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# QUANTUM CHEMICAL STUDIES ON DRUG ACTIONS

## III. Correlation of Hallucinogenic and Anti-serotonin Activity of Lysergic Acid Derivatives With Quantum Chemical Data

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ABSTRACT: The models proposed to explain the hallucinogenic activity of several psychedelic drugs, based on the indolyl-like structure of rings A, B, C, and D of LSD-25 are not adequate in explaining the wide variation in biological activities of lysergates. The quantum parameters of forty-two lysergates are reported. These data point out the relation between the total orbital energy and hallucinogenic activity of some lysergates. The correlation of HOMO energy with pharmacological activity is not meaningful. A model for the LSD-molecule with electron delocalization giving rise to effectual partial pi bonding over the rings is postulated. Of the several derivatives studied, branching in the hydrocarbon substituent in the amide group (N-19) results in significant change in HOMO energy. The effect of substituting one or both the hydrogens in the amide group is contrasted and a mathematical equation generated for the monosubstituent amide. Toxicity and pyretogenic activity did not correlate with the quantum mechanical parameters.

INTRODUCTION: There have been numerous investigations regarding the pharmacological action of d-lysergic acid diethylamide (LSD-25 or LSD) and other compounds which are very similar to it. Among all the pharmacological actions that have been studied, hallucinogenic (H) and anti-serotonin (anti-5HT) effects of LSD and its derivatives or its congeners have drawn most attention. Reviews on this subject may be found elsewhere (Sankar, 1973). The main interest lies in an understanding of the mechanism of action of hallucinogenic or anti-5HT action in terms of the molecular structure under existing biological conditions. Such an ideal study is very complex in nature and becomes almost impossible to handle due to limitations of availability of modern methods and equipments. In spite of this handicap, few studies have been advanced with an aim to understand the conformational structure of the molecule and its relation to the hallucinogenic or anti-5HT property. (Snyder, 1970; Baker et al, 1973, and Kang and Green, 1970). Chothia and Pauling (1969) have used the x-ray analysis of some salts of LSD. Snyder and his group have used the molecular models. Green and his associates (1970) have utilized the molecular orbital calculations. Even though these three group of workers have used the different techniques in their studies, the basic idea in all of them is the same; namely, that a conformational analogy between indoles and hallucinogens may be implicated in the action of a given hallucinogen. These models have been useful in explaining the hallucinogenic activity of LSD and non-lysergate psychoactive compounds. It is proposed that, the compounds like amphetamine and its derivatives, or tryptamine derivatives elicit the hallucinogenic response by assuming the conformation of LSD molecule. The degree of response may depend,

however, on the ability of the molecules to approximate the conformation of the amine and/or of LSD-25.

The above-mentioned theories have primarily been developed to explain the hallucinogenic activity. However, Chothia and Pauling (1969) have extended the same idea to explain the anti-5HT action of LSD molecule. Even though the idea of conformational resemblance between indoles and LSD is conceivable, it is questionable that this hypothesis is adequate in explaining the activities of LSD and its many substituent lysergate derivatives.

The present paper concentrates on the correlation between structure, quantum parameters and biological activities of the several lysergate derivatives.

METHOD: The methods used in the present investigation have been described previously (Kumbar, Sankar, 1972). In brief, the HOMO energy and LEMO energy, electronic charges, bond orders are computed by the procedure given by Pullman and Pullman (1963). The highest frontier electron density (Fukui et al, 1954 and 1957) and highest superdelocalizability (Fukui et al, 1951) for electrophilic reaction only are obtained. The positions of these parameters in each compound have been indicated in Table II. The $\pi - \pi^*$ transition is listed in the last column of this Table. The distribution of electron densities and the bond orders have been reproduced for all the compounds. In each compound, the first and the second figures respectively indicate the electron densities and the bond orders.

RESULTS: The available data on the several biological activities of the lysergate derivatives are shown in Table I. Table II contains the energy and the structural indices for the forty-two LSD deriva-

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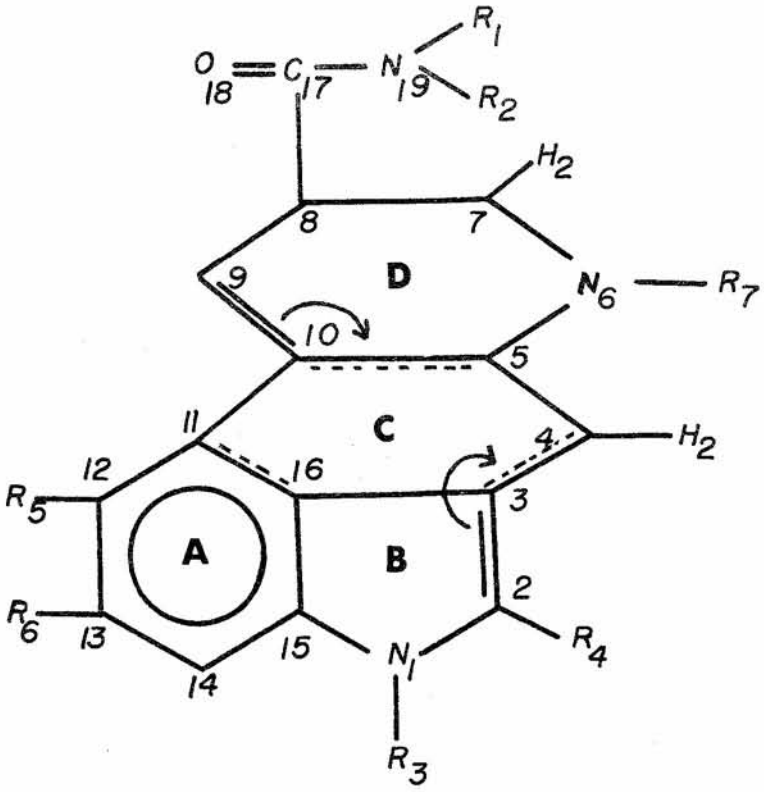


Fig.1

Numbering and substitutions in the lysergate series of compounds. The dotted lines indicate the possible shifting of double bonds as shown by arrows.

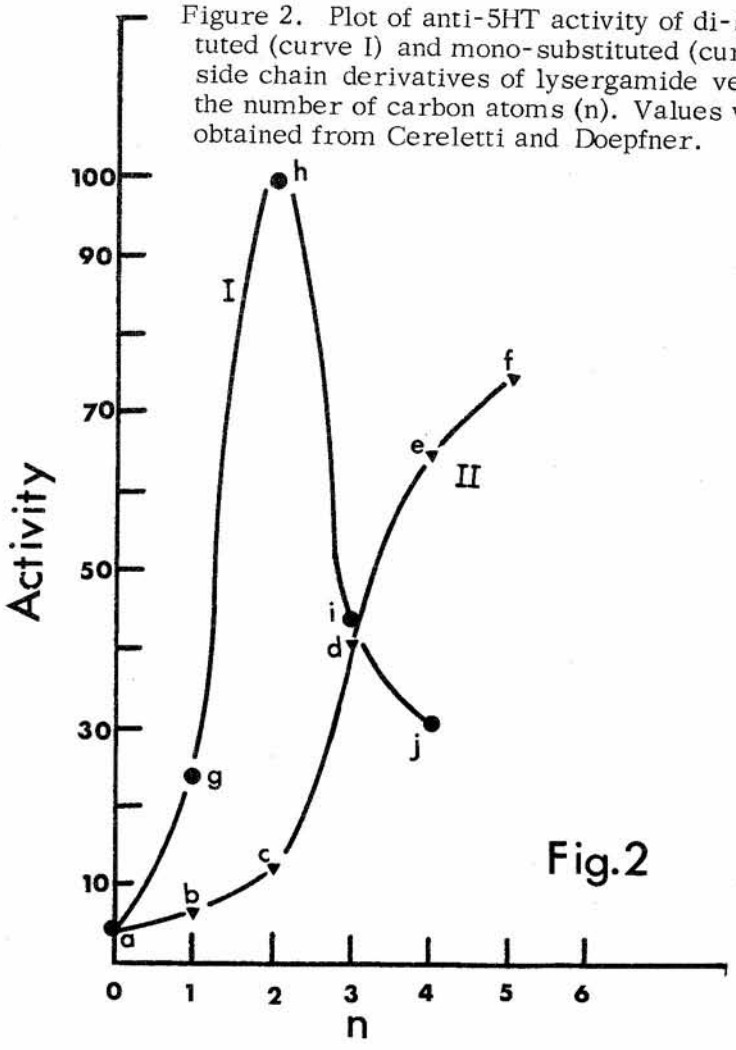


Figure 2. Plot of anti-5HT activity of di-substituted (curve I) and mono-substituted (curve II) side chain derivatives of lysergamide versus the number of carbon atoms (n). Values were obtained from Cereletti and Doepfner.

tives. The LEMO energy values for all the compounds (except compound #2) are merely the same indicating that all these compounds have comparable electron acceptor ability. The HOMO energy values for all the compounds are also close to one another except the compounds numbered 2,7,8,24,25,26,27,28,29 and 30 which indicate that these derivatives are the better electron donors than the rest of the compounds in their neutral and planar configuration.

The nature of the compounds that are deviant in their HOMO energy values is interesting to note. Compound 2 is obtained by substituting N-6 with a carbon atom. In other words, this is not a tryptamine derivative, but a propylindolyl derivative. Compound 7 is obtained by substituting with iodine at carbon 2. Substitution with chlorine or bromide did not alter the properties radically whereas substitution with iodine did alter the HOMO energy significantly. This could be due to the considerable difference between iodine and the other halogens. Compound 8 has a carbonyl function on carbon 2 and again displays a different value for the HOMO energy. Coming to compounds 24,25,26,27,28,29 and 30, one would notice that these compounds are obtained by substitution in the side chain. These substituents are mostly branched substituents and are considerably bulky. The properties of these compounds are also quite different. For example, compound 29 is UML-491. UML has four times the anti-serotonin activity of LSD, but 0.6% of the hallucinogenic activity of LSD. The difference in the HOMO energy of UML and LSD is striking. Comparing the HOMO and the LEMO energy values of the LSD derivatives with those of the serotonin, it is clear that LSD and its derivatives are better electron donors as well as acceptors. The highest frontier electron density and

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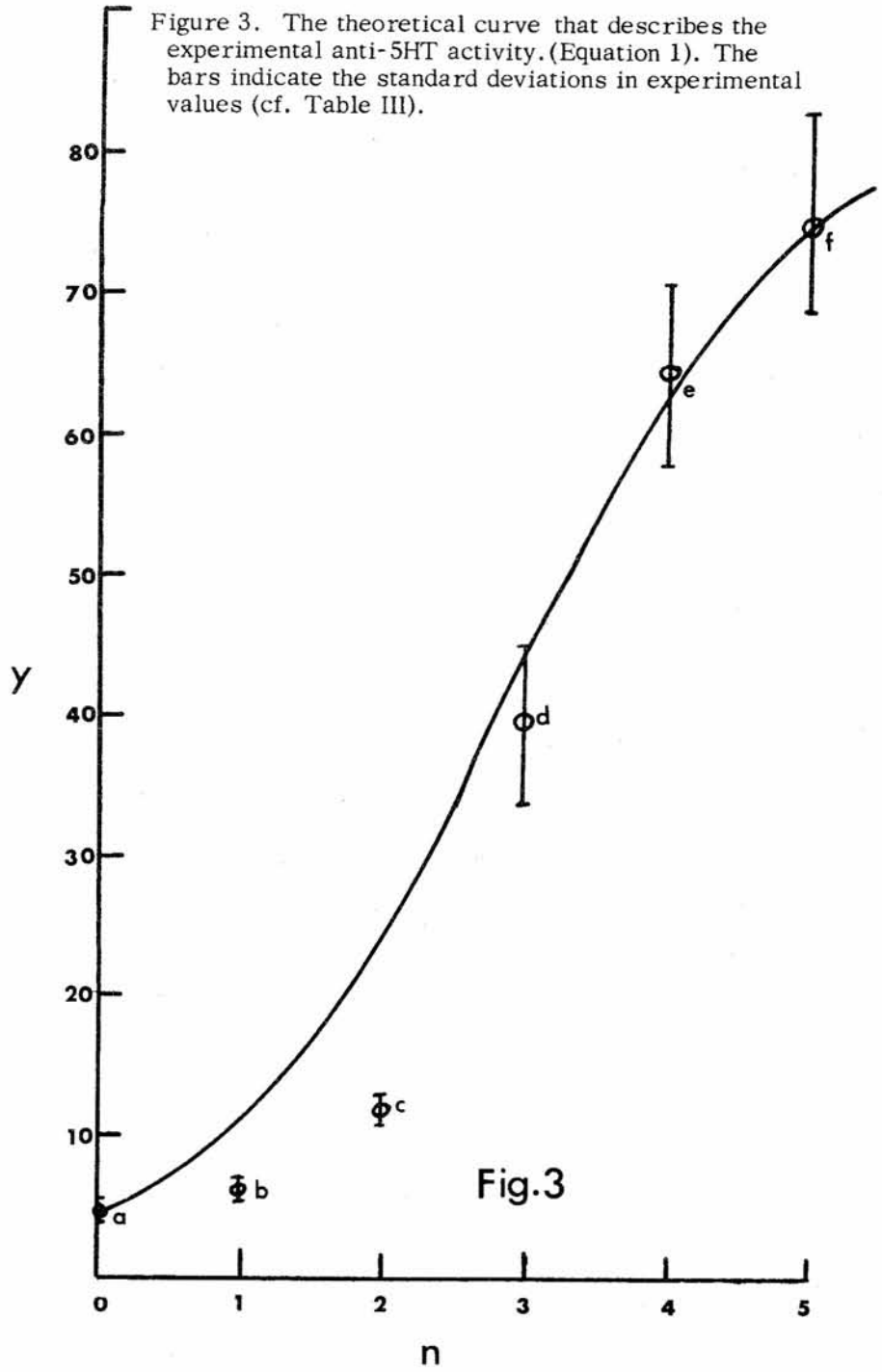
Figure 3. The theoretical curve that describes the experimental anti-5HT activity. (Equation 1). The bars indicate the standard deviations in experimental values (cf. Table III).



