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Brief Report

5-Methoxy-α-Methyltryptamine (α,O-Dimethylserotonin), A Hallucinogenic Homolog of Serotonin

Robert E. Kantor,[1] Sharon D. Dudlettes,[1] and Alexander T. Shulgin[2]

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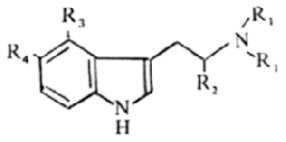
INTRODUCTION

Most of the hallucinogenic (psychotomimetic) drugs are chemically or functionally related to one or the other of the two major neurotransmitters, dopamine or serotonin. A number of these with the tryptamine nucleus are not active orally as the basic nitrogen function is lost through oxidative deamination (see Table I for a listing of the known active tryptamines, their structures, relative potencies, and routes of administration). Steric interference with this enzymatic step either by the addition of a methyl group alpha to the nitrogen, an increase in the bulk of the nitrogen substituents, or a zwitterionic ring conformation permitted by a four-position hydroxyl group, allows the drug to be effective orally. With a free hydroxyl group located in the indolic five-position there is interference with entry into the central nervous system.

A serotonin derivative that in principle should circumvent these structural impediments is α,O-dimethylserotonin (α,O-DMS) in which the deamination process would be blocked by α-methylation and the hydrophilic hydroxyl group would be masked by O-methylation. This compound has been shown to have serotonin agonist activity in several biological models (Barlow and Khan, 1959; Vane, 1959), to have direct access to serotonin receptors within the CNS (Vane *et al.*, 1961), and to be

[1]Pacific Graduate School of Psychology, Palo Alto, California.
[2]Lafayette, California.

Table I. Human Potency of the Hallucinogenic Tryptamines



R_1	R_2	R_3	R_4	Name	Dosage (mg)	Route	Reference
H	H	H	H	Tryptamine	100[a]	Par	Martin and Sloan, 1970
CH_3	H	H	H	DMT	60	Par	Szara, 1956
C_2H_5	H	H	H	DET	60	Par	Boszormenyi *et al.*, 1959
n-Pr	H	H	H	DPT	60	Par	Szara and Hearst, 1962
i-Pr	H	H	H	DIPT	30	Oral	Shulgin, 1976
CH_3	H	OH	H	Psilocin	12[b]	Oral	Hofmann *et al.*, 1958
C_2H_5	H	OH	H	CZ-74	15[b]	Oral	Leuner and Baer, 1965
H	H	H	OH	Serotonin	100[c]	Oral	Murphree *et al.*, 1960
CH_3	H	H	OH	Bufotenine	16[d]	Par	Fabing and Hawkins, 1956; Fischer, 1968
CH_3	H	H	OCH_3	5-MeO-DMT	6	Par	Shulgin and Nichols, 1978
i-Pr	H	H	OCH_3	5-MeO-DIPT	12	Oral	Shulgin and Carter, 1977
H	CH_3	H	H	IT-290	30	Oral	Murphree *et al.*, 1960; Hollister *et al.*, 1960
H	CH_3	OH	H		20[c]	Oral	Murphree and Bircher, 1971
H	CH_3	H	CH_3	MP-809	60[e]	Oral	Azima *et al.*, 1962
H	CH_3	H	F		25[f]	Oral	Anon., 1973; French, 1976
H	CH_3	H	OCH_3	α, O-DMS	3	Oral	Shulgin and Nichols, 1978

[a] Largely autonomic in nature; little central effect.
[b] The phosphate esters of psilocin and CZ-74 are psilocybin and CEY-19, respectively. They are stoichiometrically equivalent to the free hydroxy indoles.
[c] Largely cardiovascular and autonomic distress.
[d] A pressor rather than a hallucinogen in man.
[e] An antidepressant rather than a hallucinogen in man.
[f] Reports are from the lay press. No clinical studies have been published.

orally active centrally in man (Shulgin and Nichols, 1978). This report presents some of the quantitative and qualitative aspects of the effects induced in normal human subjects.

RESULTS AND DISCUSSION

The following generalized outline is drawn from some 16 experimental sessions conducted amongst six adult volunteers. Effective dosages were found to be between 2.0 and 4.0 mg, administered orally as the

hydrochloride salt, prepared as described by Young (1958). The chronology of the observed effects is consistent, with nausea and gastrointestinal disturbances occuring during a 1-hr period commencing ½ hr following administration. For some subjects the physical malaise lasted throughout the experiment. During the period of maximum intensity (2-4 hr following administration) there are perceptual alterations experienced including enhanced color awareness, visual distortions, and extensive retinal activity (see below) that was largely unpleasurable. There is anoxeria, some time distortion (expansion, not contraction), and considerable analgesia but without any decrement in fine motor coordination. Recovery requires an additional 8 hr or more, and several subjects experienced sleep disturbances.

There are two outstanding features which were consistently observed and of sufficiently long duration to constitute valid properties. The first was a clear dissociation of inward feelings from outward affect, as if the two aspect of the psyche were operating independently and out of synchrony with each other. The clearest example of this was a 3-hr long cheerful and drunken behavior of one subject who kept reporting that the "high" that he was exhibiting was not authentic or in accord with his true mental state. Nevertheless he kept on behaving as if energized and in an exhilarated mood. This dissynchrony was paralleled in another subject whose hands played coordinated piano music while he was cognitively unable to cope with such complex action.

The second feature has to do with invard visual experiences of apparent destructive events whenever the eyes were closed. This took place 12 hr after the administration of the material. Sleep was impossible due to the unusual clarity and negative emotional impact of these visual phenomena (collapsing buildings, falling bridges, sky flashes, tumbling bodies). The loss of logic and irreality of this experience were similar to those described by Freud as "primary process." It is an interesting speculation that this material may implicate some explicit neurological pathway in the mechanism of this fundamental psychological concept. Although sleep was eventually achieved (at 18 hr following the start of the experiment) these visions continued in a minor but irritating way through recalled dreams and concomitant fatigue for the following day.

α,O-Dimethylserotonin is the most potent indolic hallucinogen yet described, and its close chemical affiliation with serotonin should allow it to serve as a valuable probe in the study of the nature of this neurotransmitter.

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