Psychotomimetic Agents Related to the Catecholamines

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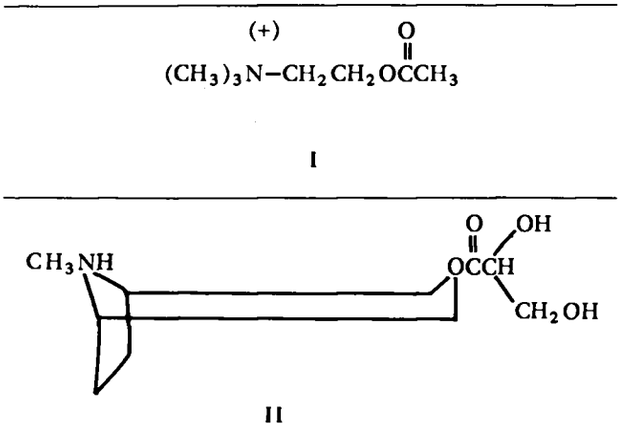
Many of the drugs which have been shown to have an influence on the integrity and function of the nervous system are related in some way chemically to the mediators that effect these functions. A drug may serve as a chemical imitator of a neurotransmitter, and in part take the latter's place. The consequence of such an action is continued neural function, albeit in a somewhat abnormal manner. Conversely, the drug may, through chemical imitation, block and interfere with normal neurohumoral function, the consequence of which is the loss of such function to varying degrees.

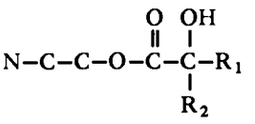
The centrally active drugs known as the psychotomimetics (or hallucinogens, psychodysleptics, or psychedelics, depending upon one's field of interest or training) may be divided into chemical groups which bear a close structural relationship to the principle neurohumors, and which, at the same time, allow some generalization regarding the qualitative nature of their actions. The clearest classification arranges these compounds into groups of materials which resemble acetylcholine, serotonin and norepinephrine, respectively. The first two will be discussed briefly; however, the last group contains agents in which certain behavioral consistencies become evident, and certain relationships to metabolic pathways seem obvious.

ACETYLCHOLINE-RELATED PSYCHOTOMIMETICS

A very large group of psychotomimetic drugs can be closely related to the neural transmitter, acetylcholine, and have been collectively called "anticholinergic agents." With notable exceptions, they are substituted ethanolamines (as is acetylcholine itself) in which the nitrogen is alkylated and the alcohol function esterified with an appropriate acid. The structural relationship between acetylcholine (I) and atropine (II) is demonstrated in Figure 1, wherein atropine is drawn in a conformation that gives emphasis to the geometric separation of the nitrogen atom and the ester function. In the case of both atropine and scopolamine, the compounds that have served as paradigms in this area of research and study, there is admittedly a three-carbon chain separating these positions, but the capability of achieving the boat-configuration shown allows a close resemblance to acetylcholine.

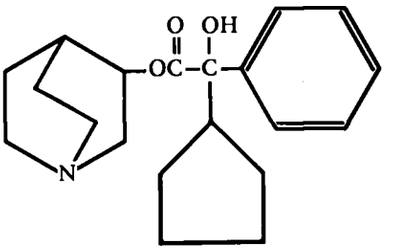
Most of the synthetic extensions of these materials have involved esters between a glycolic acid and a cyclic ethanolamine. The general structure (III) shows the flex-





III

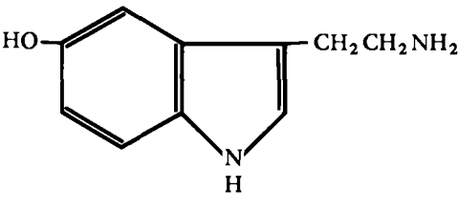
ibility of substituents possible. The glycolic acid may carry one phenyl group (R_1 = C_6H_5-, mandelic acid with an aliphatic component at R_2; refer to Figure 2) or both substituents may be aromatic (benzylic acid). The ethanolamine moiety may be open-chain (as with the diethylaminoethyl- group seen in benzactyzine) or a heterocycle (as the N-ethylpiperidyl and pyrrolidylmethyl groups seen in ditran). Substitution with the guinuclidinol ring, as shown in IV (Figure 2), represents structural variations that can lead to compounds of high potency in this family.



