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REVIEW ARTICLE

Psychotomimetic Phenethylamines

KARL A. NIEFORTH

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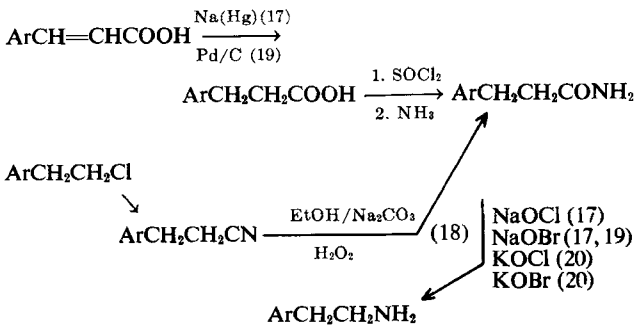
Psychotomimetic activity has been observed following ingestion, inhalation, or injection of materials representing numerous chemical classes, many of which are rather complex (*e.g.*, lysergic acid diethylamide, yohimbine, and tetrahydrocannabinol). Synthetic difficulties have, therefore, precluded extensive studies into the various chemical and physical properties that might influence mind-altering capabilities. Substituted phenethylamines are relatively easy to synthesize; with minimal time and effort, several compounds may be obtained with a variety of ring modifications which may then be related to biological potency.

This review, which is supplemental to an excellent manuscript by Patel (1), covers four basic areas: synthesis and biosynthesis, identification and assay, biological implications, and structure–activity relationships. The period covered is from 1966 to early 1970. It will familiarize the reader with past accomplishments in this area and also indicate the direction future research will follow. During the next few years, research should decide the conformational requirements for phenethylamine psychotomimetics and perhaps yield more information concerning their mechanism of activity.

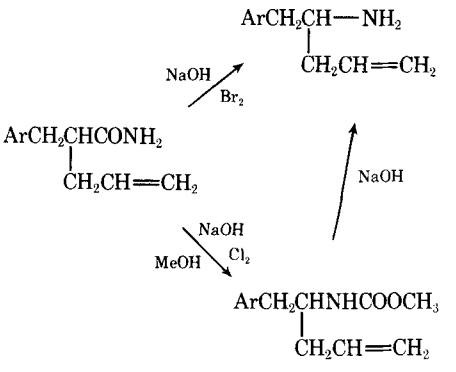


Scheme I

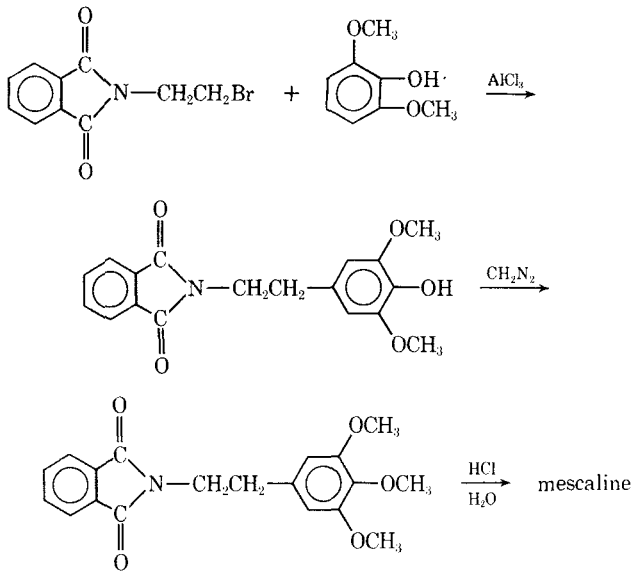
SYNTHETIC ROUTES

A variety of procedures are available to the medicinal chemist desirous of preparing possible psychotomimetic methoxylphenethylamines. The nature of the selected synthetic route is limited by the sensitivity of substituent groups and the imagination of the scientist.

Greatest synthetic utility is made of the reaction between appropriately substituted aldehydes or olefins



Scheme II



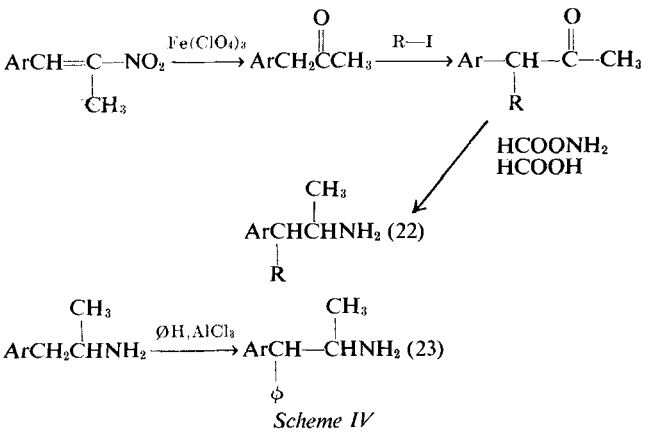
Scheme III

and nitroalkanes followed by reduction of the resultant nitrostyrenes (2–11). Excellent yields are obtained from either the primary nitro compound: $ArCHO + CH_3NO_2 \rightarrow ArCH{=}CH{-}NO_2$, or the secondary compound: $ArCHO + C_2H_5NO_2 \rightarrow Ar{-}CH{=}C(-CH_3){-}NO_2$ (4, 11), or $ArCH{=}CH{-}CH_3 + C(NO_2)_4 \rightarrow Ar{-}CH{=}C(-CH_3){-}NO_2$ (3, 11).

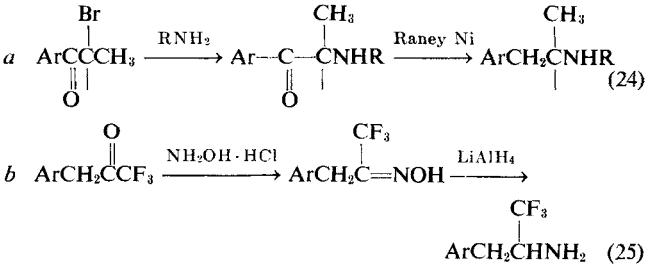
Reduction of the nitrostyrene to the corresponding phenethylamine is usually accomplished with $LiAlH_4$ [$LiAlH_4$-^3H (5)] in ether or tetrahydrofuran (2–5, 7–9, 11). The same reduction has been conducted using amalgamated zinc and hydrochloric acid (10) or palladium (6).