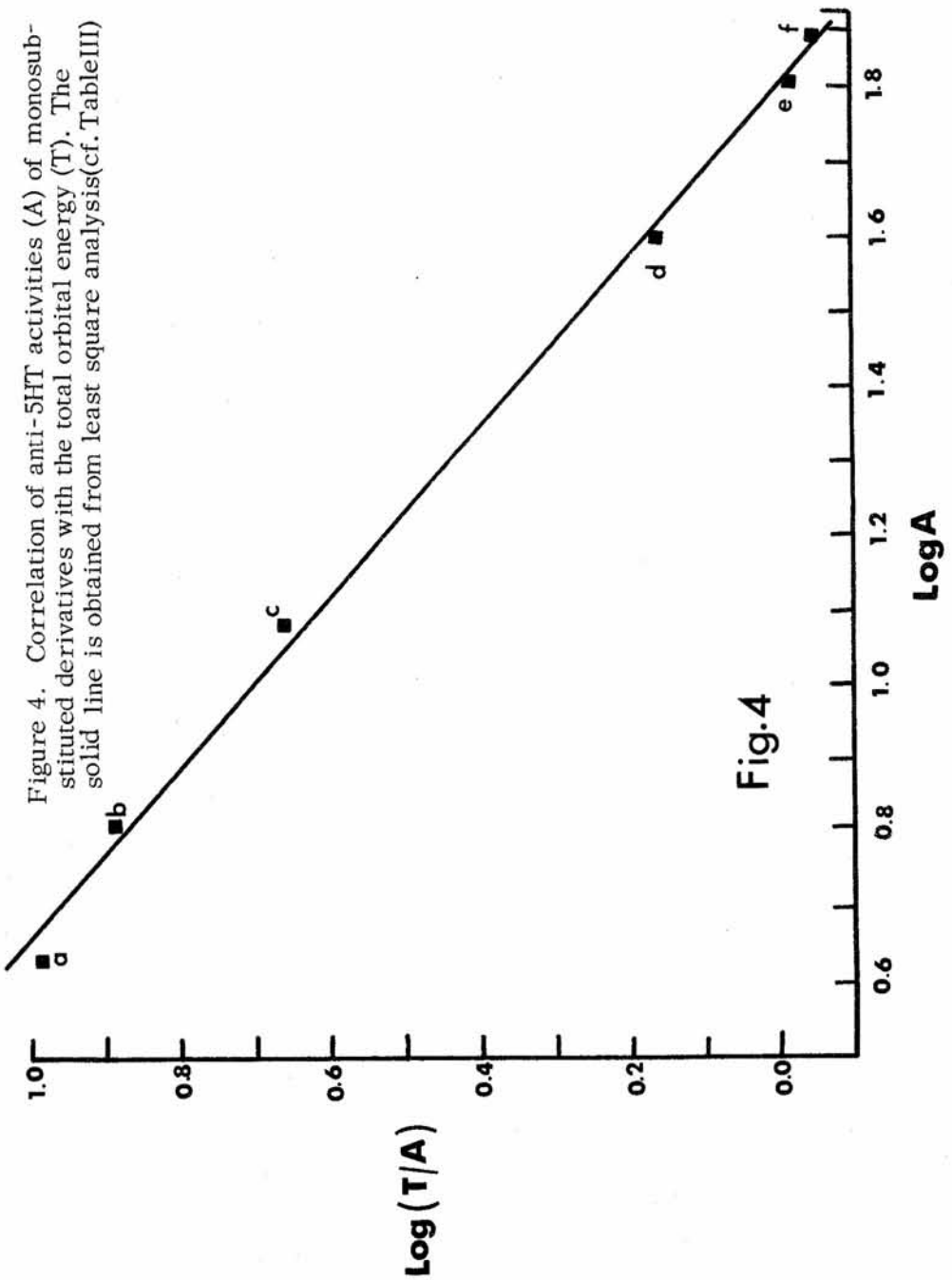



Figure 4. Correlation of anti-5HT activities (A) of monosubstituted derivatives with the total orbital energy (T). The solid line is obtained from least square analysis(cf. TableIII)

Fig.4

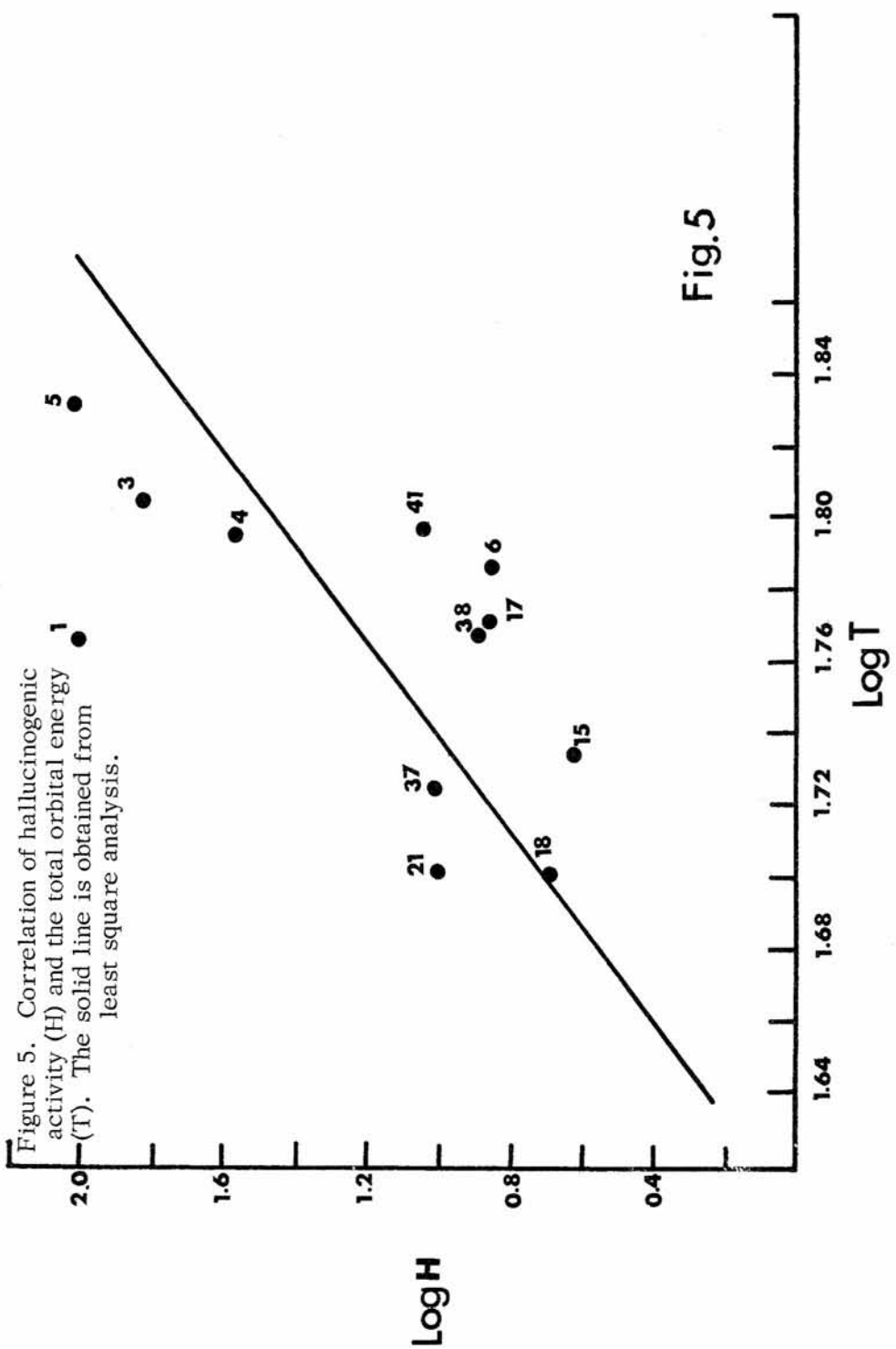



Fig.5

Figure 5. Correlation of hallucinogenic activity (H) and the total orbital energy (T). The solid line is obtained from least square analysis.

TABLE I

STRUCTURE AND SEVERAL BIOLOGICAL ACTIVITIES OF LYSERGATES

| Compound No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Hallucinogenic Activity | Pyretogenic Effect | Anti-5HT | Excitation Syndrome | Toxicity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_2H_5$ | $C_2H_5$ | H | H | H | H | $CH_3$ | 100 | 100 | 100 | Yes | 100 |
| 2 | $C_2H_5$ | $C_2H_5$ | H | H | H | H | $CH_3$ ($N6=C_6$) | | | | | |
| 3 | $C_2H_5$ | $C_2H_5$ | $OCH_3$ | H | H | H | $CH_3$ | 66 | | 58.9 | | |
| 4 | $C_2H_5$ | $C_2H_5$ | $CH_3$ | H | H | H | $CH_3$ | 33,36,40 | 5 | 370 | Yes | 5.6 |
| 5 | $C_2H_5$ | $C_2H_5$ | $COCH_3$ | H | H | H | $CH_3$ | 91,100 | 13 | 200,210 | Yes | 19 |
| 6 | $C_2H_5$ | $C_2H_5$ | H | Br | H | H | $CH_3$ | <2,7.2 | 5 | 103,150 | no | 5 |
| 7 | $C_2H_5$ | $C_2H_5$ | H | I | H | H | $CH_3$ | | | 57.4 | | |
| 8 | $C_2H_5$ | $C_2H_5$ | H | O | H | H | $CH_3$ | | | | | |
| 9 | $C_2H_5$ | $C_2H_5$ | H | OH | H | H | $CH_3$ | | | | | |
| 10 | $C_2H_5$ | $C_2H_5$ | $CH_3$ | Br | H | H | $CH_3$ | <1 | 0.0 | 533 | no | 2 |
| 11 | $C_2H_5$ | $C_2H_5$ | H | H | $OCH_3$ | H | $CH_3$ | | | | | |
| 12 | $C_2H_5$ | $C_2H_5$ | H | H | H | $OCH_3$ | $CH_3$ | | | | | |
| 13 | $C_2H_5$ | $C_2H_5$ | H | H | H | H | $CH_2OH$ | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | $C_2H_5$ | $CH_2CH_2OH$ | H | H | H | H | $CH_2OH$ | | | | | |
| 15 | H | $C_2H_5$ | $CH_3$ | H | H | H | $CH_3$ | 4.0,5.0 | 0.0 | 835 | Yes | 3.2 |
| 16 | H | $C_2H_5$ | $OCH_3$ | H | H | H | $CH_3$ | | | | | |
| 17 | H | $C_2H_5$ | $COCH_3$ | H | H | H | $CH_3$ | 5,7 | 1.0 | 39 | Yes | 6 |
| 18 | H | $C_2H_5$ | H | H | H | H | $CH_3$ | 3.4,5 | 17 | 12 | Yes | 34 |
| 19 | H | H | H | H | H | H | $CH_3$ | 0.0 | | 4.0,4.3 | | |
| 20 | H | $CH_3$ | H | H | H | H | $CH_3$ | | | 6.3 | | |
| 21 | $CH_3$ | $CH_3$ | H | H | H | H | $CH_3$ | 10 | 43 | 23.2 | Yes | 78 |
| 22 | $CH_2OH$ | $CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 23 | $CH_2OH$ | $CH_2OH$ | $CH_3$ | H | H | H | $CH_3$ | | | | | |
| 24 | H | $CH(CH_3)CH_3$ | H | H | H | H | $CH_3$ | | | | | |
| 25 | H | $CH(CH_3)CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 26 | H | $CH_2CH(CH_3)-CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 27 | H | $CH_2CH_2CH-(CH_3)CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 28 | H | $CH(C_2H_5)-CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 29 | H | $CH(C_2H_5)-CH_2OH$ | $CH_3$ | H | H | H | $CH_3$ | 0.6 | | 400 | | |