IV

The qualitative nature of the intoxication of this large group of parasympatholytic agents is quite constant, and distinctly different from the syndrome to be described below for the indoles and for the phenethylamines. In a most general sense, there is the development of a state of confusion, stupor, and delirium rather than a state of sensory and emotional constructiveness, and there is usually amnesia and aphasia as opposed to the generally excellent recall and self-expression associated with the families to be discussed below. Sensory syntheses tend to be auditory rather than visual, and the overall effect is better described as anaesthetic and depressant, rather than stimulatory.

Mention should be made of several compounds that must be classified here because of the symptomology of their effects, if not the exact nature of their chemical structures. Phencyclidine (Sernyl®) is representative of such anaesthetics and tranquilizers. Although it is chemically unrelated to the esters discussed above, it is of similar psychopharmacology, and it has been encountered frequently in the illicit drug trade, most often under the difficult-to-justify title of "synthetic THC."



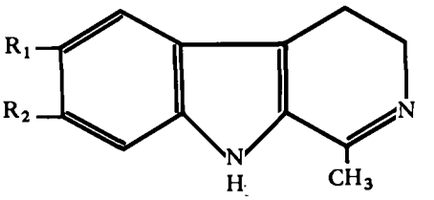
V

SEROTONIN-RELATED PSYCHOTOMIMETICS

A second class of the psychotomimetics can be gathered together due to their chemical resemblance to the biologically active material, serotonin (V; Figure 3). These materials are all indoles, as is serotonin, and have been evaluated most closely as to their capabilities in interfering with neural systems that involve, or respond to, serotonin as a mediator.

Only brief note should be made here of the extremely complex indoles such as LSD and ibogaine. Although LSD is one of the most potent and thoroughly studied of all the indole psychotomimetics, it is as yet impossible to relate its structure to any conceivable metabolic chemistry. It is thus classifiable *lusus naturae* (although admittedly it is not found in nature, but is a semi-synthetic derivative of the natural lysergic system of alkaloids), and does not bear much resemblance to serotonin. The same casual treatment must here be given to the components of *Cannabis sativa.* Although the activity of marihuana can to a large measure be attributed to one of the components, tetrahydrocannabinol, the total dissimilarity of this chemical to any known neurochemical pathway suggests that it should be considered apart from this general discussion.

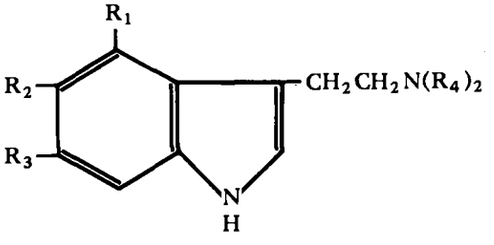
A closer relationship may be seen with the alkaloids of the Harmala group, such as harmaline (VIa; Figure 4). This material along with its dehydro- and dihydro- counterparts (harmine and leptaflorine) are found in a



	R_1	R_2
VI a	H	OCH_3
b	OCH_3	H

number of intoxicating plants. It could be argued that they are generated through the cyclization of a positional isomer of serotonin (6-hydroxytryptamine) with some two-carbon compound. More intriguing are the isomers of marmaline wherein the methoxyl group is relocated to the position entirely analogous to serotonin. This material is 6-methoxyharmalan (VIb; Figure 4), and its dehydro- and dihydro- counterparts (6-methoxyharman and 6-methoxytetrahydroharman) are all several times more potent than the 7-methoxy compounds. They have yet to be found in nature. They have, nonetheless, been generated *in vitro* by the cyclization of melatonin, and although such reactions are most appealing in the hypothesis of the *in situ* generation of an active psychotogen from a known pineal metabolite, all searches for this product in the intact living system have failed.

A more obvious analogy to serotonin, from the structural point of view, is seen with the variously substituted tryptamines. The several N,N-dialkyltryptamines (DMT; DET; DPT; VIIa, VIIb, and VIIc; Figure 4) all are recognized hallucinogens, active parenterally, and of decreasing potency in the order shown. The 4-hydroxy analog of DMT is psilocin (VIId; Figure 4) which is found along with its equivalent phosphate ester, psilocybin, in the sacred mushroom *Psilocybe mexicana.* These are the only orally active serotonin analogs. The N,N-dimethyl derivative of serotonin itself is bufotenine (VIIe; Figure 4), which is found both in the plant and animal worlds. Although it shows pressor effects upon intravenous studies in man, it can by no means be called a psychotomimetic. Its O-methyl ether, however, 5-OCH_3-DMT, is a component of several tropical snuffs, and is highly active. The 6-hydroxy analog of DMT (VIIf; Figure 4) is possibly a metabolite of DMT, but appears to be inactive. The 7-hydroxy counterpart has apparently not been evaluated.