A longer synthetic pathway involves the conversion of a substituted benzyl alcohol to the chloride, then to the cyanide, and finally to the amine (12–16): $ArCH_2OH \rightarrow ArCH_2Cl \rightarrow ArCH_2CN \rightarrow ArCH_2CH_2NH_2$. Earlier references to this procedure (1) indicated that $LiAlH_4$ is the agent of choice to reduce the nitrile. More recent publications showed the utility of a variety of reducing conditions, including Al/Ni (15) and Ni/Cr_2O_3 (13, 14). This more lengthy route appears to offer few advantages over the nitrostyrene pathway and would be selected only where suitably substituted aldehydes are not available.

Some investigators made use of the Hofmann reaction to prepare suitably substituted phenethylamines (17–20)



Scheme IV



Scheme V

(Scheme I). This procedure was used for the conversion of naturally occurring materials such as coumarin (17) and piperonal (20) to biologically active derivatives of mescaline. Careful control of the reaction conditions (Scheme II) permits the preparation of interesting compounds (19).

Other recognizable reactions have been utilized in the synthesis of the title compounds with varying success. Rabusic and Gregor (21) (Scheme III) conducted an interesting sequence of reactions, with the overall yield of 30% competing quite favorably with previous procedures.

Beta-substituted compounds may be synthesized by the routes shown in Scheme IV.

Several mescaline analogs have been prepared by reduction of a suitable precursor, as in the examples shown in Scheme V.

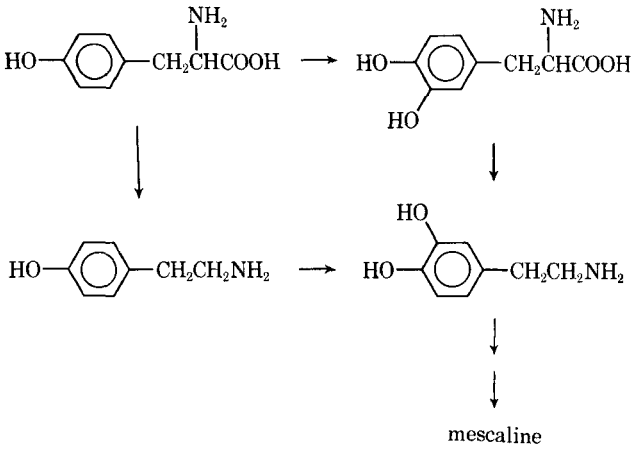
BIOSYNTHESIS

Mescaline occurs in several cacti and has been utilized as a sacrament in religious ritual. It has been isolated from the cacti *Lophophora williamsii*, *Trichocereus pachanoi* Br. and R., *Trichocereus bridgessi* (SD) Br. and R., and *Trichocereus macrogenus* (26).

Through the use of radiolabeled precursors, certain assumptions have been made concerning the biogenesis of mescaline. Agurell *et al.* (27) reported the presence of two possible routes to mescaline because *L. williamsii* was capable of incorporating both ^{14}C-labeled tyramine and DL-3,4-dihydroxyphenylalanine into mescaline. Since both are possible products of tyrosine, the route shown in Scheme VI was indicated.

An excellent chromatographic technique (28) was designed to separate the possible precursors. Later work by the same investigators (29) indicated that phenethylamine, tyramine, dopamine, and 3,4,5-trihydroxyphenethylamine were progenitors of mescaline, although phenethylamine was only slightly incorporated. Neither 4-methoxyphenethylamine nor 3,4-dimethoxyphenethylamine was an efficient precursor. This finding is not in complete agreement with a later publication (30) which reported efficient incorporation of 3,4,5-trihydroxyphenethylamine. Agurell (26) published a proposed biosynthesis (Scheme VII) of mescaline which is common to *L. williamsii* and *T. pachanoi*.

Compounds 5, 6, and 7 have not been tested as precursors, and Compound 6 has not been isolated



Scheme VI

from the mescaline-producing cacti. Compound 7*a* occurs in *Trichocereus werdermannianus* and *T. pachanoi*, and Compound 7*b* occurs in peyote. 3,4-Dimethoxyphenethylamine is described as a by-product arising from methylation of Compound 5.

Paul *et al.* (30), working exclusively with *L. williamsii*, reported a rather high (3.75%) incorporation of 3,4-dimethoxyphenethylamine, which strongly supported their hypothesis that it was a direct precursor resulting in a different biosynthesis (Scheme VIII).

Subsequent publications by Paul's group (31, 32) supported Agurell's pathway based on later findings of poor incorporation of 3,4-dimethoxy-5-hydroxyphenethylamine into mescaline isolated from *L. williamsii*. Their separation procedure did not exclude contamination of the mescaline by the labeled 3,4-dimethoxyphenethylamine precursor.

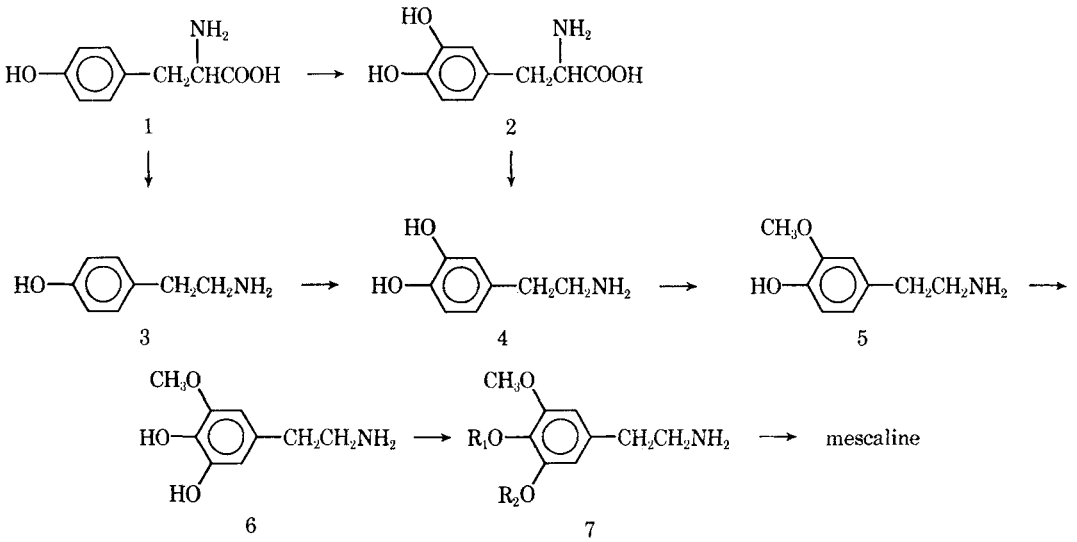
IDENTIFICATION AND ASSAY

Major interest in this area has centered around two topics, schizophrenia and drug abuse. Rather widespread acceptance of the methadone rehabilitation program for heroin addiction has necessitated a great number of urine analyses. Such programs require periodic unannounced urine analysis for the presence of opium derivatives, other depressants, stimulants, and hallucinogens. Most of the procedures are based on TLC techniques (33–38), although paper chromatography (36, 39), GC (28, 40, 41), IR spectrophotometry (40, 42), mass spectrometry (43), and ion exchange (44) have been utilized.

