

## CHEMISTRY AND STRUCTURE-ACTIVITY RELATIONSHIPS OF THE PSYCHOTOMIMETICS

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This meeting is a discussion of the psychotomimetics, and since no one has yet defined the word, and I am the first to speak, I will define it. The first voice heard is the one that is argued against later.

The definition of the word is worthy of a few minutes. This entire group of materials can be arranged in a variety of ways. They could be, for example, considered from the point of view of their site of action. Thus, if you will classify a chemical as active at a cellular level or at a molecular level, you can argue that this is its primary site of action, and all such materials can be classified depending upon their action at this specific site. Secondly, they have an action upon man, which is incidental to its classification. A material may be primarily cytolytic, and only incidentally cure some bacterial infection in man.

Quite separately, you can take all of the compounds assembled in the *U.S. Pharmacopoeia* and arrange them on the basis of their action on the human organism. The primary classification would describe the action on the intact individual, and only secondarily would it suggest how this action came to be. For example, a material may be a contraceptive and it is classified as such in the drug manuals. It is incidental whether it is a contraceptive because it inhibits ovulation or because it disturbs the cervical mucosa.

I would like to suggest a third way of organizing these materials. The psychotropic materials, as a special entity in the drug classification, can only be defined by their effect upon the interrelationships between people. This definition involves relationships such as mood, which, after all, have no

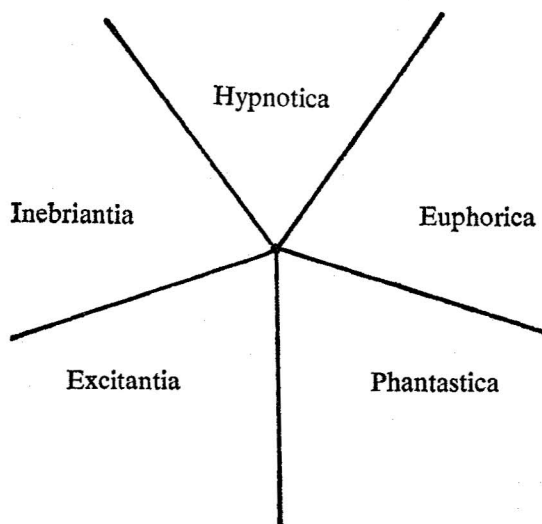
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absolute value. One can only evaluate a change in mood relating one person to another in his society, or even to himself at some separate time. One has a tenuous assignment of sanity, for sanity is a statistical thing. You have to have three people to decide which one is insane. It is a minority concept. The specific terms, sanity, insanity, psychosis and psychotomimetic, must be defined at a social or human level of interaction. This classification describes the general term "psychotropic," which is literally from the Greek  $\psi\chi\eta$ , the mind or the soul, and the turning or changing of it.

One is confronted with an apparent paradox regarding sanity in the definition of psychotomimetics. When one changes from a real environment to a different environment, and this second environment seems as real as the first but is different from the first, then there seems to be no absolute way of determining which of the two real worlds is the "real" real world.

The psychotropic chemicals were subdivided into five groups some thirty or forty years ago by Lewin (1927). These form a useful way of cataloging psychotropic chemicals. They are presented in a circular form which allows a convenient classification of chemicals, for many of these drugs have more than one action.

The first of his classifications was an area known as "Excitantia," literally, chemicals that cause excitement and stimulation. Included here are such synthetic materials as amphetamine, methedrine and Ritalin. Here also are such natural materials as caffeine and khat.



The adjacent and very closely allied classification is entitled "Inebriantia." Here one finds inebriants which cause intoxication in the social sense, rather than in the pharmacological sense. There is a host of organic compounds known to all: ethanol, chloroform, ether, the various materials that have an initial phase of excitement and that cause mental distortion and mental depression, leading quite smoothly into the area of "Hypnotica," the third classification.