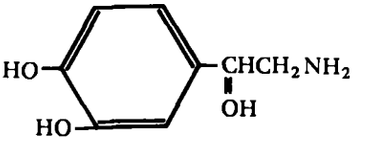
	R_1	R_2	R_3	R_4
VII a	H	H	H	CH_3
b	H	H	H	C_2H_5
c	H	H	H	C_3H_7
d	OH	H	H	CH_3
e	H	OH	H	CH_3
f	H	H	OH	CH_3

From the qualitative point of view, many of these indole or indole-like psychotomimetics can be grouped together as displaying a remarkably similar pattern of mental changes. As has been mentioned above, this, and the following family of phenethylamines, are quite distinct from the anticholinergic group, in that there is recall and general access to the events that occurred during the period of intoxication. One cannot be too dogmatic in such assignments, for it is certain that for every example of successful categorization, there will be someone, somewhere, who will know of an exception.

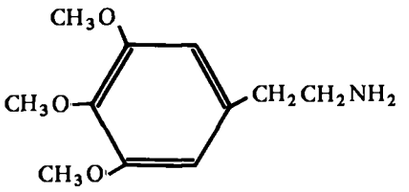
Nonetheless, this family of psychotomimetics, those that in substance mimic the structure of serotonin, lends itself to the generation of illusions (or constructive delusions) that are highly introspective and are of an immediate personal nature. If the interpretative changes are based on objective fact and confirmable observations, they may be accepted as being instructional; if they are subjective and apparently unique without tangible source, they may be accepted as being mystical or religious. The effects are nonetheless mainly interpretational rather than sensory, and thus appear to be meaningful rather than being predominantly entertaining.

NOREPINEPHRINE-RELATED PSYCHOTOMIMETICS

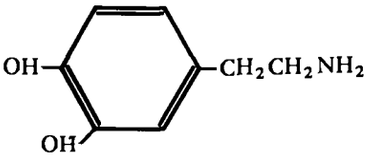
The third classification of psychotomimetics, although the simplest from the structural point of view, is most closely related to well-established neurochemical metabolic pathways. A principle neuro-effector of the sympathetic nervous system is norepinephrine (VIII; Figure 5) which is paramount in the definition of the adrenergic synapse. It is beta-3,4-trihydroxyphenethylamine, and is closely related to the well-studied psychotomimetic, mescaline (3,4,5-trimethoxyphenethylamine, IX; Figure 5). The precursors and metabolites of norepinephrine have chemical structures which could possibly reflect the capability of the normal organism to produce chemicals that might be related pharmacologically to mescaline. The immediate precursor to norepi-



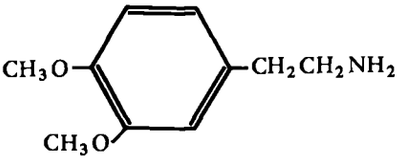
VIII



IX



X



XI

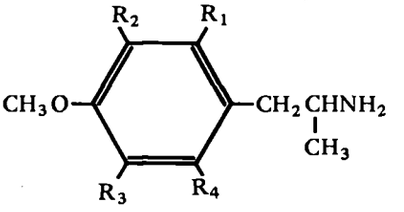
nephrine is 3,4-dihydroxyphenethylamine (dopamine, X; Figure 5). The dimethyl ether of dopamine is 3,4-dimethoxyphenethylamine (DMPEA; XI; Figure 5) which has been identified as a component of human urine, and has been associated with the clinical diagnosis of schizophrenia. Although this assignment, as well as its origins, are controversial points, this material, wanting a single methoxyl group to become a known psychotomimetic, demands attention. The capability of the human at least to monomethylate these catechols is certain, as this is a normal disposition procedure for both norepinephrine and its N-methyl homolog, epinephrine (adrenaline).

Yet another point of potential *in vivo* chemistry is worthy of mention here. Dopamine has been shown to undergo aromatic hydroxylation, possibly at the meta-position to form 3,4,5-trihydroxyphenethylamine, and with certainty at the ortho-position to yield the 2,4,5-trihydroxy counterpart. Both materials can be methylated *in vivo*, and the totally methylated analogs of these materials are psychotogens; the first is mescaline and the second is the two-carbon analog of TMA-2 (v.i.).

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS

Of the large number of substituted phenethylamine derivatives that have been chemically synthesized and characterized (perhaps 2,000), about thirty have been evaluated in clinical trials which have established their relative potencies, and have allowed a preliminary estimation of the qualitative nature of their intoxication. Certain structural features appear meaningful in the interpretation of the activity values which can be assigned to them.

