NOTES ON CURRENT RESEARCH

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Molecular Structure of Hallucinogenic Drugs

Explanations of the action of hallucinogenic drugs have been offered on the psychological level (e.g. "de-activation of perceptual filters"), on the physiological level (e.g. "interference with functioning of midbrain reticular activating system"), or on the biochemical level (e.g. "competition with neural transmitter substances such as serotonin"). Recent work by Snyder and Merrill at NIMH focussed on the electronic configurations of hallucinogenic drugs, and attempted to determine the nature of the relationship between chemical structure and hallucinogenic potency.

Substances known to differ in hallucinogenic potency, such as mescaline, TMA, TMA-2 and TMA-3; or DMT, Bufotenine, 6-hydroxy-DMT, psilocin; were compared on a variety of electronic parameters such as "pi charge," "free valence," "energy of the highest filled molecular orbital" (HFMO), "frontier electron density" and "superdelocalizability." Significant relationships were found between hallucinogenic potency and HFMO, which is considered to be an index of the propensity of a molecule to donate electrons.

Few conclusions can be drawn from this work though it is certainly suggestive.". . . The correlation of HFMO energy with hallucinogenic activity only implies that these compounds may act as electron donors, but does not describe a mechanism for hallucinogenesis."

The research is reported in: Snyder, S.H. and Merrill, C.R. "A Relationship between the Hallucinogenic Activity of Drugs and their Electron Configuration," Proc. Nat. Acad. Sci., 54 (1), pp. 258-266, 1965; and in: Snyder, S.H. and Merrill, C.R. "A Quantum-Chemical Correlate of Hallucinogenesis" in Amines and Schizophrenia, Pergamon Press, New York, 1966, pp. 229-245.

STP and Other Compounds Related to Amphetamine and Mescaline

The appearance of a mysterious psychedelic drug, named after a fuel additive, on the underground market touched of a wave of widespread amazement and confusion. It was rumored to be related to a lethal nerve-gas and, most terrifying, the common LSD-antidote thorazine was said to fatally potentiate its effects.

Since the FDA's statement, as it appeared in the New York Times (Aug. 3, 1967), it is clear that STP, or DOM as it is labeled in establishment chemistry, is one of a whole family of compounds which are structurally related to both mescaline and amphetamine. This group, on which a considerable literature has already been published, includes several variants of TMA, MMDA, MDA, DMMDA and others whose pharmacologic properties still remain to be explored.

Table I gives the average effective dosage (in mg), computed for a 70 kg adult, and the approximate potency relative to mescaline equals 1. The toxicity (LD_{50}) is derived from studies in rats or mice, and is expressed as the dose (in mg per kg) which is lethal to 50% of the experimental population.

In duration most of these chemicals are similar to the mescaline pattern (8-12 hours), except for STP, which lasts around 16-24 hours. STP is not related to toxic nerve-gas, although it is possible that tablets containing atropine-like substances appeared temporarily on the market under the label "STP". It is this pseudo-STP which could interact unfavorably with thorazine.

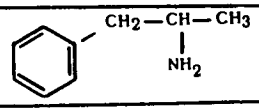
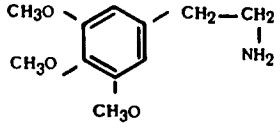
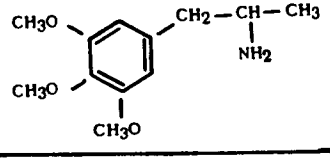
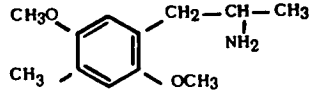
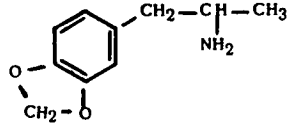
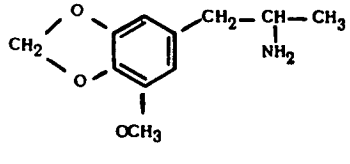
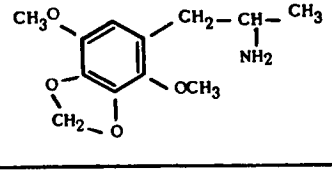
Discontinuance of the use of thorazine as an antidote to LSD or STP "freak-outs" must in any case be regarded as a positive consequence of this whole episode. Thorazine is equivalent to a temporary chemical lobotomy and is known to damage brain and retinal cells. Psychologically, it does not allow the person to assimilate and "work through" the experiences triggered off by the LSD.