Fike (33), working in a coroner's office, determined R_f values for 140 drugs, including many of the presently abused agents. The determinations were conducted in five different systems, using a 1% solution of iodine in methanol as a general locating agent. Specific color sprays were used, although total separation and identification of all agents were not attempted. General correlations were made between the structure of the drug and the R_f values in the five systems. Fike observed that steric hindrance adjacent to groups responsible for binding to silica, basicity of the compounds, and presence or absence of a pyridyl ring had the greatest influence on the R_f.

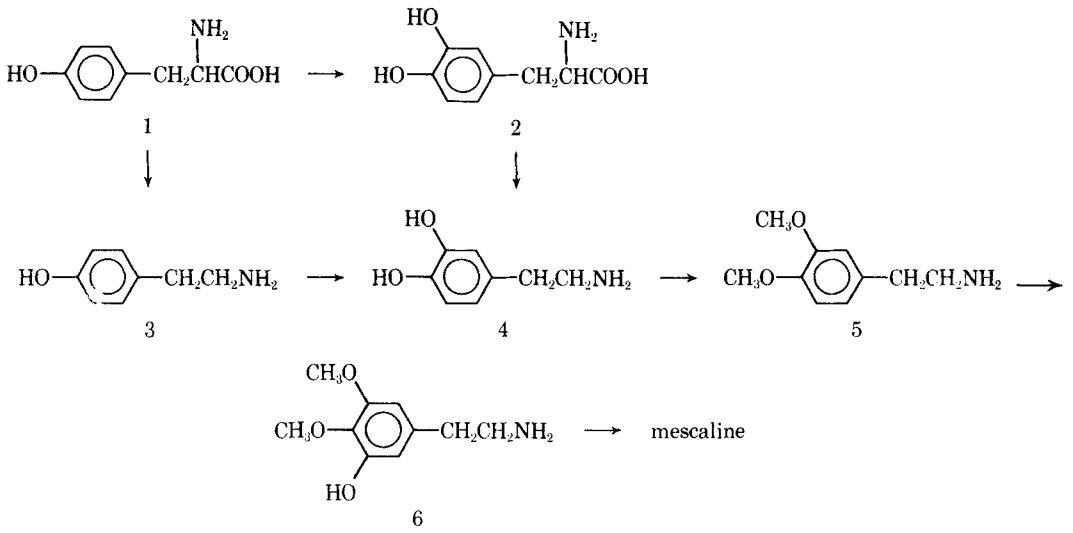
One- and two-dimensional separations of 1-dimethylaminonaphthalene-5-sulfonyl derivatives of several phenethylamines were reported (35). Seventy-one compounds of possible biological interest were evaluated in various systems. The amide derivatives were also separated by the use of thin-layer electrophoresis.

Closely related compounds of pharmaceutical (34) and forensic (34, 38) interest were separated and identified using TLC. Silica gel was used as the absorbing layer in the majority of the reports. Clarke (36) published a separation and identification procedure for LSD, methylsergide, psilocin, psilocybin, bufotenin, 6- and 7-hydroxytryptamine, 5-methoxydimethyltryptamine, and mescaline which uses both ascending paper chromatography and TLC. Particular interest in 4-methyl-2,5-dimethoxyphenyl-2-aminopropane stimulated the publication of a separation and identification procedure for



7*a*: $R_1 = H$, $R_2 = CH_3$
7*b*: $R_1 = CH_3$, $R_2 = H$

Scheme VII



Scheme VIII

the title compound in the presence of amphetamine, methamphetamine, mescaline, bufotenine, and dimethyltryptamine. Compound identification was accomplished by spraying with 10% sodium acetate and 1% 2,6-dibromo-*p*-benzoquinone-4-chlorimine in ethanol and exposing to iodine vapor. They also reported GC separation of the same compounds.

Separation of those compounds closely related to mescaline was effected (37) in several solvent systems. Those compounds that serve as biogenic precursors are separated on the basis of the presence or absence of phenolic groups. Successful separation (28) of these compounds was prerequisite to the publication of the probable mescaline biosynthetic pathway.

GC separation (28, 36, 40) has been particularly useful in combination with mass spectra for identification of the title compounds. Bistrimethylsilylacetamide was found to be quite useful in the separation of 3,4-dimethoxyphenethylamine and tryptamine, both of interest in Parkinson's disease (40). Further discussion of the implications of these materials in the urine appears later in this paper.

Several procedures have been recommended for application in urine-monitoring programs with limited success (45 and references therein). These procedures must be specific, rapid, sensitive, uncomplicated, and inexpensive due to the large number of samples that must be analyzed in a large methadone program. A very successful procedure, developed by Dole *et al.* (46), used ion-exchange paper to absorb the drugs followed by elution with a series of buffer solvent systems. This procedure is reported (44) to satisfy the listed requirements for the identification of narcotic analgesics, barbiturates, amphetamines, and several psychoactive drugs.

Several assay procedures were described in Patel's review (1) and were used by this reviewer. Optimum results in this laboratory were achieved with the procedure described by Woods *et al.* (47).

Bell and Somerville (39) described a fluorescence method for identification and quantitative assay of biologically interesting amines. The materials were spotted on paper and dried. The papers were sprayed with 5% glycine, adjusted to pH 3.0 with HCl, and suspended in a Kilner jar containing moistened paraformaldehyde. After heating at 80° for 3 hr., the papers were viewed under UV light at 360 nm. The fluorescent compounds were eluted with 0.1 *N* HCl and measured in a spectrofluorometer.