TABLE I

STRUCTURE AND SEVERAL BIOLOGICAL ACTIVITIES OF LYSERGATES

| Compound No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Hallucinogenic Activity | Pyretogenic Effect | Anti-5HT | Excitation Syndrome | Toxicity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | H | $CH(C_2H_5)$-$CH_2Cl$ | H | H | H | H | $CH_3$ | | | | | |
| 31 | H | $CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 32 | H | $CH_2CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 33 | H | $CH_2CH_2Cl$ | H | H | H | H | $CH_3$ | | | | | |
| 34 | H | $CH_2CH_2$-$CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 35 | H | $CH_2CH_2$-$CH_2CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 36 | H | $CH_2CH_2CH_2$-$CH_2CH_2OH$ | H | H | H | H | $CH_3$ | | | | | |
| 37 | $-CH_2-CH=CH-CH_2-$ | | H | H | H | H | $CH_3$ | 10 | | 4.1,5 | | |
| 38 | $-C_2H_4-C_2H_4-$ | | H | H | H | H | $CH_3$ | 5.3,10 | 10 | 5 | Yes | 73 |
| 39 | $-C_2H_4-C_2H_4-$ | | $CH_3$ | H | H | H | $CH_3$ | <5,7 | 0 | 130 | Yes | 4 |
| 40 | $-C_2H_4-CH_2-C_2H_4-$ | | H | H | H | H | $CH_3$ | | | 8.5 | | |
| 41 | $-C_2H_4-O-C_2H_4-$ | | H | H | H | H | $CH_3$ | 11.0,20.0 | 10 | 2 | Yes | 43 |
| 42 | Lysergic Acid | | H | H | H | H | $CH_3$ | | | | | |

the highest superdelocalizability for all the compounds is again the same except those compounds mentioned above.

For most of these compounds the frontier electron density and the superdelocalizability is situated at atom No. 8. Previously, Snyder and Merril (1965) who also used the simple Hückel method (hetero atom model) have claimed that the frontier electron density in LSD is present at the carbon No. 2. They suggested that the No. 2 carbon atom might be an active site for the charge transfer reactivity if this mechanism is involved in hallucinogenic activity. Contrary to that, our calculations show that the frontier density is present at the carbon atom No. 8 instead of 2, even in our simple Hückel method without omega technique. The substituents present not only at position 2 or 8, but also at other positions alter the activity. Therefore, it can not be claimed that the positions 2 and 8 are unique and may be the only active sites in charge transfer mechanism. The frontier density obtained at position 2 or 8 is simply a result of the chosen model and the parameters needed in the calculation.

The total orbital energies and $\pi - \pi^*$ transitions have also been tabulated. The value for the $\pi - \pi^*$ transitions vary from 0.189 for compound 30, which is chloro analog of UML, to 0.716, the latter being the most frequent value. The few exceptions to this $\pi - \pi^*$ value are compound No. 2 and again compounds Nos. 7,8 and 9 and compounds 24 through 30.

Figure 2 shows the plot of the anti-5HT action of branched side chain derivatives as a function of number of carbon atom in each branch. Fig. 3 describes that of monosubstituted side chain derivatives. An approximate theoretical equation which relates

TABLE II

QUANTUM PARAMETERS OF LYSERGATES

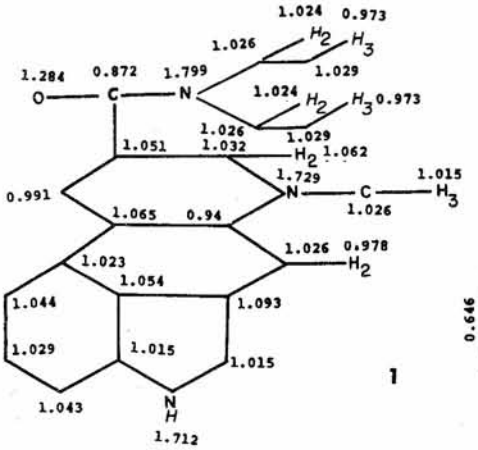
| Compound No. | HOMO $\beta^{-1}$ | LEMO $\beta^{-1}$ | Highest Frontier Electron Density | Highest Super-delocalizability $\beta$ | Total Orbital Energy $\beta^{-1}$ | $\pi-\pi^*$ |
|---|---|---|---|---|---|---|
| 1 (LSD) | 0.148 | -0.567 | 0.2724(8) | 2.3686(8) | 58.2500 | 0.715 |
| 2 | -0.052 | -0.855 | 0.3683(8) | 1.4610(17) | 56.626 | 0.803 |
| 3 (OML) | 0.148 | -0.567 | 0.2703(8) | 2.5041(8) | 62.294 | 0.715 |
| 4 (MLD) | 0.136 | -0.569 | 0.2427(8) | 2.5567(8) | 63.718 | 0.705 |
| 5 (ALD) | 0.153 | -0.564 | 0.2784(8) | 2.4740(8) | 67.824 | 0.717 |
| 6 (BOL) | 0.145 | -0.569 | 0.2663(8) | 2.5312(8) | 61.304 | 0.712 |
| 7 | -0.009 | -0.599 | 0.3986(3) | 1.4592(19) | 59.516 | 0.590 |
| 8 | -0.047 | -0.580 | 0.5909(3) | 1.5724(20) | 62.087 | 0.533 |
| 9 | 0.123 | -0.519 | 0.2973(3) | 3.6088(3) | 61.532 | 0.642 |
| 10 | 0.144 | -0.569 | 0.2644(8) | 2.5295(8) | 65.352 | 0.713 |
| 11 | 0.121 | -0.581 | 0.2519(8) | 2.7954(8) | 66.600 | 0.702 |
| 12 | 0.138 | -0.572 | 0.2552(8) | 2.5768(8) | 66.600 | 0.710 |
| 13 | 0.146 | -0.569 | 0.2726(8) | 2.5358(8) | 62.482 | 0.715 |
| 14 | 0.146 | -0.569 | 0.2726(8) | 2.5358(8) | 66.726 | 0.715 |
| 15 | 0.148 | -0.568 | 0.2705(8) | 2.5075(8) | 54.228 | 0.716 |
| 16 | 0.136 | -0.570 | 0.2429(8) | 2.5602(8) | 55.652 | 0.706 |
| 17 | 0.153 | -0.565 | 0.2786(8) | 2.4772(8) | 59.756 | 0.718 |
| 18 (LAE) | 0.148 | -0.568 | 0.2726(8) | 2.5090(8) | 50.180 | 0.716 |
| 19 | 0.148 | -0.569 | 0.2727(8) | 2.5130(8) | 42.092 | 0.717 |
| 20 | 0.148 | -0.568 | 0.2726(8) | 2.5089(8) | 46.188 | 0.716 |
| 21 (DAM) | 0.149 | -0.567 | 0.2724(8) | 2.5055(8) | 50.262 | 0.716 |
| 22 | 0.148 | -0.568 | 0.2724(8) | 2.5070(8) | 58.726 | 0.716 |
| 23 | 0.148 | -0.567 | 0.2703(8) | 2.5054(8) | 62.776 | 0.715 |

TABLE II (cont.d)

| | | | | | | |
|---|---|---|---|---|---|---|
| 24 | -0.384 | -0.585 | 1.1183* | 2.5489(8) | 51.024 | 0.201 |
| 25 | -0.394 | -0.586 | 1.1187* | 2.5564(8) | 55.252 | 0.192 |
| 26 | -0.106 | -0.568 | 1.2365* | 2.5087(8) | 58.886 | 0.462 |
| 27 | -0.090 | -0.568 | 1.2406* | 2.5090(8) | 63.090 | 0.478 |
| 28 | -0.394 | -0.586 | 1.1186* | 2.5564(8) | 59.246 | 0.192 |
| 29 (UML) | -0.394 | -0.585 | 1.1186* | 2.5544(8) | 63.294 | 0.191 |
| 30 | -0.396 | -0.585 | 1.1186* | 2.5500(8) | 59.064 | 0.189 |
| 31 | 0.148 | -0.568 | 0.2726(8) | 2.5097(8) | 50.418 | 0.716 |
| 32 | 0.148 | -0.568 | 0.2726(8) | 2.5090(8) | 54.424 | 0.716 |
| 33 | 0.148 | -0.568 | 0.2726(8) | 2.5090(8) | 54.230 | 0.716 |
| 34 | 0.148 | -0.568 | 0.2726(8) | 2.5090(8) | 58.420 | 0.716 |
| 35 | 0.148 | -0.568 | 0.2726(8) | 2.5090(8) | 62.410 | 0.716 |
| 36 | 0.148 | -0.568 | 0.2726(8) | 2.509(8) | 66.414 | |
| 37 | 0.148 | -0.568 | 0.2732(8) | 2.5144(8) | 52.968 | 0.716 |
| 38 (LPD) | 0.148 | -0.567 | 0.2724(8) | 2.5057(8) | 58.444 | 0.715 |
| 39 | 0.148 | -0.567 | 0.2703(8) | 2.5048(8) | 62.502 | 0.715 |
| 40 | 0.148 | -0.567 | 0.2724(8) | 2.5057(8) | 62.442 | 0.715 |
| 41 (LSM) | 0.148 | -0.567 | 0.2724(8) | 2.5057(8) | 62.728 | 0.715 |
| 42 | 0.150 | -0.563 | 0.2712(8) | 2.4555(8) | 43.960 | 0.713 |
| Serotonin | 0.425 | -0.926 | 0.5120(3)** | 1.5840(3)** | 28.792 | 1.351 |

*These atoms are the secondary carbons where branching occurs in the substitutions on amide nitrogen.

