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A Comparison of Common Interatomic Distances in Serotonin and Some Hallucinogenic Drugs

J.M. Kelley and R.H. Adamson

Laboratory of Chemical Pharmacology, National Cancer Institute, National Institutes of Health, Bethesda, Md.

Abstract. There exists a common triangular arrangement of atoms composed of two nitrogen atoms and one oxygen atom of definite interatomic distances in the indole containing hallucinogenic drugs. A similar intermolecular arrangement has been observed in the neurohumoral agent serotonin. This structural feature may be important in the binding of these drugs to the receptor site(s) involved in hallucinogenesis.

Key Words
Hallucinogenic drugs
N-N-O triangulation
Serotonin

The hallucinogenic drugs, occasionally referred to as phantastics, psychedelic, or psychotomimetic agents are subjects of concern and debate in medical and physiological circles. There is particular interest in the relationship of the hallucinogenic drugs to the neurohumoral agents. It has been noted that a number of the hallucinogenic drugs contain indole rings and bear a structural resemblance to serotonin (1) and the structural relation between mescaline and epinephrine and norepinephrine has also been observed (1). In addition, molecular models of psychedelic tryptamine and methoxyamphetamines demonstrate a conformation simulating in part the indole ring system of lysergic acid diethylamide (LSD) (4). Using molecular orbital calculations on serotonin, *Kier* (2) has shown that LSD contains some of the essential features necessary for binding at a serotonin receptor.

We have noted a common structural feature among serotonin and many of the indole containing hallucinogens. This structural feature, reported in this paper, consists of a triangulation composed of two nitrogen atoms and one oxygen atom with a rather definite interatomic distance.

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Materials and Methods

Dreiding Stereomodels, made by W. Büchi, Scientific Apparatus, Switzerland, were used to construct molecular models of various hallucinogenic drugs. These models were then measured and converted to Angstroms. Each model was constructed several times and an average made of the measured interatomic distances. Many of the structures, upon construction, did not exhibit a rigid conformation, hence, measurements were made according to the flexibility of the molecule, and maximum and minimum distances were then recorded. A model of serotonin was also made and measured in an attempt to find a possible structural explanation for relationships between it and some of the hallucinogenic drugs.

Results and Discussion

As can be seen in table I, there appears to be a common structure among the hallucinogenic drugs in that they contain a common triangular pattern involving two nitrogen atoms and one oxygen atom containing definite interatomic distances (fig. 1). These distances are N-N 5.04 ± 1.07 Å, N_1-O 4.93 ± 1.07 Å and N_2-O 7.43 ± 1.53 Å. Due to the flexibility of several structures, measurements were reported as maximum and minimum distances for different possible conformations of the molecule. Hallucinogenic compounds containing this triangular pattern with these distances include *d*-LSD, N,N-diethyl-6-hydroxytryptamine, bufotenine, psilocybin, psilocin and ibogaine. In addition, several tryptamine derivatives which contain the N-N distances but do not contain any oxygen atoms may well be hydroxylated in the body, e.g. N,N-diethyltryptamine. Thus, these compounds would also fit this triangular pattern.

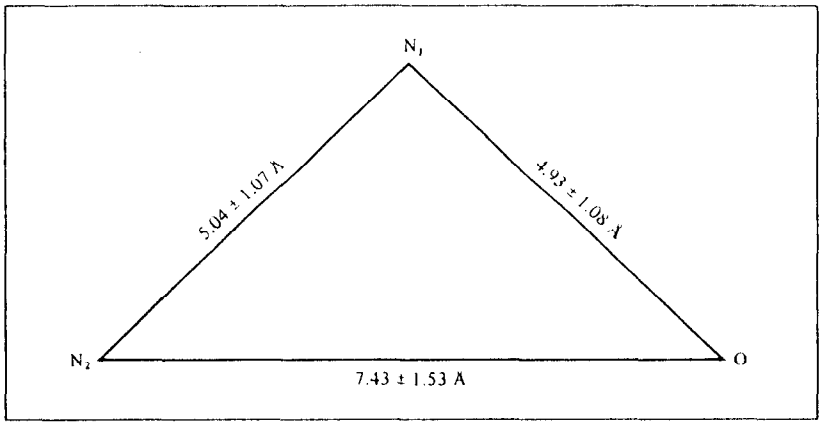
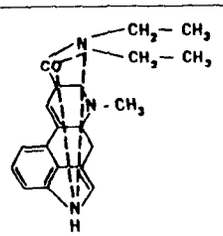
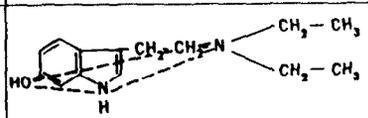
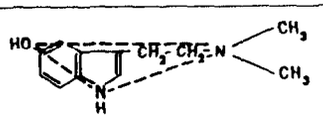
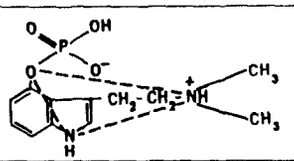
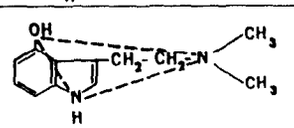
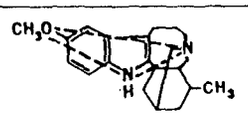
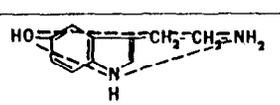


Fig. 1. N-N-O triangular pattern.

Table I

Chemical name	Formula	Distance Å		
		N_1-N_2	N_1-O	N_2-O
d-Lysergic acid diethylamide (LSD-25)		6.0–6.04	4.46–4.84	8.72–9.44
N,N-diethyl-6-hydroxy-tryptamine		3.80–6.04	4.68 (rigid)	6.88–9.16
Bufotenine		3.80–6.04	5.48 (rigid)	6.08–8.0
Psilocybin		3.80–6.04	4.68 (rigid)	4.6–6.12
Psilocin		3.80–6.04	4.68 (rigid)	4.6–6.12
Ibogaine		4.4	5.1	8.3
Serotonin (5-hydroxy-tryptamine)		3.80–6.04	5.64 (rigid)	3.80–8.0

These interatomic distances also reveal an apparent similarity in the possible conformations of the hallucinogenic agents and serotonin. In considering a predicted conformation of serotonin (2) with distances calculated as: N-N 5.84 Å; N-O 5.71 Å; and N-O 6.96 Å, it can be seen that it is possible for the hallucinogenic agents to occupy the same receptor site for serotonin and thereby replace the normal function of this neurohumoral agent.

Admittedly, this observation is quite empirical and it is not the only factor involved in the serotonin receptor site (or hallucinogenic site) since λ-lysergic acid diethylamide, λ-isolysergic acid diethylamide and 2-bromo LSD also fit this triangular pattern but are devoid of psychic activity. It is likely, however, that this pattern is involved, at least in part, to binding to the serotonin receptor site.

Triangular patterns of different distances, atoms, and shapes have previously been reported in explaining other receptors (2, 3, 5). The triangular pattern observed here may be useful in designing and explaining the activity of these and other hallucinogenic agents. In addition, it also lends additional support to the speculation, that certain cases of mental illness may involve abnormal metabolism of serotonin or formation of serotonin analogs in the body, with the result that the metabolite occupies the serotonin receptor triggering various psychotic reactions.

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Request reprints from: *Mrs. J.M. Kelley,* Laboratory of Chemical Pharmacology, National Cancer Institute, National Institutes of Health, *Bethesda, MD 20014* (USA)