This region is best characterized by the barbiturates. In this area one finds the first challenge to the meaning of the real world. There is a replacement of reality with amnesia or confusion. Here, in addition to the sedatives and anesthetics, there are drugs such as atropine, scopolamine, benactyzine, phencyclidine, and other delusional and mentally deranging psychotropic chemicals that will be discussed later in this meeting.

Adjacent to "Hypnotica" is the area entitled "Euphorica," best illustrated by the opiates, in which there is a replacement of the unremembered and unrecalled "not" world with a synthetic substitute that circumvents all problems. This satisfies the user without any constructive benefits.

The last of Lewin's classifications, the one which fascinated him most, is the "Phantastica." This is the area which we will discuss during the next two days. Here, one replaces a real world with an alternate real world which is equally real and yet different. We must return to this philosophic argument: How can one determine which of these two is the "real" real world? There are people in South America, for example, who use the native drug ayahuasca, and who live as much of their lives as possible in a drug-modified world. They consider that state the real world, and it is only when the body becomes purged of these chemicals that they inhabit what we accept as our real world. They consider our world an idyllic heaven, but they soon return to their drugged state which is their real world, whereas ours is the escape world. Which of these two exclusive states is real?

The class of "Phantastica," thus defined, is presented as a working definition of the term "psychotomimetic." The word psychotomimetic is from "psychoto," implying the origin of psychosis, and "mimetic," meaning the imitation of it. This is, admittedly, a controversial definition because in many ways these compounds do not imitate psychosis, but produce some recognizable symptoms. They have been called the hallucinogens as another synonym, but this is questionable, as hallucinations are rare things. They have been called psychedelics, but this name reflects some anticipation of virtue. Whatever they are, these are the classes of compounds which cause a change of reality but still allow recall.

I would like to discuss briefly the several principal families of compounds that fall into this "Phantastica" classification. (See Usdin and Efron, 1967,

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for leading references.) Several of these families will be talked about at length by others, therefore I will not go into detail on those. These various families can be organized quite nicely from the chemically complex to the chemically simple, from the polycyclic to the monocyclic, from the very potent to the relatively non-potent compounds. Interestingly, in the same arrangement, the compounds are ranked from those which are without apparent relationship to known metabolic pathways, progressively to the compounds that can be more and more easily rationalized as being involved in known metabolic schemes. It is with the simplest of these families, with the compounds related to mescaline, that I will discuss recently evolved structure-activity relationships.

The first of these families contain the compounds related to the ergot alkaloids. LSD (Fig. 1a) is among the most potent of all of the compounds

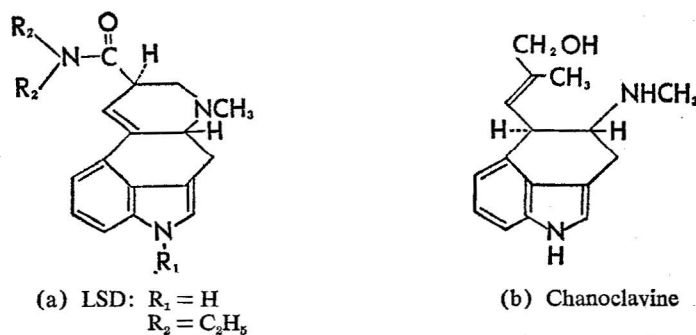


FIG. 1.

known in this area, and among the most widely publicized of the materials. The compound is an indole. Through much of this discussion there will be a continual reference to indoles or to the tryptamine nucleus, which is, with very few exceptions, present. I shall not elaborate much on the structure-activity relationships of these. Most changes in the structure of LSD lead to a loss of potency; very few changes appreciably increase it. Methylation or acetylation of the indole nitrogen at  $R_1$  and replacement of the diethyl group with the pyrrolidine ring,  $R_2 = -(CH_2)_4-$ , are modifications that, to a large extent, do not change the activity of the compound. LSD appears to be of nearly optimum structure as it stands, as no single structural variation grossly increases its activity. Conversion of either of the asymmetric positions to the corresponding isomers, bromination of the nucleus of the indole, removal of one of the ethyl groups, or the replacement of the two ethyl groups with methyls, all reduce the potency of the compound.