**These numbers refer to numbering in the indole ring.



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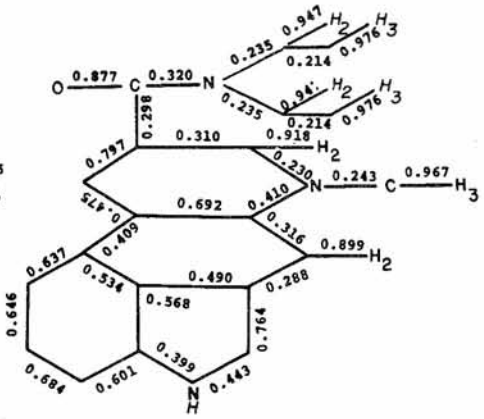

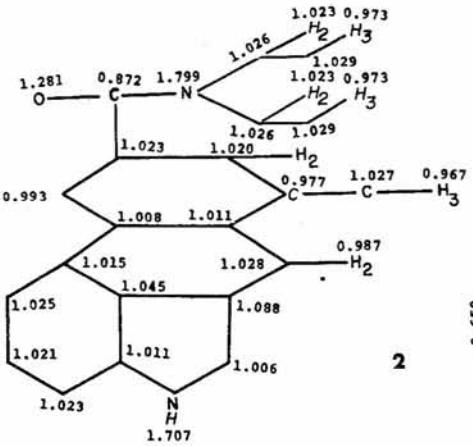

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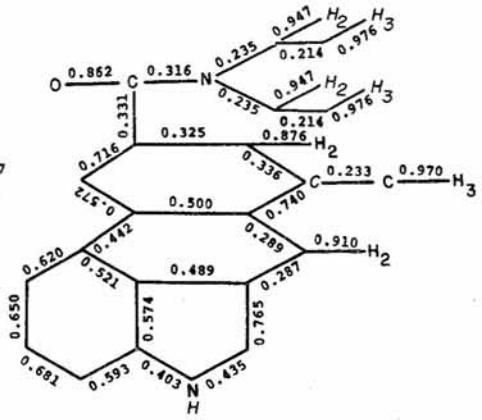

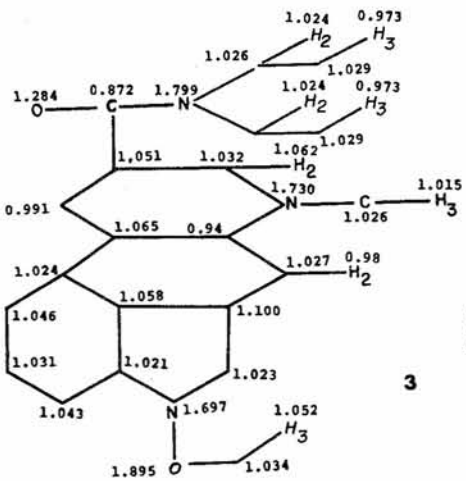

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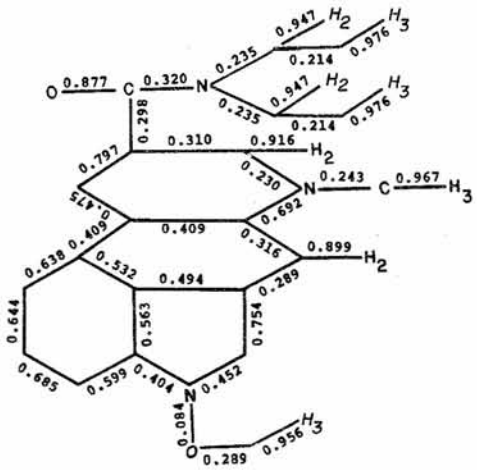