One of the most apparent of these parameters is the length of the aliphatic side-chain. Although mescaline is a primary amine, it appears to be completely ineffective as a substrate for the monoamine oxidase enzyme system, which is responsible for the oxidative deamination of most phenethylamines. This inertness may be due to the presence of an extremely basic aromatic ring, which serves as a second base site and renders the molecule immune to metabolism. Along these lines, the mono- and the dimethoxy- analogs of mescaline (4-methoxyphenethylamine and DMPEA, XI; Figure 5) are both readily deaminated by this enzyme system, and both have been shown to be inactive in human studies. A second mechanical stratagem to circumvent enzymic destruction is the simple addition of a branched methyl group on the carbon adjacent to this amine group. In this manner phenethylamine, which is rapidly metabolized to inactive phenylacetic acid, is to be compared to amphetamine which is virtually immune to detoxification, at least in humans. The phenylisopropylamine counterparts of both the 4-methoxyphenethylamine and 3,4,5-trimethoxyphenethylamine yield products (4-MA,



XII

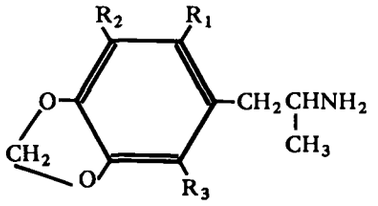
	R_1	R_2	R_3	R_4
a 4MA	H	H	H	H
b TMA	H	OCH_3	OCH_3	H
c DMA	H	OCH_3	H	H
d TMA-2	OCH_3	H	OCH_3	H
e TMA-6	OCH_3	H	H	OCH_3

XIIa and TMA, XIIb; Figure 6) that are of distinctly increased potency. Neither of the 3,4-dimethoxy- counterparts (3,4-dimethoxyphenethylamine, XI; Figure 5 or 3,4-dimethoxyphenylisopropylamine, DMA, XIIc; Figure 6) have been found to be centrally active in human subjects at any level, so this point is as yet unresolved.

A methodological study of the various positions that can be substituted about the aromatic ring in TMA (XIIb; Figure 6) has shown that the 2,4,5- orientation is the most potent of all. This compound (TMA-2, XIId; Figure 6) is about an order of magnitude more effective than the 3,4,5- isomer, but retains much of the qualitative nature of the latter. This will be discussed later. The symmetrical analog, 2,4,6-trimethoxyamphetamine (TMA-6, XIIe; Figure 6), again retains this style of biological activity, but lies intermediate in potency.

An unexpected but rather consistent change is observed when two adjacent methoxyl groups are replaced with the five-membered heterocyclic ring containing the oxygen atoms. The potency of these products is generally increased over that of the open chain analogs. It is in the realm of the qualitative features that there is most noticeable change. There is little if any of the profound insight or religious significance that is so characteristic of the indolic psychotomimetics or of the methoxylated amphetamines. This is the loss of the property most generally accepted as "psychedelic." In its place there is the generation of a form of dream-world; for some subjects this is structured in the framework of past events, while for others it appears to be merely a dream-like entertainment.

This third type of psychotomimetic event seems to be a general feature of the methylenedioxy-containing chemicals. Both MDA and MMDA (XIIIa and XIIIb; Figure 6) are equivalent in potency (1.5 to 2.0 mg./kg.) and have similar capabilities for the generation of this eyes-closed visual effect. The 2,4,5- 2,3,4- and 2,3,4,5- analogs (XIIIc, XIIId, and XIIIe; Figure 6) are again similar qualitatively and are about four times as potent.



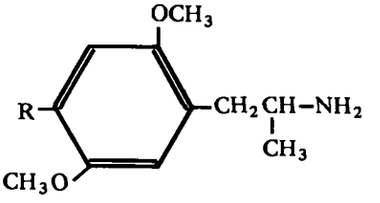
XIII

	R_1	R_2	R_3
a MDA	H	H	H
b MMDA	H	OCH_3	H
c MMDA-2	OCH_3	H	H
d MMDA-3a	H	H	OCH_3
e DMMDA	H	OCH_3	OCH_3
f DMMDA-2	OCH_3	OCH_3	H

The tetra-substituted analog with the two methoxyl groups vicinal (DMMDA-2, XIIIf; Figure 6) lies intermediate. It is this property of apparently valid memory recall, coupled with the capability of maintaining to some extent normal behavior through voluntary visual contact with the surroundings, which has justified their evaluation in psychotherapy. Limited studies with the six-membered analogs (ethylenedioxy-amphetamines) have failed to reveal any central activity in humans.