This compound does not occur as a natural material, although there are closely related natural psychotomimetic substances. Ololiuqui is a name for the seeds of various *Convolvulaceae*, such as *Rivea corymbosa* and *Ipomoea spp.*, the morning glory. For example, there are analogs of lysergamide itself, and compounds wherein the carboxyl group in ring D is reduced to the carbinol. Chanoclavine (Fig. 1b) represents materials present in the natural product, in which the D ring is actually open. The morning glory contains a large variety of these indole alkaloids, very few of which have had any individual clinical evaluation. Most experiments have employed the entire mixture, which to a large extent produces an LSD-like response.

Ibogaine (Fig. 2;  $R_1 = \text{OCH}_3$ ,  $R_2 = \text{H}$ ) is another example in the family of psychotomimetics, with complex structures and no resemblance to known metabolic materials. It is not a highly potent compound. It is, however, a material that has been widely used in Africa and has had sufficient improper

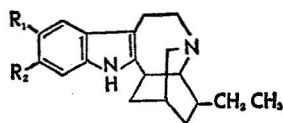


FIG. 2.

use recently in this country that it has now been added to the federal government's list of dangerous drugs. It has a reputation in the native usage of causing alertness, immobility, and attention that can be maintained for hours or even days. This allows the user to stalk game with minimum motion and without a need for food. I believe the compound may allow the native to think that he has been motionless for a long period, because this property has not been objectively observed in controlled studies. The analog with the methoxy group in the indolic-6 position, similar to the harmala alkaloids rather than to serotonin, is known as tabernanthine (Fig. 2;  $R_1 = \text{H}$ ,  $R_2 = \text{OCH}_3$ ). It is a local anesthetic, but it has shown no central effects.

The next class of compounds to be discussed is a bit simpler in structure. It is the group from the plant *Cannabis sativa*, and its active components are known as the cannabinoids. They are characterized by either a three-ring system or a system that can be easily converted into a three-ring system. The totally aromatic compound is cannabiol (Fig. 3a), and it displays the carbon skeleton common to the group. All the materials found in the native plant have an amyl group in the 5-position of the resorcinol.

It is worth a moment here to discuss the numbering systems employed

with these compounds. One hears continuously of the chemistry of delta this-or-that tetrahydrocannabinol, and it sounds as if there are dozens of possible isomers known. In reality, there are only a few, but they can be numbered in several different manners. The ring system itself is quite often numbered according to *Chemical Abstracts*. This is shown with cannabinol (Fig. 3a). The aromatic hydroxyl group establishes the number 1 position, numbers 5 and 6 are in the heterocyclic ring; and numbers 7, 8, 9 and 10 complete the third ring which is in this case aromatic, but which in the active compound is tetrahydrogenated. A severe disadvantage to this numbering system becomes apparent when one notes that many of the compounds that are present have the center ring open. This results in a diol system with some form of unsaturation in the isopropyl group, as seen in cannabidiol (Fig. 3b). As a consequence, the above numbering system is totally invalid. Two additional numbering methods exist, one based on a benzopyran skeleton and one on a diphenyl nucleus, but they both have the same limitation, *i.e.*, applicability to only one of the two types of systems found in the cannabinoids.