Mescaline may be determined spectrophotometrically in unadulterated systems (48). Concentrations of approximately 20 mg./100 ml. may be assayed directly by scanning from 330 to 248 nm. after previously blanking with water at 330 nm. The maximum absorbance, which occurs at approximately 268 nm., is compared to a standard solution of the sulfate or hydrochloride.

The procedures were utilized and modified by several scientists (49–63) studying the significance of 3,4-dimethoxyphenethylamine, which is proposed to be the end-product of aberrant metabolism of the catecholamines. The presence of this compound, the "pink spot" in schizophrenic urine, has been discarded as an artifact by some authors (49, 50, 55, 60–62) and isolated conclusively by others (52, 54, 63) (Table I).

Factors such as patient's diet, time of urine collection, volume of collection, and drug history appear to be critical in this research. A negative nitrogen balance during night hours results in very low concentrations in morning urine. Plant-free diets have given rise to negative findings. Perry and his coworkers (61, 63) carefully screened chronic schizophrenics' urine for 3,4-dimethoxyphenethylamine and bufotenine without success. The patients had been taken off drugs 6 weeks before assay and fed a diet free of plants and cheese for 2 weeks. Urine was collected during 48 hr. and subjected to rigorous assay. Their failure to locate the spots may have been the result of the special diet or drug restriction, or it may possibly have been due to the use of chronic rather than acute schizophrenics. They concluded that no convincing evidence has yet been presented to implicate either ring-methoxylated phenethylamines or *N*-methylated indoleamines in the etiology of the schizophrenias.

The presence of 3,4-dimethoxyphenethylamine in the urine of schizophrenics was apparently confirmed by Creveling and Daly (56), as the presence of 3,4-dimethoxyphenylacetic acid has been by Kuehl *et al.* (64).

They utilized chromatography and mass spectrometry to confirm identification. No further implications concerning the presence of the material were made. The "pink spot" was shown to consist of a mixture of at least seven different compounds. Pind and Faurbye (53) published a critique of the various analytical procedures, including a possibility of confusion between 3,4-dimethoxyphenethylamine and a metabolite of chlorpromazine. Two excellent reviews are available (52, 57) for further reading in this area.

BIOLOGICAL IMPLICATIONS

For a drug to possess hallucinogenic properties, it must, of course, be capable of penetrating the blood–brain barrier. Of all the psychotomimetic methoxylated phenethylamines, mescaline appears to be one of the least successful. Denber and Teller (65) showed that <0.002 of an intravenously injected dose of mescaline was taken up by the CNS of young white rats. A maximum of 0.14% of the dose in the brain was attained in 30 min. (66). Although the mitochondrial fraction bound a small amount of drug, the largest amount appeared in the nerve-ending fraction. The mitochondrial fraction increased with time in mescaline content at the expense of nerve endings, probably reflecting drug metabolism. The authors suggested that the large number of empty vesicles in the myelin supernatant would indicate that the pharmacologic effect of mescaline may be clarified by studying the mechanism of catecholamine release (67).

Korr *et al.* (68) determined the half-life of mescaline in mice to be approximately 55 min. One hour after injection, the highest levels of the drug were to be found in the cortex and the brain stem. Six hours after injection, the radioactive material was found in the hippocampus. Interestingly, the increase in motility of the animals paralleled the increasing concentration in the *cornu ammonis*.

The close structural relationship of amphetamine and its hallucinogenic methoxylated derivatives suggests a subtle difference in the distribution of these compounds. Amphetamine, although an active stimulant, is not usually considered as hallucinogenic. In a recent study (69), amphetamine, methamphetamine, 4-methoxyamphetamine, 3,4-dimethoxyamphetamine, 2,4,5-trimethoxyamphetamine, and 2,5-dimethoxy-4-methylamphetamine were evaluated as to their sites of action on the basis of EEG alerting. The effective mean doses for EEG alerting were 4.0 ± 0.74 mg./kg., 2.8 ± 0.44 mg./kg., 2.6 ± 0.30 mg./kg., 6.0 ± 0.30 mg./kg., 3.1 ± 0.31 mg./kg., and 0.3 ± 0.15 mg./kg., respectively. Those compounds without methoxy groups induced typical EEG alerting in the midbrain level, whereas the methoxy compounds brought about alerting in an area caudal to the midbrain and cephalad to the first cervical spinal segment. 3,4-Dimethoxyamphetamine and 3,4,5-trimethoxyamphetamine were capable of EEG alerting at both the midbrain and medullary regions. The potencies of these drugs for evoking EEG alerting approximated to some degree their psychotomimetic potencies in man. The mechanism of activity of these drugs at the synaptic level is not known, but different sites for EEG alerting would indicate different mechanisms for this response. Fujimori and Himwich (69) suggested that the psychotomimetic methoxy derivatives of amphetamine may act by inhibiting the synchronizing mechanism in the lower brain stem, releasing from its restraint the midbrain-activating system. Bridger and Mandel (70) also suggested different sites of activity for mescaline, 3,4-dimethoxyphenethylamine, and amphetamine based on studies in intact animals.

Table I—Identification of 3,4-Dimethoxyphenethylamine in Urine

Group	Source	Present	Absent	Inconclusive	Total
A	Normal volunteers	1	249	—	250
	Mentally normal inpatients	—	120	—	120
B	Schizophrenics	44	12	11	67
	Paranoid schizophrenics	2	15	—	17
C	Nonschizophrenics	—	16	1	17
	Schizophrenics	20	30	19	69
	Paranoid schizophrenics	2	54	6	62
	Schizophreniform syndromes	5	58	25	88
	Nonschizophrenics	1	68	8	77

Synaptic activity of mescaline was further indicated by findings of Denber and Teller (71). Subcellular levels in the cortical region were attained in 30 min. in the myelin microsomal supernatant and in 45 min. in the nerve endings. 2,5-Dimethoxy-4-methylamphetamine was further studied by Idanpaan-Heikkila *et al.* (72). High levels of radioactivity were found in the hippocampus, amygdaloid nucleus, medial and lateral genticulate bodies, and the putamen. Closer to the midline, the drug appeared to accumulate in the thalamic nuclei, caudate nucleus, and hypothalamus. In the frontal region of the brain, the drug was found in the cerebellum, fastigial nucleus, and olfactory nuclear area. As discussed later, the drug appeared to concentrate in those areas that would be suggested by its symptomatology.