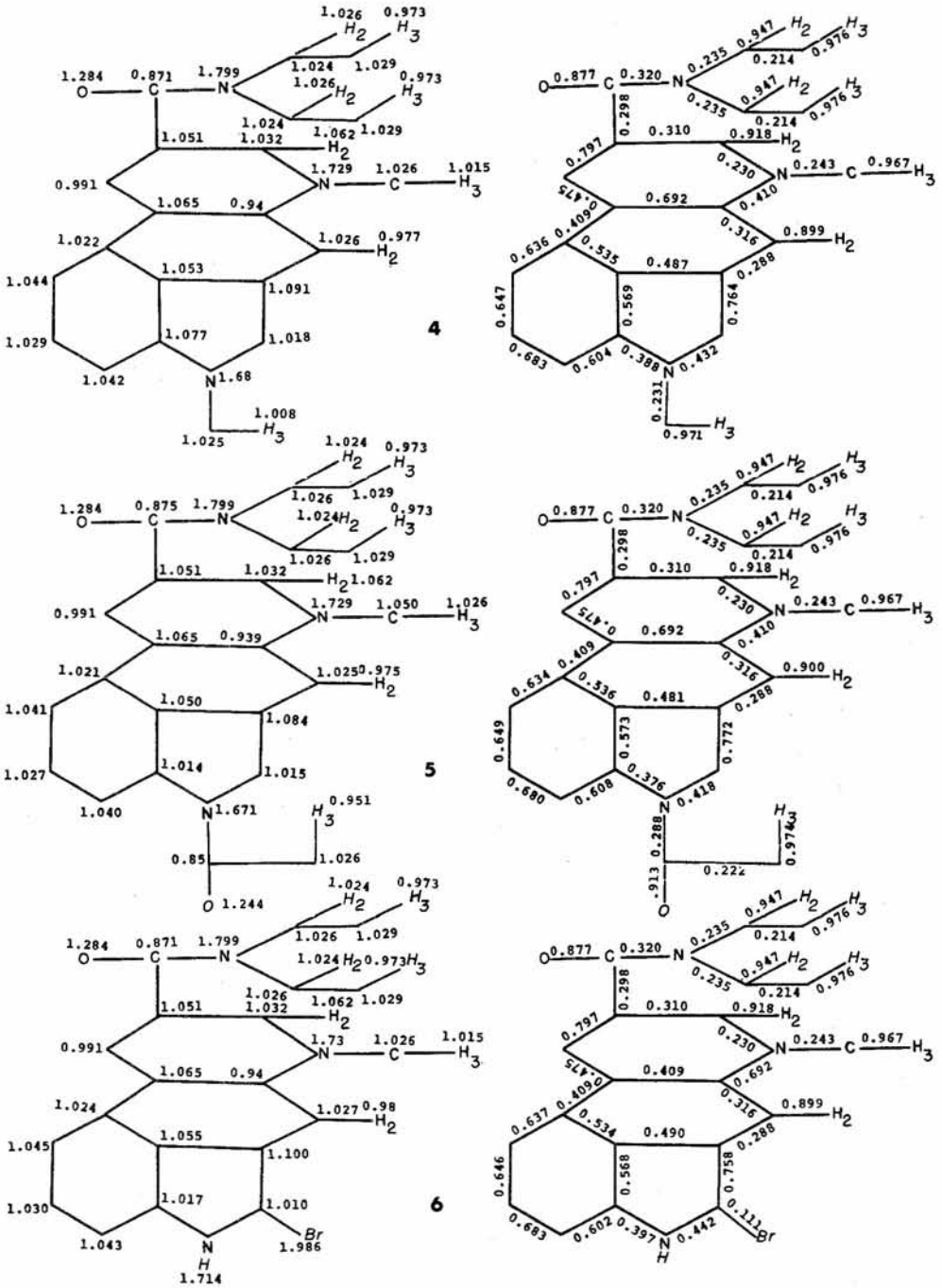

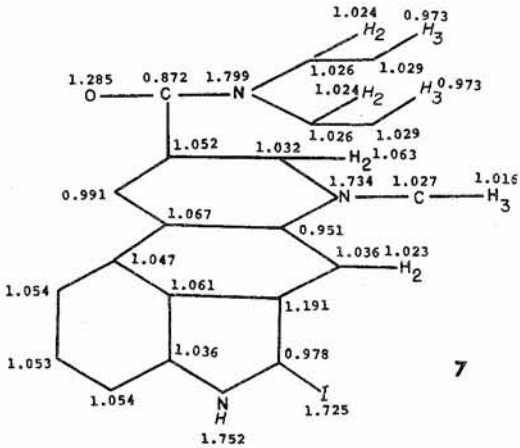

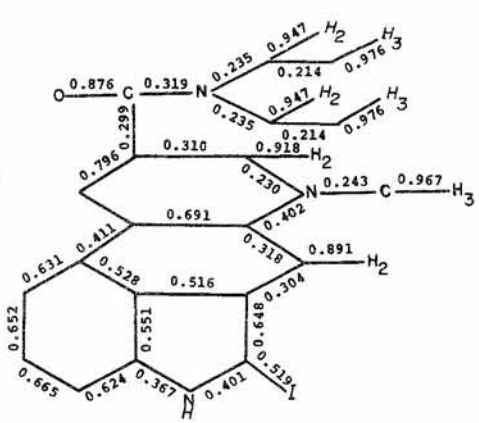

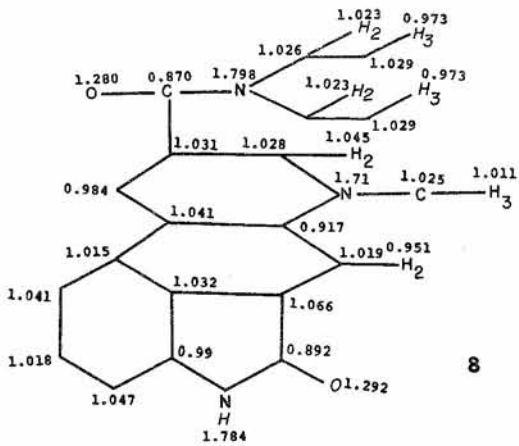

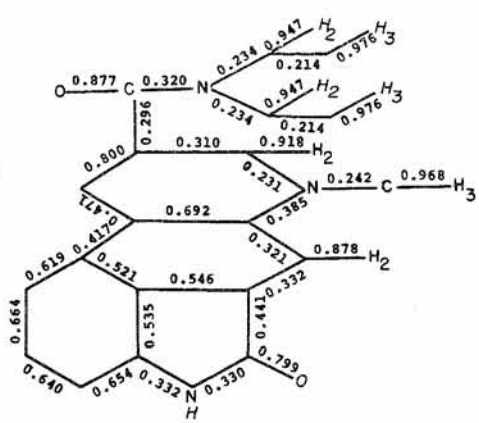

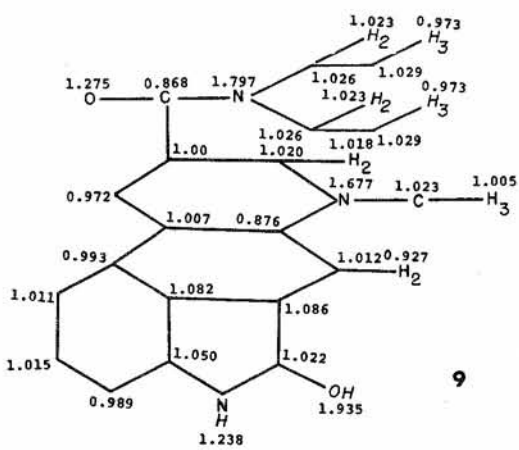

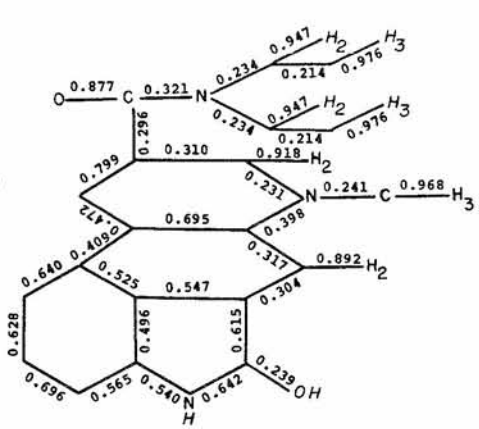

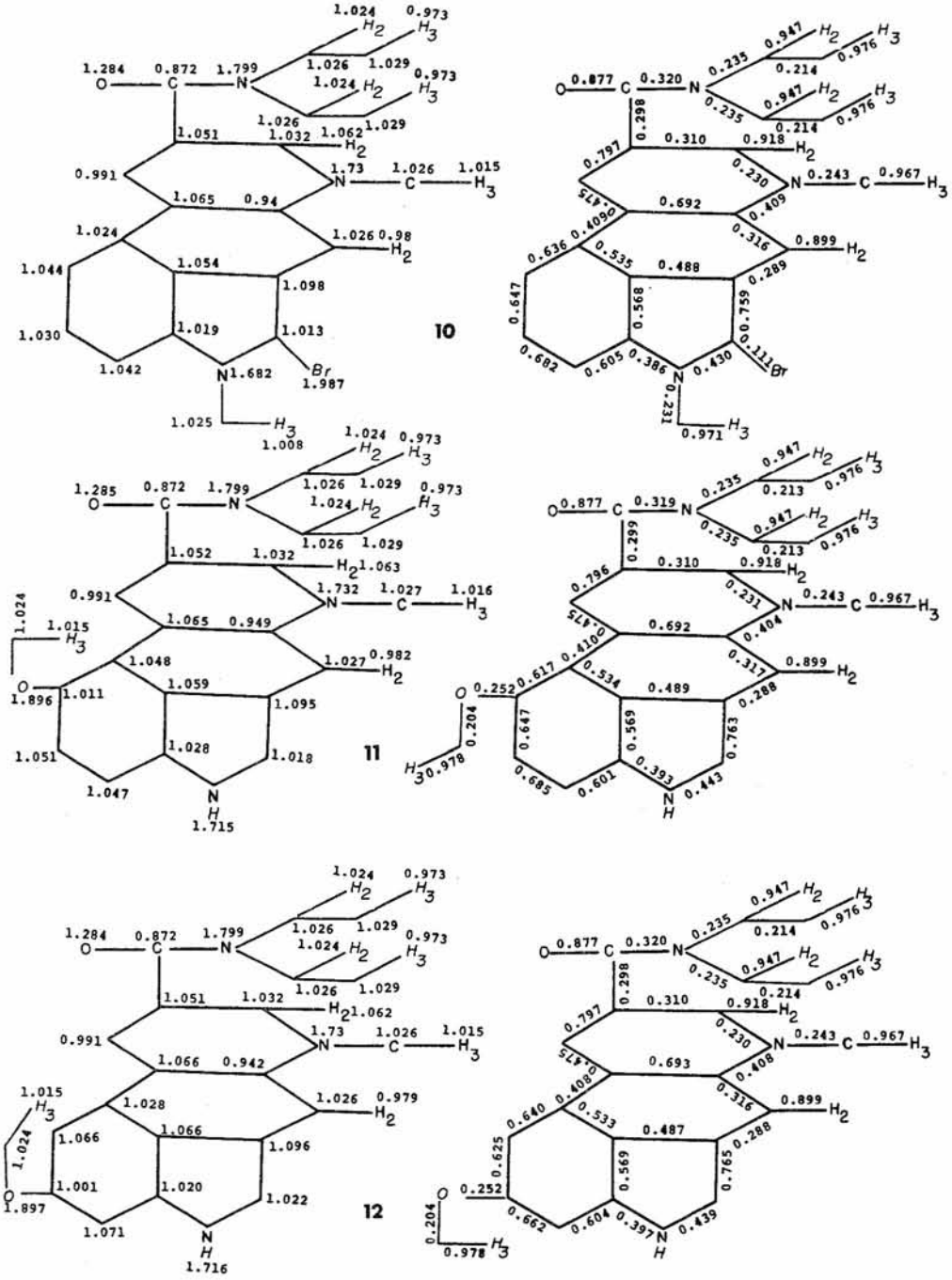

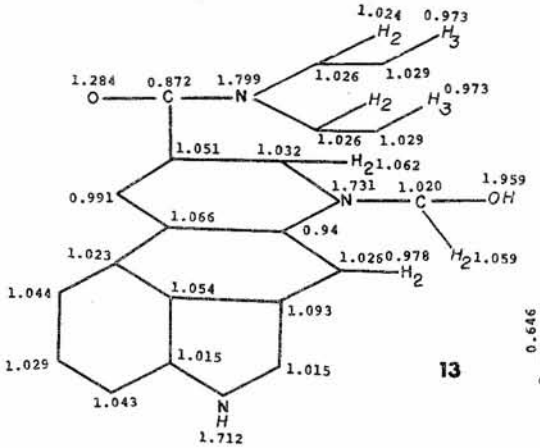

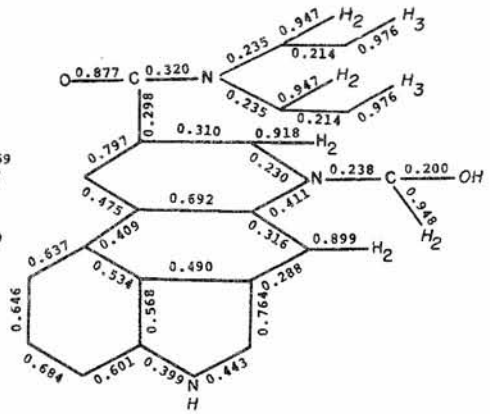

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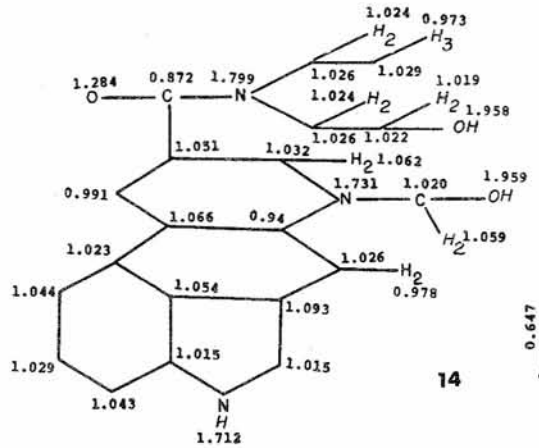

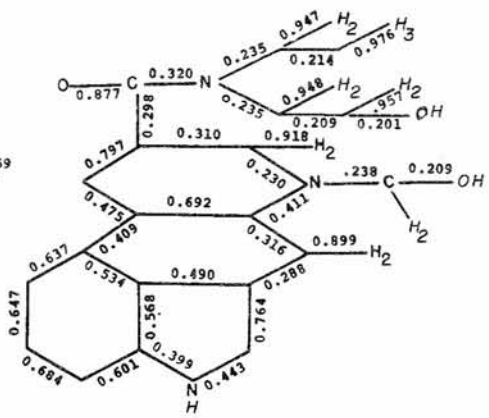

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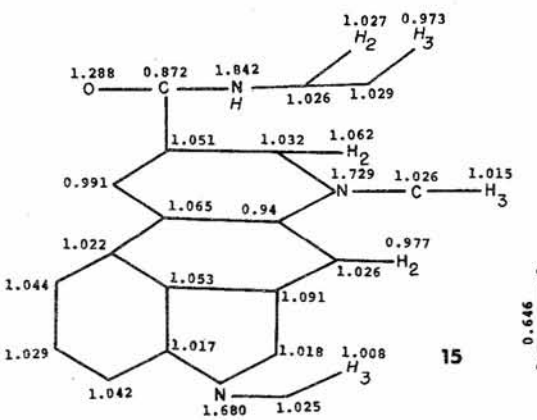

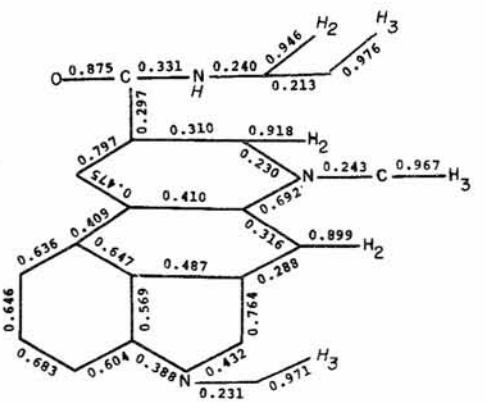

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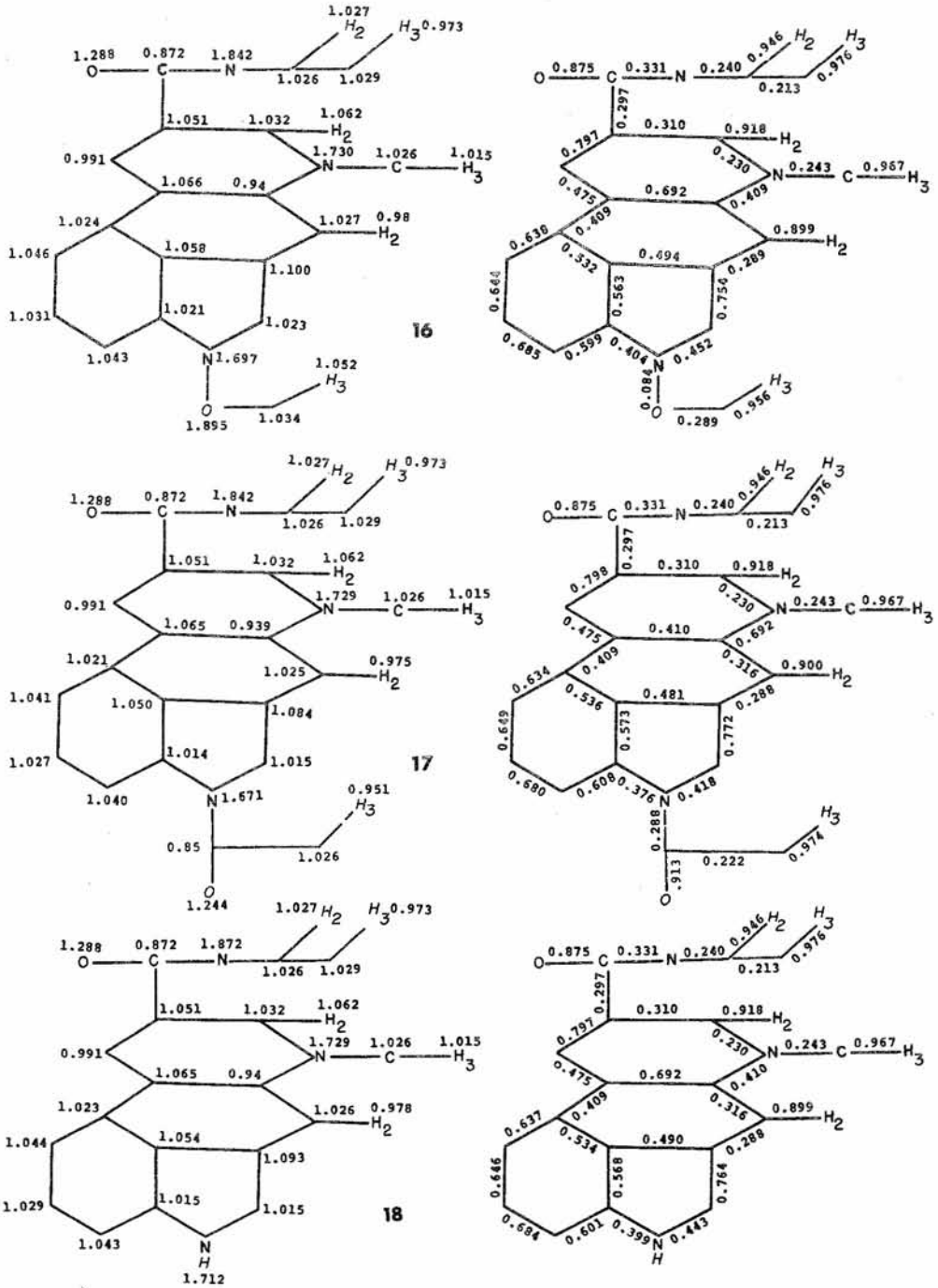