It can be seen that changes in the mere positioning of the methoxy groups can lead to appreciable changes in potency. For example, TMA-2 is six times as potent as TMA, whereas TMA-3 is not active at all, even in doses exceeding those adequate for TMA or MMDA.

Qualitatively, these compounds seem to be similar in some respects, different in others. According to Shulgin(12) "as a generalization, the MMDA series leads to the more emphatic and pleasant responses, whereas personal anxiety and restlessness are common with TMA." It is suggested of TMA "that its characteristic property is one of causing projection, in the psychological sense, by the subject."(15)

Studies on MDA have "shown modest, if any, distortion or change of either visual or auditory perception, but rather a pronounced increase in emotional affect, which has proved to be of considerable value in psychotherapy."(6) MMDA appears to be similar to MDA, "but in addition some 30% of the subjects reported rather vivid and well-structured images appearing when the eyes are closed,

Table I*. Amphetamine-Related Compounds

			Toxicity (LD_{50}), mg/kg	Dosage, mg	Relative Potency (Mescaline = 1)
	Amphetamine	phenylisopropylamine	---	---	---
	Mescaline	3,4,5-trimethoxyphenethylamine	370	250	1
	TMA TMA-2 TMA-3	3,4,5-trimethoxyamphetamine 2,4,5-trimethoxyamphetamine 2,3,4-trimethoxyamphetamine (not active)	260 120 ?	120 20 N.A.	2 12 0
	STP (DOM)	4-methyl-2,5-dimethoxyamphetamine	?	5	50
	MDA	3,4-methylenedioxyamphetamine	?	100	2-3
	MMDA MMDA-2 MMDA-3a	3-methoxy-4,5-methylenedioxy-amphetamine 2-methoxy-4,5-methylenedioxy-amphetamine 2-methoxy-3,4-methylenedioxy-amphetamine	150 130 40	100 13 15	2-3 20 17
	DMMDA DMMDA-2	2,5-dimethoxy-3,4-methylenedioxy-amphetamine 2,3-dimethoxy-4,5-methylenedioxy-amphetamine	? ?	18 42	12 5

*Note that the toxicity given is not directly comparable to the dosage. Toxicity is determined for rats and mice, as mg per kg of body weight. Dosage is determined for adult humans of average (70 kg) weight.

although there are virtually no changes in eyes-open perception."(15) With DMMDA "there were only mild perceptual distortions, and in common with MDA, there were increased generalizations of the thought process, increased emotional affect and empathy, as well as euphoria and a lack of anxiety."(16) These qualitative differences have led some authors to suggest that MDA and DMMDA should not be classified as "psychotomimetics".(16)

The following hitherto unpublished observations may be added to the statements from the literature quoted above. They are based on reports of between 20 and 30 persons familiar with the effects of LSD and other more widely known psychedelic compounds.

MDA's effect is primarily on the emotions and body-sensations, and produces a state of "centeredness" free from the perceptual and mental distortions and hallucinations so common with LSD. One does not go "out of the mind," one "comes to the self." Acceptance, honesty, openness, "here-and-now" feeling, affirmation, confrontation—these are terms typically used to describe the subjective effects of MDA. Anxiety and confusion are almost totally absent. Its application in psychotherapy and personality change seems much more promising than LSD. It is a different type of compound and deserves a different name, perhaps "affect-amplifying."

As a cautionary note, the physiological effects of MDA are not yet completely understood. Recently, in the San Francisco Bay Area, one person died while on MDA. This person was taking Eutonyl, a hypotensive agent which is potentiated by amphetamine-type compounds. Anyone for whom amphetamines are contraindicated should avoid MDA (or STP). STP is not unlike mescaline in its time-course and feelings of visceral involvement. It seems, in doses of 5 mg and above, to produce a state of heightened present-functioning energy, as well as the oft-described multidimensional visionary cosmic kaleidoscope. These generalizations should be regarded as very tentative first approximations only. Of the many apocryphal stories circulating about STP, there is one which relates how a psychic medium took it and asserted that it originated in the laboratory of an alchemist from Atlantis and was not suitable for consumption by humans of the present degenerate age.

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