Peripheral distribution of mescaline was thoroughly discussed by Patel (1). The proposed implications of methoxy derivatives of phenethylamines encouraged studies of the binding of these agents (72–74). VanVunakis *et al.* (75) utilized mescaline and other compounds as haptens and elicited the production of antibodies toward the 3,4,5-trimethoxyphenyl, 3,4-dimethoxyphenyl, and 4-methyl-2,5-dimethoxyphenyl groups. This immunological approach offers a new tool for the detection of these compounds in biological fluids, a method of determining cross-tolerance, and possibly an antidote for the pharmacological effects of these compounds. Rundire and Sehon (76) were able to inhibit the subcutaneous effects of serotonin in mice by using a specific antiserum.

Oh *et al.* (73) studied the binding of mescaline and other biologically active amines to plasma protein fractions. Considerable binding of 3,4-dimethoxyphenethylamine was realized with Cohn fraction III, with negligible binding by other fractions. Mescaline and the other amines were not bound to any extent by the various plasma fractions. No significant differences

between normal and schizophrenic plasma binding were noted.

Proteolipid protein (77) bound mescaline and related compounds irreversibly. This binding was much stronger than the complexes formed between mescaline, 3,4-dimethoxyphenethylamine, or serotonin and casein, ovalbumin, serum albumin, or a serum protein mixture.

The close structural relationships of psychotomimetic phenethylamines and the catecholamines would suggest some impact of these compounds on adrenergic receptors. Evidence (78) was presented to demonstrate the activity of mescaline at several α-adrenergic sites as an agonist. It is capable of antagonizing the effects of α-stimulatory drugs and, in the presence of specific β-blocking agents, can inhibit the effects of epinephrine. The β-stimulatory action of mescaline appeared to be very slight, and it did not stimulate cholinergic receptors.

Structurally unrelated hallucinogens including LSD, mesaline, psilocin, and 2,5-dimethoxy-4-methylamphetamine have been observed to facilitate the flexor reflex and evoke the stepping reflex in the chronic spinal dog. Similar responses have been reported for methoxamine, amphetamine, and mescaline. The facilitory action of the former compounds was felt to be an agonistic action (79) because chlorpromazine, which does not affect the flexor reflex, does antagonize the facilitory actions of D-lysergic acid diethylamide, mescaline, psilocin, 2,5-dimethoxy-4-methylamphetamine, and the serotonin antagonist, methysergide. The agonistic actions of the hallucinogens were distinguished from the anorexics in the following manner: (*a*) phenoxybenzamine antagonized the effects of amphetamine and methoxamine but not the hallucinogens; and (*b*) cyproheptadine antagonized the actions of the hallucinogens and facilitated the effects of the anorexics. The similarity of the actions to tryptamine responses suggested that LSD-like hallucinogens owe at least a part of their activity in the spinal chord to agonistic activity at the tryptamine receptor.

Early hypotheses by Gaddum (80), concerning the mechanism of action of LSD, mentioned possible interaction with serotonin, increasing concentration and decreasing turnover. The site of this activity was proposed to be at the serotonin neurons of the raphe nuclei (81) because minute doses of LSD produced a reversible cessation of the firings of single neurons in these midbrain nuclei. Aghajanian *et al.* (82) studied the interaction of the raphe neurons with 2-bromolysergic acid diethylamide, *N,N*-dimethyltryptamine, mescaline, 2,5-dimethoxy-4-methylamphetamine, scopolamine, atropine, and phencyclidine. The latter three drugs produce psychoses of a different type than LSD (83, 84). Inhibitory responses were noted with LSD, *N,N*-dimethyltryptamine, and 2-bromolysergic acid diethylamide, although the action of 2-bromolysergic acid diethylamide was incomplete. An inhibitory effect isolated in a subgroup of raphe cells was observed after mescaline and 2,5-dimethoxy-4-methylamphetamine. No effect on raphe units was seen after scopolamine, atropine, and phencyclidine.

The subtle difference in the activity of LSD and *N,N*-dimethyltryptamine as compared to mescaline and 2,5-dimethoxy-4-methylamphetamine has been reflected in their effect on serotonin metabolism. 5-Hydroxyindoleacetic acid levels are moderately lowered by LSD and *N,N*-dimethyltryptamine in a wide range of doses (85). The relative raphe inhibitory potency was roughly comparable to behavioral potency in rats.

2-Bromolysergic acid diethylamide is much less potent than LSD as a psychotomimetic, although structurally it is quite similar. A postulate for this observation has been proposed by the fact that serotonin creatinine sulfate (2×10^{-6} *M*) markedly decreased in size the postsynaptic potential induced *in vitro* in guinea pig superior colliculus slices in response to optic tract stimulation. Total block of this response was achieved by LSD (10^{-6} *M*), psilocybin (10^{-5} *M*), and mescaline (10^{-4} *M*). It was not blocked by 10^{-5} *M* 2-bromolysergic acid or morphine (86).

The total significance of the overlapping activities of the various psychotomimetics is not entirely clear at this time. Cross-tolerance exists among these compounds, and changes in metabolism resulting in conservation of serotonin (87, 88) are common to both the indolealkylamines and the phenethylamines. Mescaline as well as LSD produced slight increases in 17-ketogenic steroid excretion (89) which, although often associated with stress, was poorly correlated with other clinical or physiological signs of stress. Both drugs also produced very similar effects on eye movements, as reported by Hebbard and Fischer (90).

Recognized disruption of learned behavior upon mescaline administration and the present molecular theory of learning associated with ribonucleic acid molecules suggested that this disruption may be related to mescaline-induced instability of ribonucleoprotein particles in the brain (91). Mescaline did not, however, affect enzymic activities of isolated normal brain cortex ribosomes so that observed ribosomal changes may simply reflect generalized cellular disorganization. Demethylation of mescaline in brain cortex slices is associated with appreciable methylation of ribonucleic acid species (92). It is not unlikely that the reported instability is related to partially blocked hydrogen bonding sites in ribonucleic acid by methylation on mescaline treatment, as indicated by hyperchromicity effects.

The biphasic activity of mescaline as observed in conditioned avoidance responses suggested activity of a metabolite (93). Conditioned avoidances are first inhibited and then enhanced. Pretreatment of animals with iproniazid enhanced the activity, supporting the hypothesis that activity is due to the parent compound rather than to a metabolite (93). Tolerance and cross-tolerance studies (94) supported the concept of biphasic activity by demonstrating that successive doses of mescaline induced tolerance to the vegetative phase and increased the excitatory phase. In a like manner, tolerance developed to the predominantly inhibitory effect of 3,4-dimethoxyphenethylamine and to the excitatory effect of *N,N*-dimethylmescaline. Cross-tolerance existed among all three compounds.