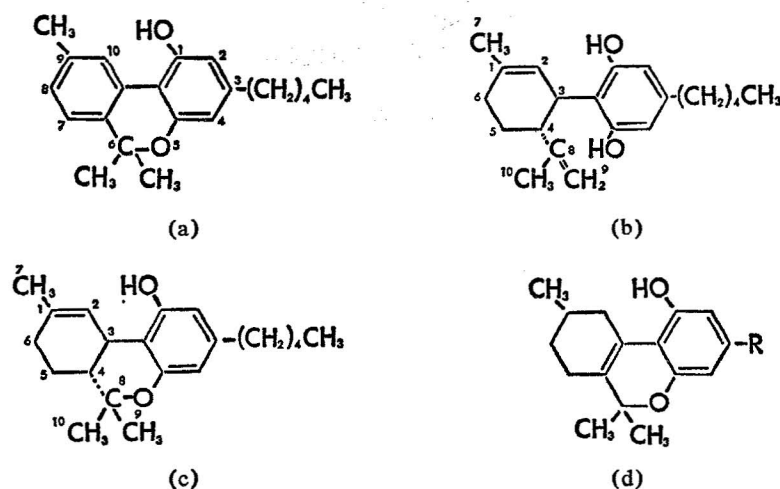


FIG. 3.

A numbering technique has been widely used that, since it is based on biogenetic grounds, can apply equally well to both ring structures. These compounds can be considered as resulting from an amalgamation of a terpene and a resorcinol. A terpene, the left-hand ring in Fig. 3, is numbered from the carbon carrying the methyl group as number 1, progressing with sequential

carbons about the ring. The methyl group becomes number 7 and the isopropyl group picks up the remaining three numbers. On that basis the ring on the left-hand side of  $\Delta^1$ -tetrahydrocannabinol, component of cannabis, is numbered 1 under the methyl group as shown in Fig. 3c. The virtue of this procedure is that it applies to all compounds, whether the oxygen ring is closed or open.

As to structure-activity relationships in this family, the most complete study that has been reported concerns variations of the unnatural  $\Delta^3$ -tetrahydrocannabinol. This work by Adams and a number of graduate students appeared twenty-one years ago (1948). Parallel studies, complementary to Adams's, were reported by Todd in England at about the same time. Of all the structural points in the molecule that were investigated, the one that led to the greatest variation in activity was the amyl group on the 5-position of the resorcinol moiety. I will not go deeply into the complete SAR studies of this work because of time limitations, and I want to talk at some length about the simplest family, the mescaline analogs. However, I will mention that variations in the identity of "R" in  $\Delta^3$ -tetrahydrocannabinol (Fig. 3d) have led to a range of biological potency that spans over three orders of magnitude. A maximum in activity was reported for a branched chain 9-carbon system. These materials proved to be many times more potent than the natural compounds, both in animal tests and in man.

This is, however, a whole chapter in its own right. I will just add that in the last two or three years, six independent syntheses have appeared, from Israel, Germany, Switzerland and this country, that describe preparations of compounds with the double bond located in the natural position. This suggests a possible series of studies that could couple the recently developed synthetic skills in double-bond orientation with the knowledge that "R" is a very sensitive point in the molecule. This whole family of compounds, with the unconjugated double bond and the variation in "R," is totally unexplored and could very well justify new research interests in the area of the cannabinoid compounds.

The area of *Cannabis* chemistry has recently been reviewed by Mechoulam (1967).

I will be brief in the discussion of the next family of compounds as they will be discussed at length later on this morning. These are materials related to *Datura*. The carbon skeleton of the natural alkaloids is shown in the parent compound, atropine (Fig. 4a). The chemical relationship here to acetylcholine (Fig. 4b), a neural transmitter to which it is an antagonist, is the first suggestion of similarity to metabolic systems. Hyoscyamine is the *l*-isomer of atropine, and is the form which is present in the plant. The epoxide of this is

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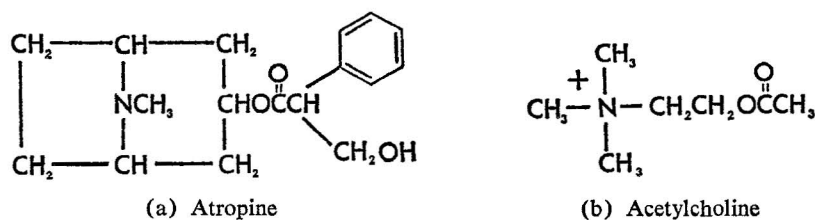


FIG. 4.

hyoscine, or *l*-scopolamine. This group represents the biologically active belladonna alkaloids. It has prompted many synthetic studies, evolving materials such as diltan and benactyzine. These will be talked about later, but I would again caution that although these have commonly been called psychotomimetics, they lead to more of a delusional state with amnesia rather than to an intoxication with recall that is the mark of the other psychotomimetics being discussed here.

