4' \Delta E^p + c') \qquad \text{(Eq. 13)}$$

where β is the resonance integral, and the constant $-(2.303RT)^{-1}$ has been absorbed in a_2', a_3', a_4', and c'.

Information on the electronic dissimilarity of both groups of compounds can be obtained by evaluating the coefficient a_1. To do so, it is necessary to have the information on the second term of Eq. 13. Since it is difficult to obtain such information, as a first approximation the second term is treated as constant. Moreover, it is assumed that the sum given in the second term remains constant even though each term in the sum might change. By comparing Eq. 13 with Eqs. 1 and 2, the first term in Eq. 13 is evaluated. For the upper group:

$$-\frac{a_1\beta}{2.303RT} = 3.415 \times 10^{-2} \qquad \text{(Eq. 14a)}$$

For the lower group:

$$-\frac{a_1\beta}{2.303RT} = 3.947 \times 10^{-2} \qquad \text{(Eq. 14b)}$$

And for the upper group:

$$a_2' \Delta E^d + a_3' \Delta E^s + a_4' \Delta E^p + c' = 0.1399 \qquad \text{(Eq. 15a)}$$

For the lower group:

$$a_2' \Delta E^d + a_3' \Delta E^s + a_4' \Delta E^p + c' = -0.7982 \qquad \text{(Eq. 15b)}$$

Since the experimental activities was derived at the physiological temperature of 37°, the values of R (2 cal/deg mole) and T (310°K) are substituted in Eqs. 14a and 14b. Then the value of $a_1\beta$ for the upper group is:

$$-a_1\beta = 48.761 \text{ cal/mole} \qquad \text{(Eq. 16a)}$$

For the lower group, it is:

$$-a_1\beta = 56.357 \text{ cal/mole} \qquad \text{(Eq. 16b)}$$

The value of the resonance integral, β, has frequently been taken as −18.0 kcal/mole for hydrocarbons (6). However, this value changes depending upon the chemical structure involved. A lengthy discussion regarding this parameter may be found in Ref. 6. As a first approximation, it is assumed that −18.0 kcal/mole is also applicable to indole systems. Then for the upper group:

$$a_1 = 27.089 \times 10^{-4} \qquad \text{(Eq. 17a)}$$

And for the lower group:

$$a_1 = 31.309 \times 10^{-4} \qquad \text{(Eq. 17}b\text{)}$$

The constant a_1, which is the coefficient of ΔE^e, might be related to an electronic factor associated with the change in the electronic energy. Hence, it is clear from the magnitude of a_1 (Eqs. 17*a* and 17*b*) or $-a_1\beta$ (Eqs. 16*a* and 16*b*) that both groups of compounds do not experience similar electronic interactions. Therefore, from this analysis, together with the apparent existence of two sterically different stable conformations, one can speculate that groups of compounds falling on the same line (upper or lower) might behave electronically and sterically similarly while acting on the same site.

The influence of electronic and hydrophobic interactions can be assessed by considering Eqs. 3–6. From the correlation coefficients of these equations, it is evident that the hydrophobic interactions are not significant in the upper group of compounds whereas they are important in the lower group. This difference can be explained in terms of the nature of the substituents. The lower group of compounds has one or two methoxy groups present on the ring portion (except Compounds 1, 16, and 22), and all of them (except Compound 10) carry a side-chain substituent. These groups (methyl, ethyl, and methoxy) present on the side chain as well as on the ring portion might engage in hydrophobic interactions.

On the other hand, the upper group of compounds carries hydroxyl and amino substituents (except Compound 29) on the ring portion, and only a few of them carry side-chain amino substituents. The hydroxyl and amino groups have much smaller hydrophobicity factors (8) compared to a methoxy group. Apart from that, the average lipophilicity of the upper and lower groups is 1.033 ± 0.756 and 2.292 ± 0.671, respectively. These values indicate that hydrophobicity does not play a large role in the upper group of compounds.

Figures 4 and 5 show the activity surface generated by Eqs. 7 and 8, respectively. For the upper group (Fig. 4), the influence of log P for a given total orbital energy is smaller, but it is larger for the lower group (Fig. 5).

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Carbon-13 Magnetic Resonance Spectroscopy of Drugs II: Antihistamines

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Abstract □ The natural abundance carbon-13 magnetic resonance spectra of a series of antihistamines (pheniramine, chlorpheniramine, methapyrilene, tripelennamine, pyrilamine, and thonzylamine) were determined using the pulse Fourier transform technique. The chemical shifts were assigned with the aid of long-range carbon-13–hydrogen coupling constants.

Keyphrases □ Magnetic resonance spectroscopy, carbon-13—various antihistamines, spectra determined using pulse Fourier transform technique □ Antihistamines—carbon-13 magnetic resonance spectra determined using pulse Fourier transform technique □ Fourier transform technique—carbon-13 magnetic resonance spectra of various antihistamines

Histamine has continuously received great attention from chemists and biologists (1). This interest is stimulated by the variety and potency of its biological effects, *e.g.*, activities in the cardiovascular system, smooth muscle contraction, and gastric acid and other exocrine gland secretions. Numerous drugs antagonize the action of histamine at its cellular site of action.

According to the classical receptor theory, the biological effect of histamine and antihistamines is the result of physicochemical interactions with the receptor sites. Any successful attempt to correlate these receptor interactions with the configuration and conformation of the drug must rely on detailed studies of the structural chemistry of antihistamines. Great effort has been made recently to characterize these compounds by various physical techniques (2–7).

The development of the Fourier transform technique has added a new tool for the study of the structure and conformation of organic molecules in solution and, potentially, when bound to receptors. Carbon-13 magnetic resonance (CMR) spectroscopy (8–11) increasingly is being directed to the study of drugs (12–20). A detailed