Presentday abuse of several methoxyphenethylamines has necessitated the development of dependable bioassay tests for identification (95). Researchers (95 and references cited therein) have developed test procedures that consist of several tests to identify psychotomimetic drugs and test procedures that may be used to evaluate relative potencies among compounds in the same class. Corne and Pickering (95) reported a possible correlation between drug-induced hallucinations in man and a characteristic head twitch in mice. Excellent relationships between effective doses in mice and hallucinogen doses in man were found for at least 15 compounds. The head twitch did not occur upon administration of compounds closely related to the hallucinogens but not hallucinogenic. Similar relationships have not been established between teratogenic effects (96, 97) in animals and man.

2,5-Dimethoxy-4-methylamphetamine has been the most popular mescaline derivative within the drug culture since its first appearance in 1967 (98). Preliminary pharmacology indicated it to be 25–50 times more potent than mescaline and substantially different than amphetamine (99, 100). Brain concentrations of 2,5-dimethoxy-4-methylamphetamine may be related to several of its actions (75): the hissing and violent rage of cats by stimulation or destruction of certain areas of the hypothalamus; the modification of information from the eye, ear, and skin by alteration of hippocampus activity; *etc.* High brain concentrations of 2,5-dimethoxy-4-methylamphetamine were found in those areas that could account for the induced behavioral effects. Chlorpromazine is not always successful in decreasing the effects of 2,5-dimethoxy-4-methylamphetamine (101). It appears doubtful that chlorpromazine is a specific antidote but its sedative effects may ameliorate some aspects of the reaction (102). Halasz *et al.* (101) suggested that the interaction between 2,5-dimethoxy-4-methylamphetamine and chlorpromazine is dose related and that it is possible to attain a tranquilizer dose which can aggravate rather than protect the patient from the hallucinogen.

3,4-Dimethoxyphenethylamine has been rather thoroughly studied (103–112) because of its possible implications in mental disorders. In high doses (200 mg./kg.), it produces catatonia or hypokinetic rigidity in rats (104). *N*-Acetyl-3,4-dimethoxyphenethylamine is more potent than 3,4-dimethoxyphenethylamine in rodents (107). In both dogs and cats, behavioral responses to the drugs would indicate hallucinogenic activity. In rats, blood pressure was initially elevated (pressor response) and subsequently lowered (β-block) (104). Antihistaminic activity of 3,4-dimethoxyphenethylamine was present in dogs but absent in guinea pigs and rabbits (105). Tolerance (94) and an absence of tolerance (106) have both been reported for this agent. 3,4-Dimethoxyphenethylamine–schizophrenic plasma (108) complexes caused amphetaminelike response in mice unlike normal plasma–3,4-dimethoxyphenethylamine complexes. Masur *et al.* (109) were unable to verify these findings.

Clinical trials of 3,4-dimethoxyphenethylamine in doses up to 800 mg. (103) revealed no psychotomimetic effects similar to those experienced with mescaline, in contrast to those experiments conducted with lower animals. This finding may be the result of rather complete metabolism of 3,4-dimethoxyphenethylamine to the corresponding acid, in contrast to the significant amounts of mescaline excreted as the free amine.

3,4-Dimethoxyphenethylamine in the rat is rapidly concentrated (within 5 min. of injection) in the kidney, liver, spleen, and heart, with relatively small amounts entering the brain (110). Within the brain, highest concentrations were found in the cerebellum and slightly less in the hemispheres, midbrain, and pons medulla. Over 90% of the drug was metabolized within 60 min., with a majority being biotransformed to 3,4-dimethoxyphenylacetic acid by monoamine oxidase. It did not appear to accumulate in sympathetic nerve endings. Clark *et al.* (111) studied the rate of oxidative deaminations of a series of ring-methoxylated phenethylamines. "Mescaline oxidase" is inhibited by semicarbazide whereas "tryptamine oxidase," both from the rabbit liver, is not. Deamination of 3,4-dimethoxyphenethylamine was found to be only partially inhibited by semicarbazide, indicating alternate routes for its metabolism. Mescaline deamination is completely blocked by semicarbazide (111, 112).

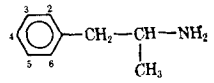
Metabolism of 3,4-dimethoxyphenethylamine was reported (58) to result in the formation of 3,4-dimethoxyphenylacetic acid, 2(3′,4′-dimethoxyphenyl)ethanol, *N*-acetyl-3,4-dimethoxyphenethylamine, *N*-acetyl-3-methoxy-4-hydroxyphenethylamine, and 2(3′-methoxy-4′-hydroxyphenyl)ethanol. Relative percentage isolations of each of the compounds were, respectively, 77, 0.1, 0.1, 6.2, and 0.1 with 15.5% of the material excreted as the free amine. This agrees with the observation of Sargent *et al.* (113) that demethylation at the C^4-methoxy was 15 times as rapid as at C^3-methoxy.

STRUCTURE–ACTIVITY RELATIONSHIPS

Ring Substituents—Smythies *et al.* (114, 115) studied the relationship between the hallucinogenic potency of phenethylamines and the methoxy substituent. Monosubstituted compounds (*o*, *m*, *p*) were inactive in doses up to 25 mg./kg. All disubstituted compounds (2,3; 2,4; 2,5; 2,6; 3,4; and 3,5) were inactive in the Sidman avoidance response technique. Previous reports (104–107) indicated rodent activity of the 3,4-isomer (3,4-dimethoxyphenethylamine). Only mescaline among the trisubstituted derivatives (2,3,4; 2,3,5; 2,3,6; 2,4,5; 2,4,6; and 3,4,5) was found to be active. Of the tetrasubstituted derivatives (2,3,4,5; 2,3,5,6; and 2,4,5,6), only the 2,3,4,5 was active (approximately 2 mescaline units). The pentasubstituted compound was the most active (7 mescaline units) of all compounds synthesized. Shulgin (116), in a recent review, reported 2,4,5-trimethoxyphenethylamine to be equal in potency to mescaline and 4-methoxyphenethylamine to be only slightly less potent than mescaline.