Another family is a group of alkaloids found in species of both *Banisteriopsis* and *Peganum*. The carbon skeleton of this family is shown in harmaline (Fig. 5a; R<sub>1</sub> = H, R<sub>2</sub> = OCH<sub>3</sub>). This is an indole, and here again, one could see a resemblance to serotonin (Fig. 5b) which is a hydroxy

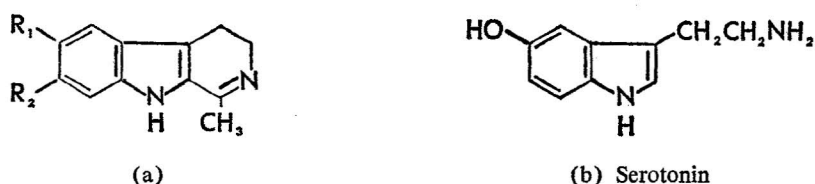


FIG. 5.

substituted tryptamine. The methoxy group in this case is in the position it was in tabernanthine from *Tabernanthe iboga*, as mentioned earlier. This compound occurs in the native drug ayahuasca along with the totally aromatic derivative harmine, and its tetrahydro derivative, tetrahydroharmine. This group of compounds constitutes the principal active constituency of these natural plants, but later on today there will be a talk by Dr. Holmstedt discussing some of the other materials that have been found in the plant. There are interesting analogs in which the methoxy group is found in the indolic 5-position.

Materials with the indole-5-methoxy substitution but with the intact harman tricyclic ring system are not known in nature. The direct analogy to harmaline would be 6-methoxyharmalan (Fig. 5a;  $R_1 = \text{OCH}_3$ ,  $R_2 = \text{H}$ ), the totally aromatic system is 6-methoxy harman, and its tetrahydro derivative would be 6-methoxytetrahydroharman. McIsaac has advanced a hypothesis that such chemicals could be generated in the pineal gland, say from melatonin by dehydration or from the corresponding methoxy ether of serotonin by the addition of acetaldehyde. As far as I know, these have not been confirmed as components of the intact brain, although spectrophotometric evidence suggests their presence. Yet these materials, the hydrogenation products of 6-methoxyharman, are two or three times more potent as psychotomimetics than the natural analogs with the methoxy group in the indolic-6 position. Since the chemical mechanisms for their generation *in situ* are certainly present, it is intriguing to speculate that such materials might arise in the abnormal synthesis or metabolism of melatonin.

The next family of psychotomimetics is represented by the indolealkylamines, and they are chemically very close to normal metabolism and normal metabolites. The simplest compound is N,N-dimethyltryptamine (Fig. 6;

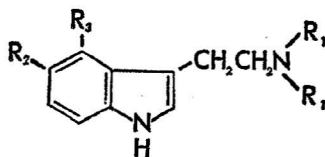


FIG. 6.

$R_1 = \text{CH}_3$ ,  $R_2 = R_3 = \text{H}$ ; DMT). This material has been found in a number of snuffs through many areas of South America and the Caribbean. The 5-methoxy-N,N-dimethyltryptamine ( $R_1 = \text{CH}_3$ ,  $R_2 = \text{OCH}_3$ ,  $R_3 = \text{H}$ ) is also a snuff component, and a recently discovered compound of the *Banisteriopsis* group mentioned earlier. Neither of these two materials is active in man orally, only parenterally. The diethyl and dipropyl homologs of DMT have been evaluated in man and the potencies and their interrelationships will be discussed later by Dr. Szara.