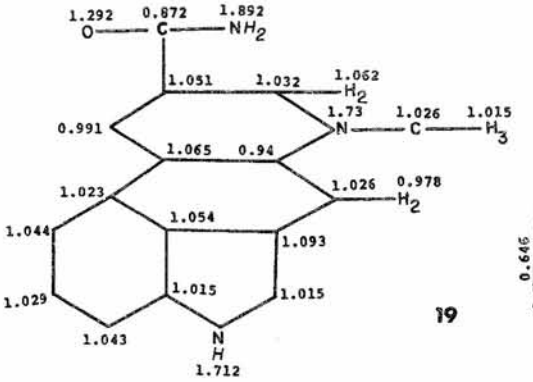
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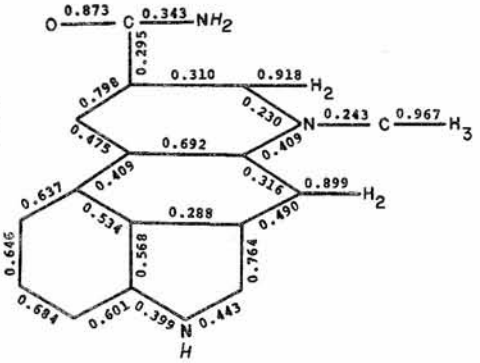
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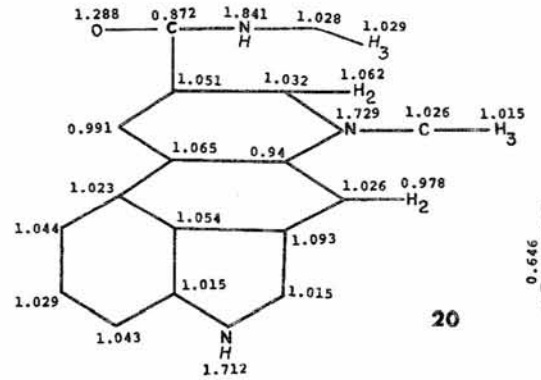
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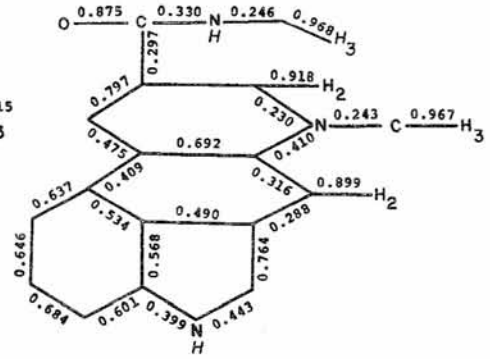
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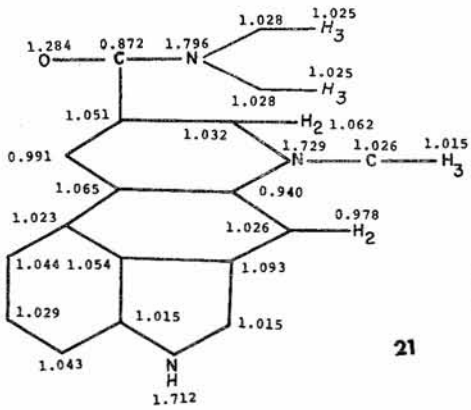
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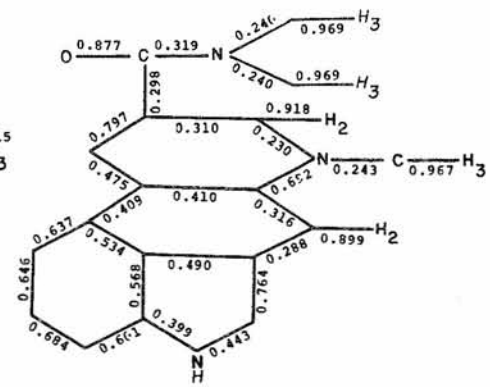
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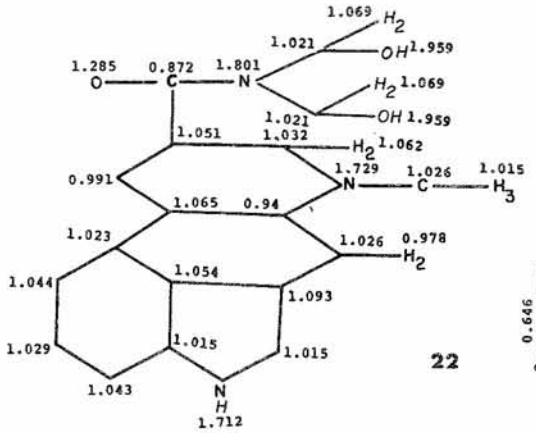

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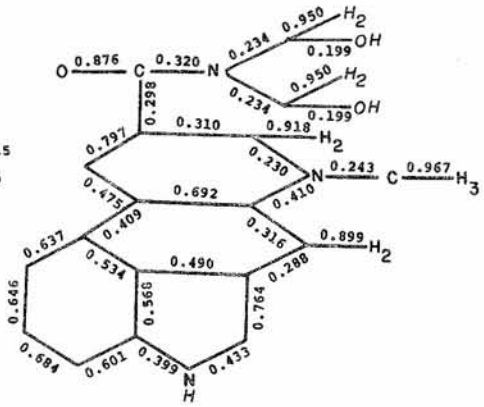

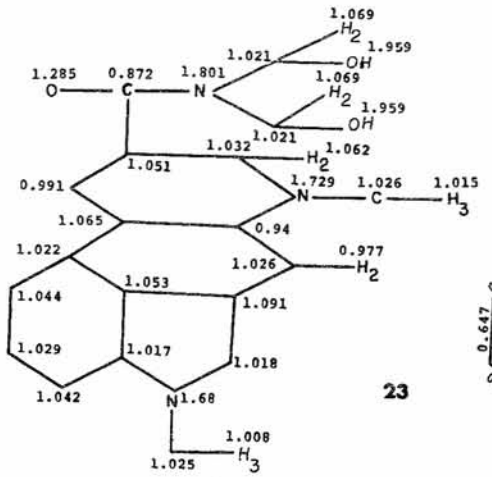

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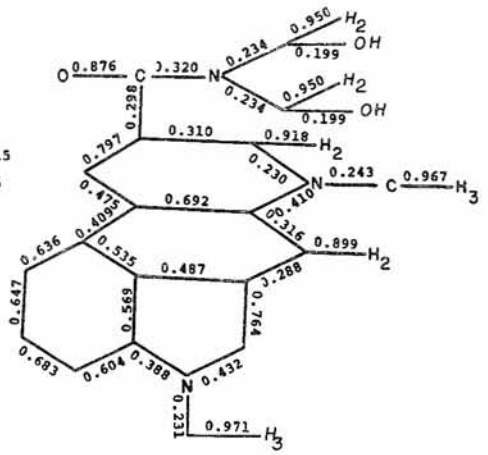

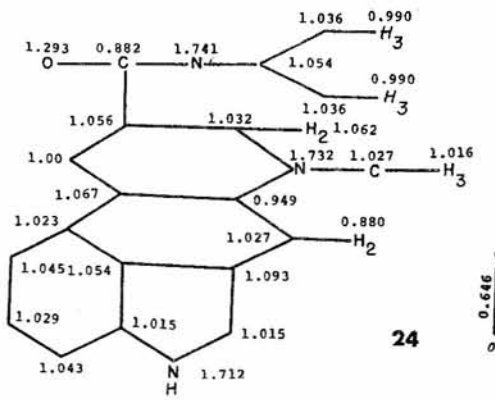

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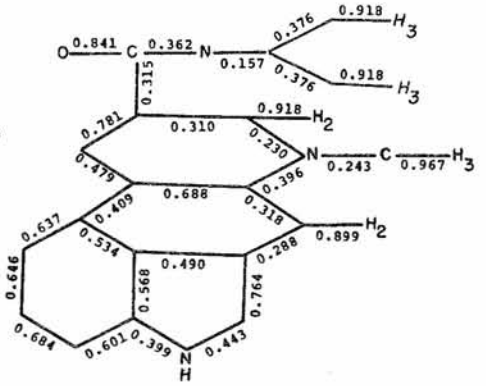

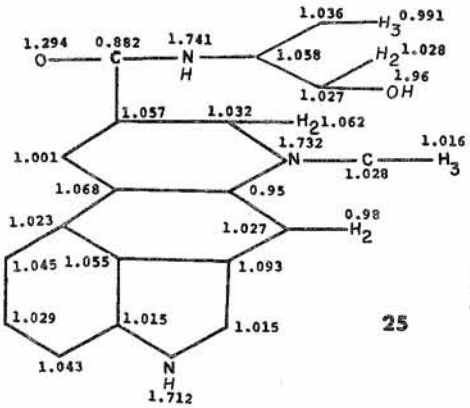

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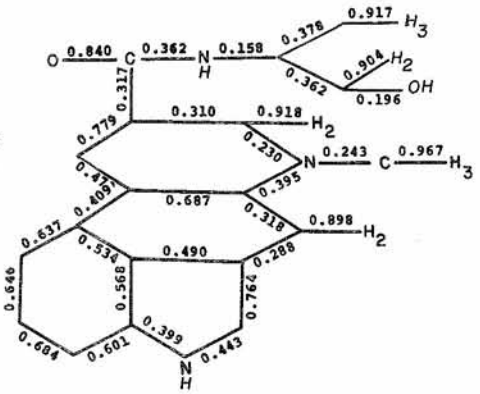

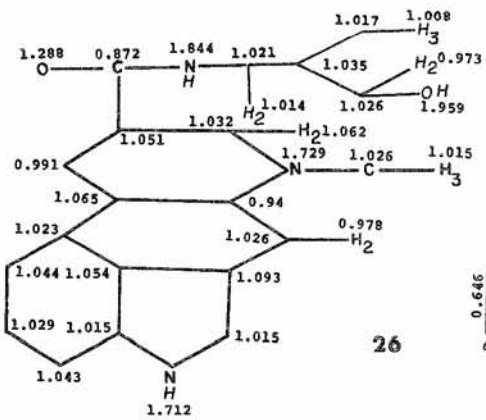

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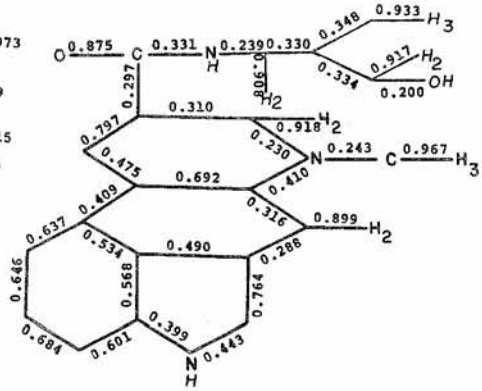

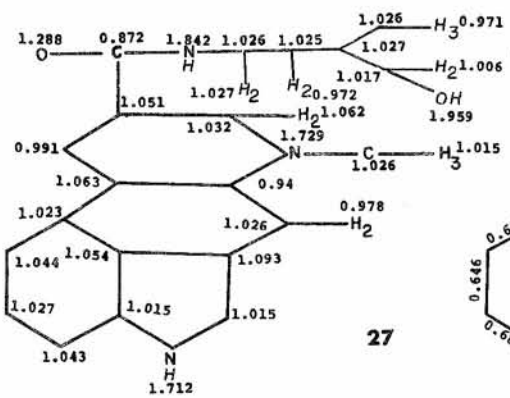

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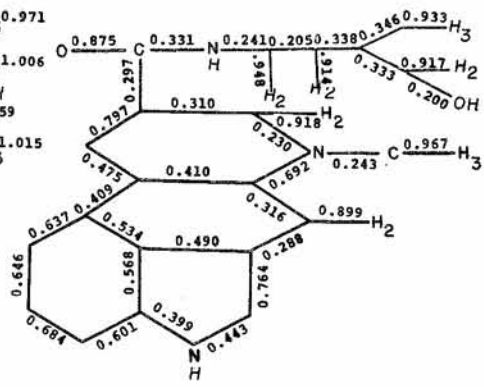

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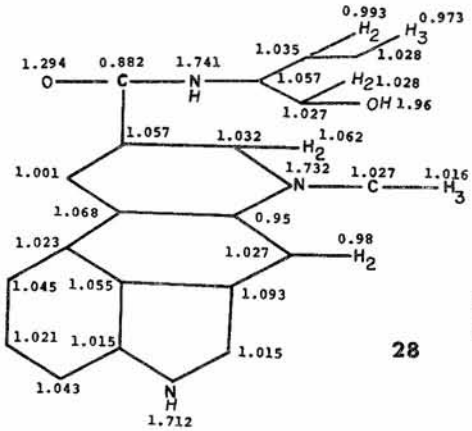

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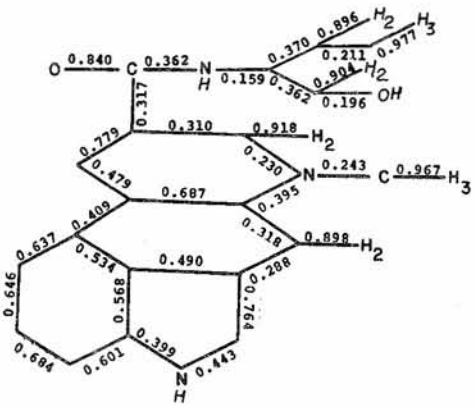