3,4-Methylenedioxyphenethylamine was less than 0.2 times as potent as mescaline, 3-methoxy-4,5-methylenedioxyphenethylamine about equipotent to mescaline, and 2-methoxy-3,4-methylenedioxyphenethylamine somewhat less than 5 times as potent as mescaline.

Table II—Structure–Activity Relationships



Compound Number	Substitution Pattern 2	3	4	5	6	Activity, Mescaline Units
1	H	H	OCH_3	H	H	5
2	OCH_3	OCH_3	H	H	H	—
3	OCH_3	H	OCH_3	H	H	5
4	OCH_3	H	H	OCH_3	H	8
5	OCH_3	H	H	H	OCH_3	—
6	H	OCH_3	OCH_3	H	H	1
7	H	OCH_3	H	OCH_3	H	—
8	H	OCH_3	OCH_3	OCH_3	H	2.2
9	OCH_3	H	OCH_3	OCH_3	H	17
10	OCH_3	OCH_3	OCH_3	H	H	2
11	OCH_3	OCH_3	H	OCH_3	H	4
12	OCH_3	OCH_3	H	H	OCH_3	13
13	OCH_3	H	OCH_3	H	OCH_3	10
14	O —CH_2—	O	H	H	H	—
15	H	O —CH_2—	O	H	H	3
16	H	OCH_3	O —CH_2—	O	H	2.7
17	OCH_3	H	O —CH_2—	O	H	12
18	OCH_3	O —CH_2—	O	H	H	10
19	O —CH_2—	O	OCH_3	H	H	3
20	O —CH_2—	O	H	OCH_3	H	—
21	O —CH_2—	O	H	H	OCH_3	—
22	OCH_3	O —CH_2—	O	OCH_3	H	12
23	OCH_3	OCH_3	O —CH_2—	O	H	5
24	H	OCH_3	O —$(CH_2)_2$—	O	H	1
25	OCH_3	OCH_3	OCH_3	OCH_3	H	6
26	OCH_3	OCH_3	OCH_3	H	OCH_3	—
27	OCH_3	OCH_3	H	OCH_3	OCH_3	—
28	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	—
29	OC_2H_5	H	OCH_3	OCH_3	H	7
30	OCH_3	H	OC_2H_5	OCH_3	H	15
31	OCH_3	H	OCH_3	OC_2H_5	H	7
32	OC_2H_5	H	OC_2H_5	OCH_3	H	—
33	OC_2H_5	H	OCH_3	OC_2H_5	H	—
34	OCH_3	H	OC_2H_5	OC_2H_5	H	—
35	OC_2H_5	H	OC_2H_5	OC_2H_5	H	—
36	OCH_3	H	CH_3	OCH_3	H	80

Larger doses of the related compounds (117) have been used to induce a hypokinetic rigid syndrome in cats which was, in turn, related to the structure. This response was caused by only the 4-methoxy, 3,4-dimethoxy, 3,4,5-trimethoxy, and 3-hydroxy-4-methoxy compounds. The latter compound was active only after iproniazid treatment, presumably prolonging the half-life of the compound permitting liver *O*-methyltransferase to synthesize 3,4-dimethoxyphenethylamine. 4-Methoxy substitution appeared to be prerequisite for activity. Ring hydroxylation apparently inhibited transfer across the blood–brain barrier. The duration of hypokinetic rigid syndrome was related to the number of methoxy groups adjacent to the 4-methoxy groups.

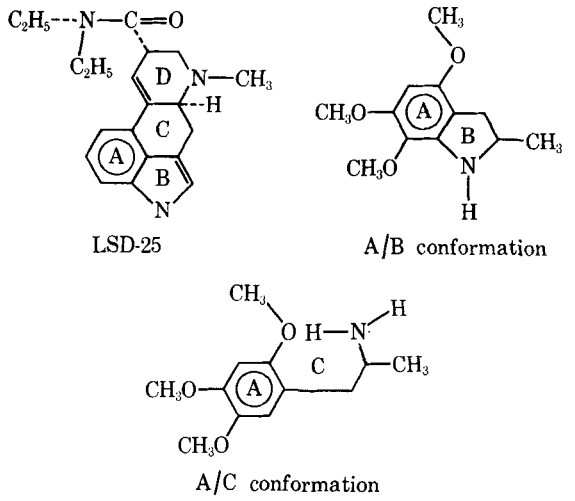
α-Methyl Derivatives—Table II summarizes the pertinent data concerned with the methoxy derivatives of phenylisopropylamine (116).

Compounds 2, 5, 7, 14, 20, 21, 26, 27, and 28 were not synthesized at the time of this report. Since that time, Compounds 2 and 7 have been synthesized (4). Compounds 32–35 have been synthesized (2) but not totally evaluated pharmacologically. Certain generalizations concerning the structure–activity relationships can be made with the information in Table II. The inclusion of an α-methyl group increases the activity of this series.

Optimum activity is found in those compounds bearing a *para*-methoxy group. The addition of an *ortho*-methoxy group usually causes an increase in activity which may be substantial. *Meta*-methoxylation with few exceptions causes a decrease in activity. Conversion of two adjacent methoxy groups to a methylenedioxy group generally brings about an increase in activity. *Para*-methylmercapto substitution is not reported (118) as inducing hallucinations.

Psychotomimetic effects have been claimed in related compounds which do not possess methoxy groups. *Ortho*-substituted *N*-methylphenyl-2-aminopropanes demonstrated remarkably high potencies expressed as approximate mescaline units (119). The authors prepared *ortho*-amino (6 mescaline units), nitro (28 mescaline units), iodo (8 mescaline units), chloro (27 mescaline units), and bromo (20 mescaline units). Similar substitutions in the *para*-position resulted in very potent psychostimulants without psychotomimetic activity. The effects of these compounds were discernible up to 48 hr. longer than LSD.

Disruption of visual discrimination with squirrel monkeys (120) yielded results very similar to those reported earlier (116). Compound 26 was approximately 5 times as potent as Compound 9, which was the most potent trimethoxy derivative. 2,5-Dimethoxy-4-ethylphenylisopropylamine was reported to be about twice as potent as Compound 26, which would give it a mescaline value of approximately 150 (121). Uyeno (122) evaluated a series of hallucinogenic compounds on the basis of their ability to alter escape



Scheme IX—Comparison of LSD to Mescaline Derivatives

tendencies of rats as measured by their swimming time through an escape tube. Compound 9 was about twice as potent as Compound 8, and both were more potent than Compound 10.