The 4-hydroxy compound is the compound psilocin, and it and its phosphate ester, psilocybin (Fig. 6;  $R_1 = \text{CH}_3$ ,  $R_2 = \text{H}$ ,  $R_3 = \text{OH}$ ;  $R_1 = \text{CH}_3$ ,  $R_2 = \text{H}$ ,  $R_3 = \text{OPO}(\text{OH})_2$ , respectively) are the active components of the teonanacatl mushroom of Mexico. Psilocybin is stoichiometrically equivalent to psilocin. Mention should be made here of the 5-hydroxy compound,

bufotenine (Fig. 6;  $R_1 = \text{CH}_3$ ,  $R_2 = \text{OH}$ ,  $R_3 = \text{H}$ ). It is N,N-dimethyl serotonin, and has been found in both animals and plants. It has been claimed to be a psychotomimetic, and has been added to the federal government's list of dangerous drugs, but I feel that this claim could not withstand serious challenge. The material is definitely biologically active; it has been shown to be present in human metabolic schemes, and there is a very close chemical relationship to serotonin, from which it could certainly arise by well known processes.

In the remaining time I would like to discuss the last of these families of psychotomimetics, the simplest of all. These stem from peyotl, the cactus *Anhalonium lewinii* (*Lophophora williamsii*), found in the southwest part of the United States and the northern part of Mexico. The principal compound present in it, and the presumed active principle, is the compound, mescaline, 3,4,5-trimethoxyphenylethylamine (Fig. 7a). Here there is a very close relationship to the neurotransmitter, norepinephrine (Fig. 7b), which is itself a



FIG. 7.

trihydroxylated phenethylamine. The three oxygens are methylated in the case of mescaline, whereas the third hydroxy group of norepinephrine is a benzylic hydroxy group. Mescaline, although one of the least active of all the psychotomimetics, is actually one of the best studied. It has served as a basis for the evaluation of several groups of derivatives. These have been designed to challenge different quadrants of the molecule, and to establish what role they play in generating the psychotomimetic syndrome.

Hopefully, from this there may come some understanding of their relationships with neural metabolic pathways. After all, the whole rationalization behind studies of this type is that perhaps one could observe a disruption, presumably in the norepinephrine path, which would lead to the accumulation within the organism of some compound not normally there, some compound that might generate the symptoms of a spontaneous endogenous psychosis.

The data to be discussed in the remainder of this presentation are all assembled in the accompanying Table I. Vertically, the various compounds are presented in accord with today's discussion, and the lettered abbreviations will

TABLE I

| Compound    | Ring position  | M.U.    | Chain length | Quinone to $\text{OCH}_3$ | Quinone to ortho- H | Ortho | Meta | $(\text{OCH}_3)_2 \rightarrow$<br>$-\text{OCH}_2\text{O}-$ |
|-------------|----------------|---------|--------------|---------------------------|---------------------|-------|------|--|
| "natural"   | Mescaline      | 3,4,5   | "1"          |                           |                     |       |      |  |
|             | TMA            | 3,4,5   | 2.2          | $3 \rightarrow 4 (<2)$    |                     |       |      |  |
|             | MMDA           | 3,4,5   | 2.8          | $3 \rightarrow 2 (1)$     |                     |       |      |  |
|             | MMDA-2         | 2,4,5   | 12           |                           |                     |       |      |  |
|             | MMDA-3a        | 2,3,4   | 10           |                           |                     |       |      |  |
|             | MDA            | 3,4     | 3            |                           |                     |       |      |  |
|             | DMMDA          | 2,3,4,5 | 12           | *                         |                     |       |      |  |
|             | DMMDA-2        | 2,3,4,5 | 5            | *                         |                     |       |      |  |
|             | Tetra-MA       | 2,3,4,5 | 6            | *                         |                     |       |      |  |
|             | DMA            | 3,4     | <1           | $3 \rightarrow 2 (<0.2)$  |                     |       |      |  |
|             | TMA-2          | 2,4,5   | 17           | $3 \rightarrow 2 (1)$     |                     |       |      |  |
|             | 4-MA           | 4       | 5            | $3 \rightarrow 2 (<1)$    | **                  |       |      |  |
| "unnatural" | TMA-3          | 2,3,4   | <2           |                           |                     |       |      |  |
|             | TMA-4          | 2,3,5   | 4            | *                         |                     |       |      |  |
|             | TMA-5          | 2,3,6   | 13           | *                         |                     |       |      |  |
|             | TMA-6          | 2,4,6   | 10           | **                        |                     |       |      |  |
|             | 2,4-DMA        | 2,4     | 5            | **                        |                     |       |      |  |
|             | 2,5-DMA        | 2,5     | 8            |                           |                     |       |      |  |
|             | EMM <i>OEt</i> | 2,4,5   | <7           |                           |                     |       |      |  |
|             | MEM <i>OEt</i> | 2,4,5   | 15           |                           |                     |       |      |  |
|             | MME <i>OEt</i> | 2,4,5   | <7           |                           |                     |       |      |  |
|             | DOM <i>Et</i>  | 2,4,5   | 80           | $3 \rightarrow 2 (<15)$   |                     |       |      |  |
|             | DOET <i>Et</i> | 2,4,5   | —            | $3 \rightarrow 4 (<15)$   |                     |       |      |  |