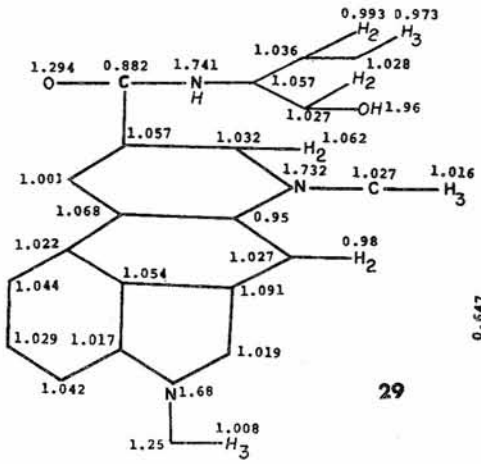

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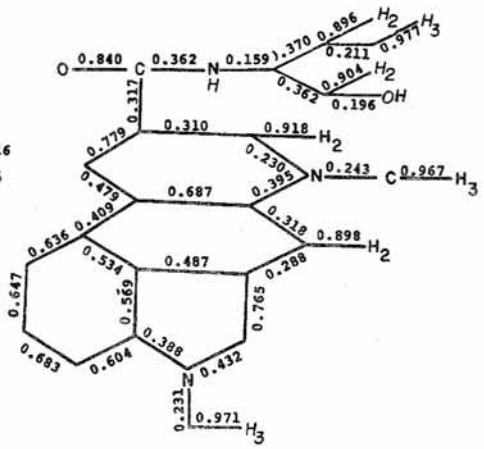

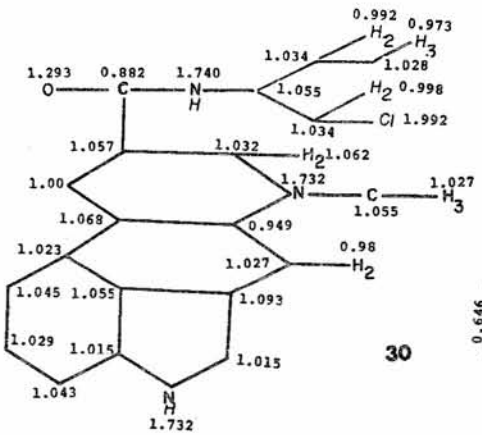

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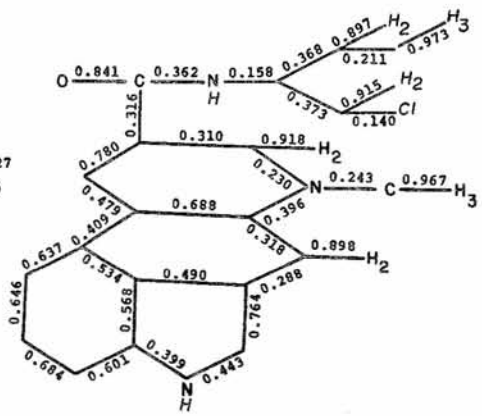

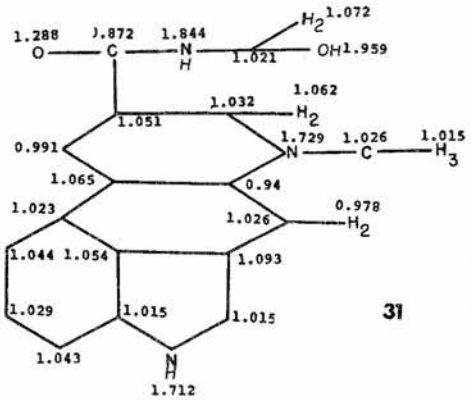

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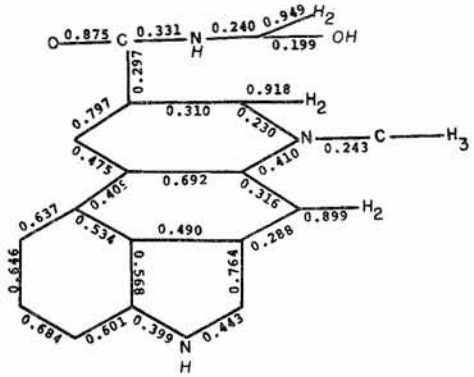

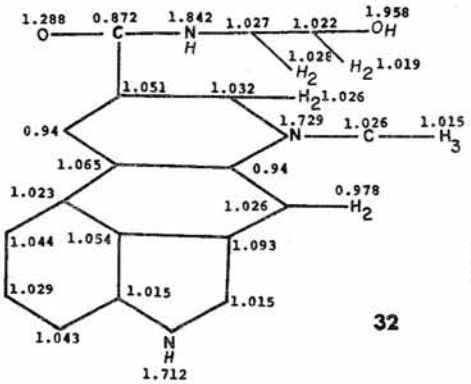

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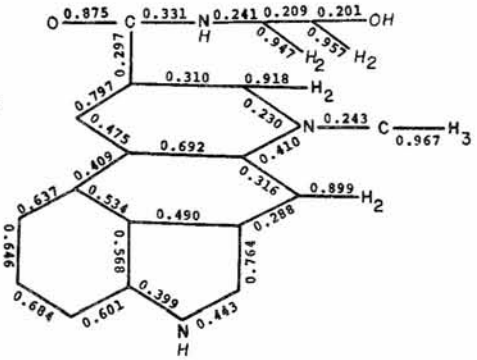

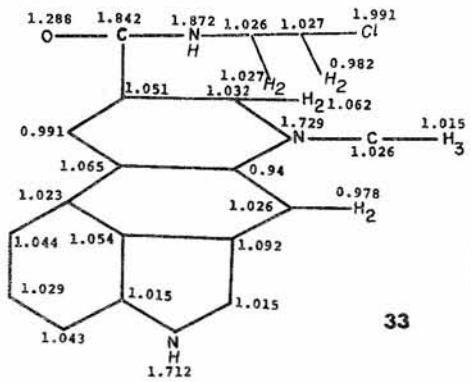

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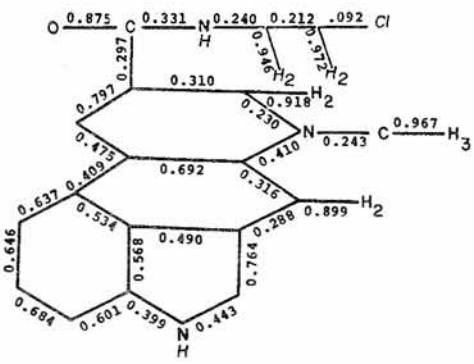

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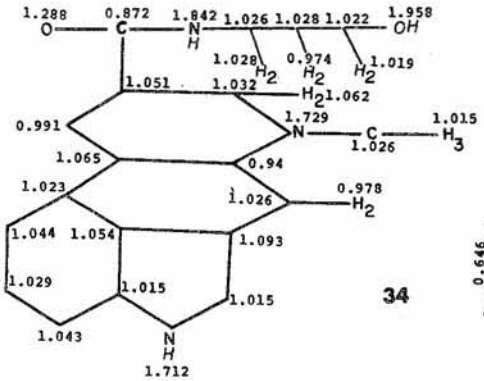

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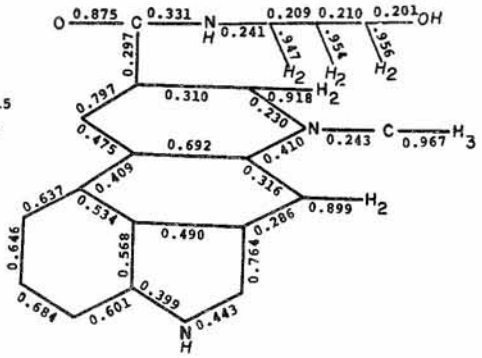

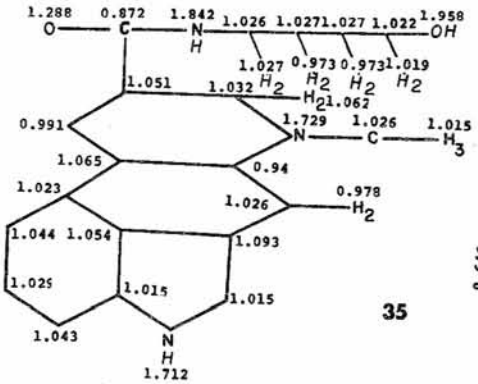

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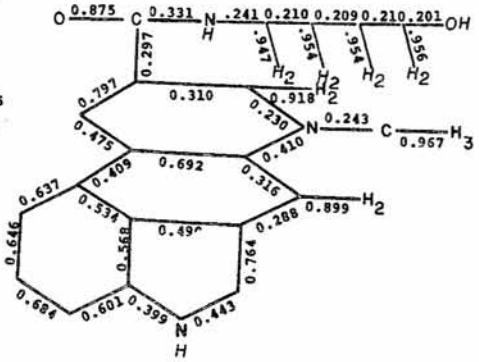

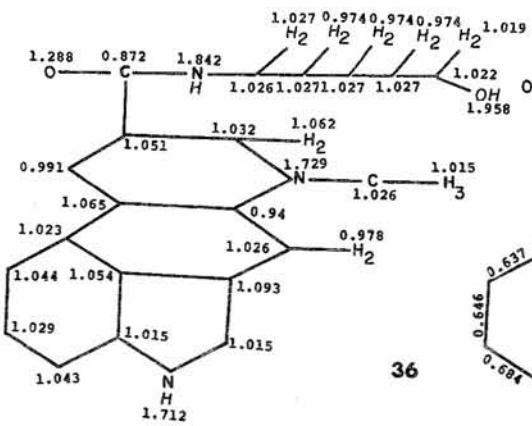

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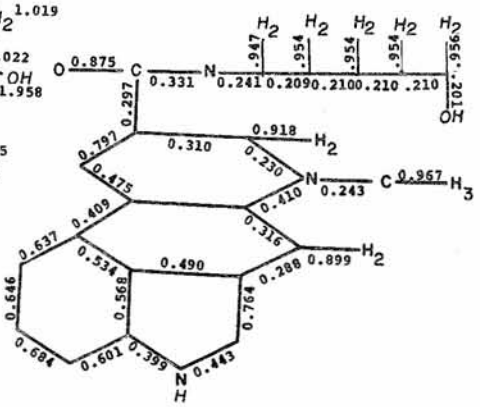

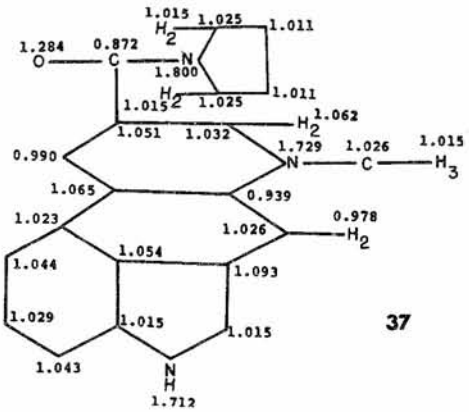

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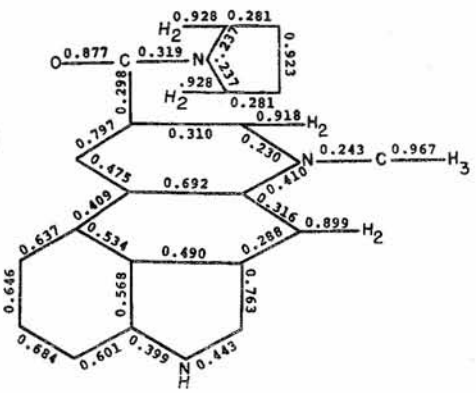

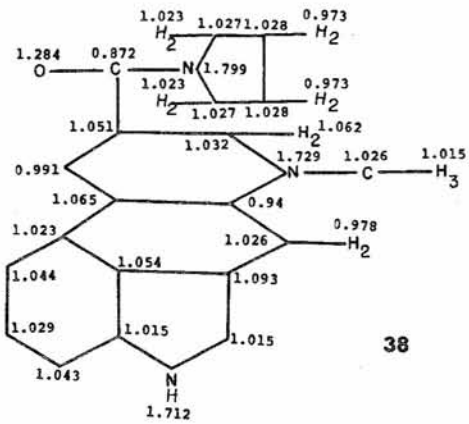

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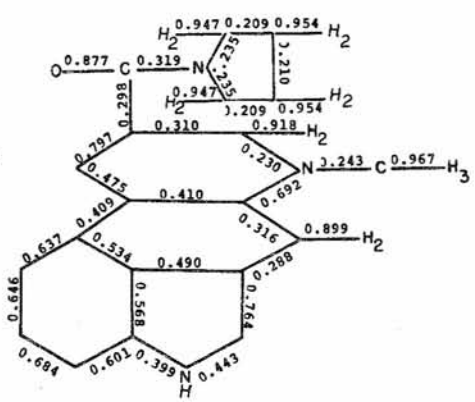