Fairchild *et al.* (123) evaluated several hallucinogen compounds by comparing their ability to produce patterns of distortion in frequency distribution of spontaneous brain electrical activity in the cat. The application of multivariate statistical techniques to the results of broad-band frequency analysis of spontaneous brain electrical activity showed Compounds 10, 15, and 16 to be more potent than Compound 6 which, in turn, was slightly more potent than mescaline.

Ho *et al.* (4) evaluated an expanded series of compounds as to their ability to disrupt mouse behavior as determined by a swim maze test. 4-Methyl-5-methoxyphenyl-2-aminopropane was as active as 2,5-dimethoxy-4-methylamphetamine and of longer duration, whereas 4-methyl-2-methoxyphenyl-2-aminopropane was inactive. 2,5-Dimethoxyphenyl-2-aminopropane was also inactive, indicating the necessity of the 4-methyl substituent. Several other new compounds were reported but not related in potency to known hallucinogens.

A limited number of novel compounds (124–127) were reported which bear resemblance to mescaline. A series of methoxyphenethylamines was synthesized (124) containing an α-trifluoromethyl group. These compounds were all less potent than corresponding methyl analogs, and only the 3,4,5-methoxy derivatives gave positive results in the head twitch assay (0.11 mescaline unit).

Walters and Cooper (125) prepared *trans*-2-(3,4,5-trimethoxyphenyl)cyclopropylamine in anticipation of prolonged mescalinelike effects. The title compounds exhibited identical changes in mice as mescaline, although its acute effects were briefer than either mescaline or tranylcypromine. It definitely had psychotomimetic effects in rodents which cannot be directly extrapolated to humans at this time.

The large number of synthesized methoxyphenethylamine derivatives has made possible certain theories concerning criteria for activity (128–130). Similar modes of activity among LSD, psilocybin, and mescaline suggest that common structural requirements may exist between the chemically unrelated series. Since LSD is the most potent compound and is additionally a rigid structure, it should make a suitable model for the hallucinogens. Only the D-lysergic acid conformation is naturally occurring and only D-LSD is psychotomimetic in man. Snyder and Richelson (128) postulated that a compound's ability to form the A and B or A and C rings of lysergic acid (Scheme IX) is critical insofar as psychotomimetic activity is concerned.

Table III—Tendency to Form A/B or A/C Ring Conformations

Compound	Tendency to Form—Ring B	Tendency to Form—Ring C	Potency, Mescaline Units
2,4,6-Trimethoxy	0	4	10
2,4,5-Trimethoxy	0.7	2	17
6-Methoxy-3,4-methylenedioxy	0.7	2	21
2-Methoxy-3,4-methylenedioxy	0.6	2	18
2,3,6-Trimethoxy	0	2	<10
3,4,5-Trimethoxy	2	—	2.2
3-Methoxy-4,5-methylenedioxy	2	—	2.7
2,3,5-Trimethoxy	1	0	<7
2,3,4-Trimethoxy	0.6	0	<2

Analogs of mescaline might possibly form either the A/B or A/C ring system of lysergic acid. Mescaline itself would be able to form the A/B ring system by intramolecular hydrogen bonding between the amine side chain and either *ortho* position. Negative π-charge calculations (129, 130) revealed that mescaline possesses the greatest charge at positions 2 and 6 and would, therefore, be most likely to form the B ring of LSD. 2-Methoxy-3,4-methylenedioxyphenethylamine may owe its greater potency to a tendency toward A/C ring conformations. 2,3,4-Trimethoxyphenethylamine is not as potent and would not share a similar tendency toward A/C ring conformations, because the 3-methoxy group would inhibit the required free rotation of the 2-methoxy group.

Methoxyphenyl-2-aminopropanes are more potent than their desmethyl counterparts (116). Major consideration in the formation of the B ring would be paid to the negative π-charge at positions 2 and 6 and the availability of these positions for hydrogen bonding. Those compounds with methoxy groups on position 2 and without substitution at position 3 would also have a tendency to form the A/C conformation. Snyder and Richelson (128) compared the combined tendencies to approximate LSD to potency for a series of methoxyphenyl-2-aminopropanes (Table III).

Snyder and Merrill (129, 130) made molecular orbital calculations for a variety of hallucinogenic drugs and their nonhallucinogenic counterparts and discovered several relationships between the electronic configurations and activity. Unfortunately, no methylenedioxy compounds were included in this study.

The energy of the highest filled molecular orbital was calculated for a series of mono-, di-, and trisubstituted phenethylamines. Progressive methoxylation resulted in an increase in highest filled molecular orbital energy. Mescaline had the highest filled molecular orbital in the series, with 2,3,4-methoxyphenethylamine a poor

Table IV—Relationship of Hallucinogenic Potency in Different Classes of Drugs to the Energy of Their Highest Filled Molecular Orbital

Drug	Energy of Highest Filled Molecular Orbital, B Units	Potency, Mescaline Units
LSD	0.2180	3700
Psilocin	0.4603	31
6-Hydroxydiethyltryptamine	0.4700	25
2,4,5-Trimethoxyamphetamine	0.4810	17
3,4,5-Trimethoxyamphetamine	0.5357	2.2

second. Confirmation of this possible relationship will depend on similar calculations for the other isomers. Activity was also related to superdelocalizability, which is a function of the highest filled molecular orbital energy related to each atom.

A series of trimethoxyphenyl-2-aminopropanes were subjected to the same calculations. The energy of the highest filled molecular orbital was greatest for 2,4,5-trimethoxy (17 mescaline units), intermediate for 3,4,5-trimethoxy (2.2 mescaline units) and lowest for 2,3,4-trimethoxy (<2 mescaline units). Activity did not correlate well with frontier electron density, π-charge, free valence, superdelocalizability, or lowest empty molecular orbital energy.

Energy calculations showed excellent relationships between highest filled molecular orbital energy and activity in a series of unrelated compounds (Table IV).

In spite of a rather crude calculation for LSD, the high potency is reflected by an energetic highest filled molecular orbital. The suggestive correlations between highest filled molecular orbital and psychotomimetic activity implies that these materials may act as electron donors. Of course, other compounds such as chlorpromazine are powerful electron donors and do not possess hallucinogenic activity. However, a combination of steric and electronic considerations would provide the possibility of designing hallucinogenic compounds of greater potency than are now in existence.

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