\* Signifies compounds with a 1, 2, 4 orientation of oxygen.

\*\* Signifies the compounds that are *para*, 2, 4, or 2, 4, 6 oriented.

be defined during their description. Sequential columns elaborate their comparisons with regard to structural parameters.

One of the first changes that was made in the structure of mescaline was the incorporation of the side chain found in amphetamine, the  $\alpha$ -methyl homolog of phenylethylamine. This compound,  $\alpha$ -methyl mescaline or 3,4,5-trimethoxyamphetamine, brings together the structures of a sympathomimetic amine and a psychotomimetic one. It is the second entry in the table, with the convenient code TMA. The use of "A" with this and most of the compounds to be discussed during the remainder of this paper is inaccurate. Amphetamine, like aspirin, is the name of a single compound, and cannot have functional groups attached to it. These substituted derivatives properly should be called variously substituted phenylisopropylamines, as this is the proper chemical name for amphetamine. Therefore, "A" here and through the code letters of the table should be thought of as standing for phenylisopropylamine. With that we will probably continue calling them amphetamines, for it is a convenient nomenclature.

TMA, and all of the compounds that follow it in the first column of the table, have  $\alpha$ -methyl groups, with certain exceptions that I will mention. Mescaline alone is a phenethylamine. The second column of the table lists the substitution positions of the oxygens on the phenylisopropylamine (amphetamine) moiety. All groups are methoxyls unless italicized; a single number in italics indicates the position of the grouping listed immediately after the compound; two numbers in italics indicate that a methylenedioxy ring is in that position. The third column is a measure of the relative potencies of each in man, compared against mescaline as a reference with unit potency. The mean effective level of mescaline is taken to be 3.75 mg/kg of the free base. All of these mescaline unit (M.U.) values must be held with a fair amount of reservation. Although most were established through rather extensive clinical trials, one must recognize that there is a wide variation between individuals and with a given individual from day to day. I would say that  $\pm 25\%$  would indicate the degree of uncertainty in these M.U. values.

TMA (Fig. 8a; 3,4,5-trimethoxy) shows about a two-fold increase in potency over mescaline. If a three-carbon chain is more effective than a two-



FIG. 8.



carbon chain, then an obvious extension is to the four-carbon chain. The  $\alpha$ -substituent was extended in a study of homologs, but the next immediate compound,  $\alpha$ -ethyl mescaline, already showed a decrease in psychotomimetic activity. On the basis of this initial study it appears that three is an optimum carbon-chain length. This will be borne out as we get further into this compilation. The function of the  $\alpha$ -methyl group may only be to make the amine group less amenable to deamination by enzymatic attack.