Yet another structural variation has been studied in which an alkoxy group has been replaced with an alkyl group. The rationale that dictated such a substitutional change was simple. In the few human metabolic studies conducted with these materials, it seemed consistant that detoxicative conjugation was preceded by either hydroxylation of the aromatic system, or by demethylation of a methoxyl group to generate such a hydroxyl group. It seemed clear that if a vital position could be blocked by a group that was not amenable to hydrolysis, the biological nature of the compound could be radically altered. The compound that would result might be more potent, as it cannot be readily disposed of through normal metabolic procedures. On the other hand, the compound might be without effectiveness, but might serve in turn as an antagonist to the action of other materials chemically related to it.

The first example of such a chemical modification corroborated the former possibility. The methyl analog



XIV

of TMA-2, the most active of the methoxylated amphetamines, led to DOM (XIV, R = CH_3). It proved to be about eighty times as potent as mescaline, and to have a psychological effectiveness that extends beyond its residence in the body. The nature of the psychological effects are again similar to those of the indoles or LSD, and are quite distinct from the methylenedioxy materials grouped above.

The extension of this methyl group to the ethyl homolog provided 2,5-dimethoxy-4-ethylamphetamine (DOET, XIV, R = C_2H_5). This compound has a dual action, in that at low dosages it appears to function as a psychic energizer, and it is only at high levels that there are indications that it may be psychotomimetic. In the

former role it is currently being evaluated clinically, and it must be held as being somewhat less potent than DOM.

METABOLIC SIGNIFICANCE

The reason for grouping this latter family of one-ring psychotomimetics under a single heading is that they are all reminiscent of the structure of norepinephrine. It is appealing to speculate that their biochemistry in the normal human organism may in some way reflect that of norepinephrine, and that their biological activity may be in such a way explained. Epinephrine is metabolized, at least in part, by 3-methylation, and it is possible that there are processes present for dimethylation. It is certainly conceivable that two of the methoxyl groups present in most of these psychotomimetics could be generated in the intact organism. Similarly, the immediate precursor of norepinephrine (3,4-dihydroxyphenethylamine, dopamine) may be capable of being dimethylated *in vivo*. This mechanism has been proposed to account for the presence of DMPEA (v.s.) in human urine. Whether this base, related to the pink spot associated with the diagnosis of schizophrenia, has metabolic significance is still uncertain. It might even be of dietary origin, but nonetheless it does serve as a close link between normal and potentially abnormal metabolism. This material is not active in man.

Yet more interesting are the observations that dopamine can be hydroxylated in the 6-position in certain *in vivo* experiments. This results in 2,4,5-trihydroxyphenethylamine which is the exact substitution pattern found in TMA-2. If one recognizes the known capacity of the intact organism to methylate this trihydroxy material, and the demonstrated ability within the human to demethylate materials such as mescaline, it is possible that there may be a metabolic intersection between exogenous psychotomimetics and endogenous neurohumors.

A lingering objection may be raised; that the natural amines in the mammalian metabolic schemes all contain the two-carbon chain whereas most of the psychotomimetics which have been studied and found active have the three-carbon chain. Most simple phenethylamines, the two-chained compounds, are excellent substrates for the monoamine oxidase enzyme system. Mescaline is an exception for reasons mentioned earlier. It is deaminated, but through a different process. It is possible that the extended activity of the amphetamines, being secondary amines and thus not substrates for the monoamine system, may persist in the normal human subject for a period of time long enough to achieve pharmacological activity.

To summarize, there is a clinical state of induced mental change which can be achieved through the application of these synthetic chemicals, and which simulates, to a degree, the conditions observed in mental illness. Some of the chemicals undergo demethylation in the course of their metabolism, and if such steps are blocked, there is an exaserbation of their activity. Further, the normal process of metabolism of the catecholamines involves a degree of methylation, and possibly nuclear hydroxylation as well. It is possible that these two pathways may converge upon an identical substitution pattern which may represent that of a potential endogenous psychotogen.

Admittedly, there is no easy explanation in such an explanation for the diverse qualitative natures observed among the various psychotomimetics. These compounds can achieve styles of intoxication that vary from the profoundly introspective to the overtly entertaining. Nonetheless, the many guises of spontaneous mental aberrations are equally diverse, and the absence of absolute correspondence should not discourage further study in this area.