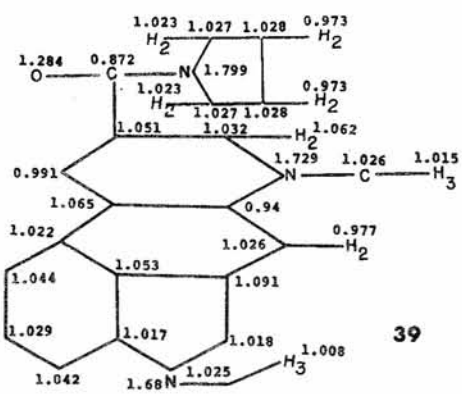

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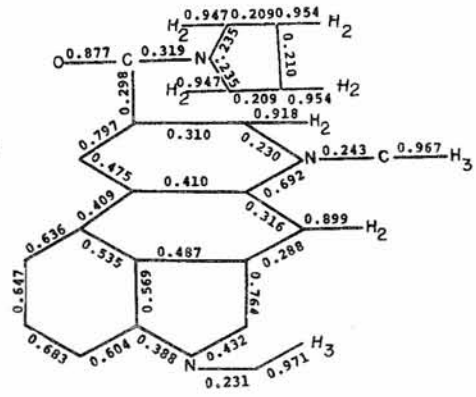

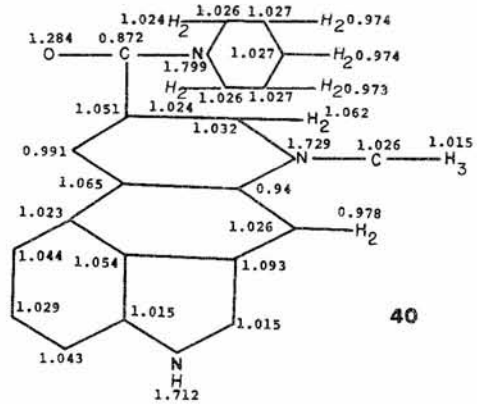

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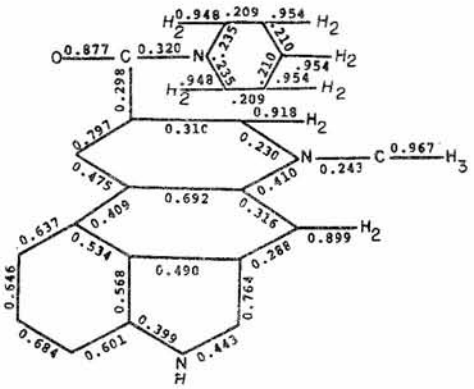

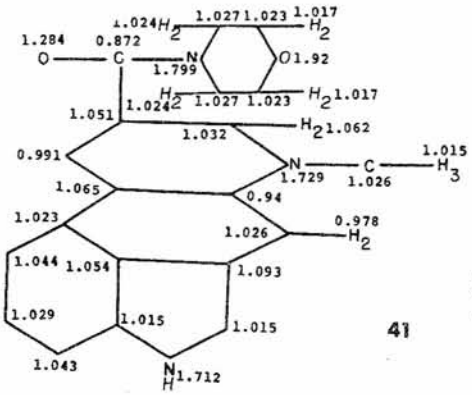

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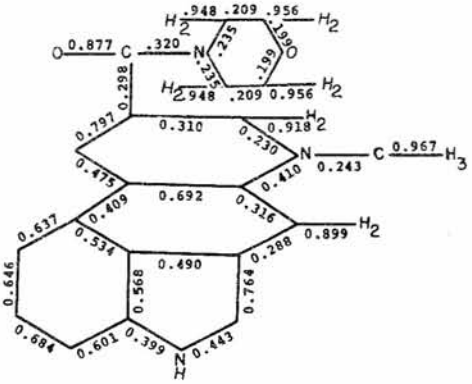

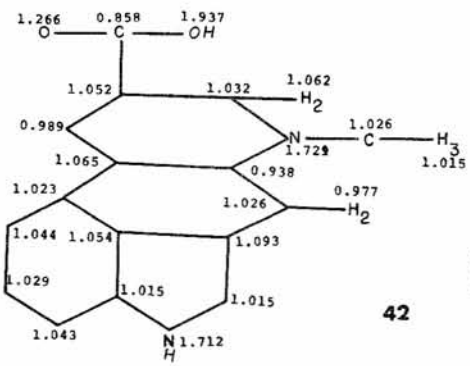

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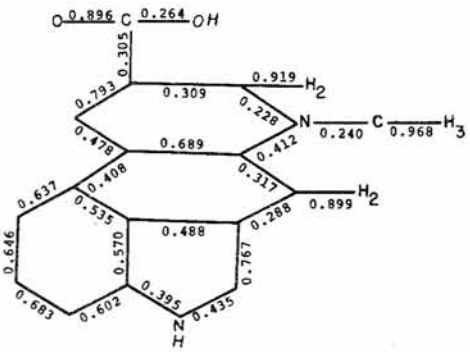

Table III

Anti-serotonin activities of mono- and di-substituted lysergates and the total orbital energies of equivalent hydroxylated compounds. The hydroxylated analogues were used for computing the total orbital energies as the computations with the hydrocarbon derivatives failed to converge even after long computer time.

| | Substituent | Anti-5HT Activity | Substituent | Total Orbital Energy $\beta^{-1}$ |
|---|---|---|---|---|
| a. | $N_{19}H$-H | 4.3±0.5 | $N_{19}H$-H | 42.092 |
| b. | $N_{19}H$-$Ch_3$ | 6.5±0.6 | $N_{19}H$-$CH_2OH$ | 50.418 |
| c. | $N_{19}H$-$CH_2CH_3$ | 11.9±0.1 | $N_{19}H$-$CH_2CH_2OH$ | 54.424 |
| d. | $N_{19}H$-$CH_2CH_2CH_3$ | 40.0±4.8 | $N_{19}H$-$CH_2CH_2CH_2OH$ | 58.420 |
| e. | $N_{19}H$-$CH_2CH_2CH_2CH_3$ | 64.9±6.1 | $N_{19}H$-$CH_2CH_2CH_2CH_2OH$ | 62.410 |
| f. | $N_{19}H$-$CH_2CH_2CH_2CH_2CH_3$ | 75.1±8.5 | $N_{19}H$-$CH_2CH_2CH_2CH_2CH_2OH$ | 66.414 |
| g. | $N_{19}(CH_3)_2$ | 23.2 | | |
| h. | $N_{19}(C_2H_5)_2$ | 100.0 | | |
| i. | $N_{19}(C_3H_7)_2$ | 42.3 | | |
| j. | $N_{19}(C_4H_9)_2$ | 31.2 | | |

the anti-5HT activity to the number of carbon atoms has been obtained, which is:

$$y \text{ or Anti-5HT activity} = \frac{1}{0.01185 + 0.2207e^{-n}}$$

where n is the number of carbon atoms in a side chain mono-substituted derivatives. The total orbital energy values of the side chain monosubstituted derivatives (Fig. 4) have been correlated with the experimental activity. The quantum mechanical properties have been obtained by replacing $^{-}CH_3$ by $CH_2OH$ (TableIII) in a side chain. It was necessary to do so due to the non-convergence of $^{-}CH_3$ derivatives within the allowed time limit. Thus, in correlating the total orbital energy with anti-5HT, it was assumed that the relative trend in $^{-}CH_3$ or $^{-}CH_2OH$ derivatives remains the same, even though, the magnitude of the total orbital energy might change. The least square correlation equation is:

$$\log \left(\frac{\text{total orbital energy}}{\text{anti-5HT act.}}\right) = 1.5766-0.8734 \log (\text{anti-5HT}) \pm 0.0227$$

or

$$\text{Total orbital energy} = 14.3773 \ (\text{anti-5HT})^{0.1266}$$

One should remember that this equation holds only for the side chain monosubstituted derivatives.

In Fig. 5 the correlation between the hallucinogenic activity of the available LSD derivatives with total orbital energy has been described. The relation that holds is:

$$\log (\text{hallucinogenic activity}) = -11.8596 + 7.3951 (\log \text{total orbital energy}) \pm 0.4003$$

We tried to correlate the toxicity and the pyretogenic activity with the quantum parameters. Due to the limited number of experimental data, it is not possible to elicit a definite conclusion regarding their correlation.

The highest frontier electron density is usally found at carbon 8 in our studies. The few exceptions to this are compounds 7,8 and 9 for which the highest frontier electron density is at carbon 3. This is interesting because these compounds have been rather exceptional in all our studies and are obtained by substitution with iodine, carbonyl function or the hydroxyl function at carbon 2 of the lysergic acid nucleus. The highest superdelocalizability is also found at carbon 8 in the majority of the compounds. In compound 7 it is found, however, on substituent atom 19; and in compound 8 on substituent atom 20; and in compound 9 on carbon 3. Compounds 24 through 30 have not proved exceptional in this case.

DISCUSSION: Among all the quantum parameters that have been calculated, only the total orbital energy correlated with the biological activities (Fig. 5). This might, to a certain extent, indicate the importance of the entire molecule rather than just part of it. From the available hallucinogenic activity of LSD derivatives, it is evident that none of the derivatives measure up to the LSD activity. The activity of each derivative, however, critically depends upon the nature of the various substituents present at various positions.

Surveying all the hallucinogenic activities of the LSD derivatives, the following facts can be noted: (i) hallucinogenic actions of double substituted compounds (one at ring and

one at side chain) are greatly reduced compared to the mono-substituted (either ring or side chain derivative). (ii) the non-polar groups such as $CH_3$ at position 1 are more effective compared to the polar groups such as $-COCH_3$ in reducing the hallucinogenic activity. (iii) if the two carbon atom branch on amide N of LSD is replaced by either with one carbon branch (e.g., d-lysergic acid dimethylamide) or with more than two carbon atom branch (such as, UML), the hallucinogenic activity decreases considerably. From these observations, it appears that the hallucinogenic activity is a function of the nature and the position of the substituents. The maximum response of the LSD molecule might be attributed to the specific geometry of the two carbon atom branch rather than the ring portion. Therefore, the two carbon atom branch on the amide N with a specific geometry is one of the required conditions for the hallucinogenic response.

Previously, three models have been proposed to relate the structure of the hallucinogenic indolealkylamines and phenylalkyl amines and the structure of LSD. Snyder and coworkers (1965) using the molecular models suggested that the tryptamine and phenylalkylamines could assume conformation simulating B and C ring (see Fig. 1) of LSD. Psilocin was then assumed to form 8-membered hydrogen bond ring involving 4-hydroxyl group and the amino nitrogen, which simulates the C ring of LSD. Chothia and Pauling (1969) have proposed a model for the conformation of hallucinogenic amines based on x-ray crystallographic data for phenyl ethylamines and tryptamines. On the

other hand, Kang and Green (1970) presented a model very similar to that of Chothia and Pauling (1969) using the molecular orbital calculations. All the three models have been generated using the same basic idea that the "psychedelic drugs" elicit hallucinogenic response by assuming the ring portion of the LSD molecule. This idea of conformational resemblance is a conceivable one, and might very well be applicable to LSD congeners. But the main question that can be posed here is whether such an idea can be extended adequately to the LSD substituents in order to explain their diversified hallucinogenic activities. The experimental results clearly indicate that the rudimentary idea of structural resemblance of rings is not adequate in explaining the activity, as the ring portion is common to all the derivatives.

We have correlated (Sankar and Kumbar, submitted for publication) the anti-serotonin activity of about 23 lysergates with quantum parameters. In this paper, we are concerned only with the side chain substituents that were not discussed before.

From our studies, we postulate a marked delocalization of electrons in rings A, B, C and D. The steric requirements for hallucinogenic activity are stringent with greatest molecular rigidity and least conformational flexibility in LSD. However, anti-serotonin activity is displayed by a variety of molecular substitutions indicating that (i) the conformational flexibility is more extensive; (ii) the receptor-drug binding may be different for the two effects; and (iii) the disubstituted side chain is much more active than the monosubstituted side chain. Fur-

ther studies on pK values, lipid solubility, biological activities, etc. need be carried out to investigate the intriguing activities of the lysergates.

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