There is a compound in nature that has the same atomic skeleton as TMA, but no nitrogen; this is the essential oil, elemicin (Fig. 8b; 3,4,5-trimethoxy). It is interesting that it is a component of nutmeg, and nutmeg has a reputation for producing peculiar mental effects. A logical step was to inquire into nutmeg and to analyze its aromatic ether fraction. This approach with nutmeg and several related natural products has resulted in the first dozen or so amphetamines in the table. They have been called the "natural" amphetamines since their ring substitution patterns are those of natural oils from which, to a large extent, they have been chemically derived.

The most prevalent essential oil in the aromatic fraction of nutmeg is the methylenedioxy counterpart of elemicin, myristicin (Fig. 8b; 3-methoxy-4,5-methylenedioxy). This served as a template for the synthesis of the next compound in this series, 3-methoxy-4,5-methylenedioxy amphetamine. This material, MMDA ("M" for methoxy, "MD" for methylenedioxy), has an increase of about 50% in potency, providing a compound that is about three times as active as mescaline itself. There is quite a change in the qualitative nature of the intoxication. A continuation of this study of the "natural" amphetamines led to the study of materials with the number, the orientation and the identity of substituents of various essential oils.

The first of the structural rearrangements involved the relocation of the methoxy group. The 2,4,5-orientation is found in oil of *Calamus*, and the 2,3,4-orientation is found in oil of *Crowei*. The two corresponding amphetamines are MMDA-2 and MMDA-3a (Fig. 8a; 2-methoxy-4,5-methylenedioxy and 2-methoxy-3,4-methylenedioxy, respectively). Their potencies were increased five-fold, about ten times the potency of mescaline.

Another modification, other than rearranging the methoxy group, is the removal or addition of methoxy groups. Demethoxylation leads to a compound derived directly from safrol, known as methylenedioxyamphetamine (MDA). On the other hand, the addition of a methoxyl group to MMDA leads to bases that are structurally related to apiole and dillapiole.

These compounds (DMMDA and DMMDA-2; 2,5-dimethoxy-3,4-methylenedioxy; and 2,3-dimethoxy-4,5-methylenedioxy, respectively, were prepared, and they have the potencies shown. They are an order of magnitude more potent than mescaline. The third tetraoxygenated amphetamine based on

natural oils is 2,3,4,5-tetramethoxyphenylisopropylamine (Tetra-MA). The essential oil counterpart is found in oil of parsley and oil of *Calamus*; the derived amine has a potency of 6 M.U. Dimethoxyamphetamine, DMA (Fig. 8a; 3,4-dimethoxy-) is a direct analog of methyleugenol. This base appeared to be without biological activity, the only one of the natural orientations that is not active. The compound, TMA-2, with a 2,4,5 orientation, is derived from the essential oil asarone, and is the most potent of all materials that have been found within this "natural" system.

The next logical step was to complete those series that were mentioned above. For example, in the trimethoxyamphetamines, the 3,4,5-isomers were related to elemicin, and the 2,4,5 was based on the compound asarone. This left four more isomers possible, the 2,3,4, the 2,3,5 and 2,3,6, and the 2,4,6 counterparts. The first of these, TMA-3, has been found to be inactive, but the other three are quite active. None of them, however, exceeds the 2,4,5-trimethoxy orientation in potency. Two of the "unnatural" dimethoxyamphetamines have been prepared, the 2,4- and 2,5-dimethoxyphenylisopropylamine (2,4-DMA; 2,5-DMA). They have a potency of about five times that of mescaline.

With most of these compounds, the style and the qualitative nature of the intoxication has been found to vary quite radically from one to another, and, therefore, the device of jamming them all into the common mold of mescaline potency has serious limitations. However, I have mentioned earlier the flexibility expected with these numerical values. The trimethoxy compound with a 2,4,5-orientation appeared to be the most potent of this group, and all possible ethyl homologs of this compound, TMA-2, were prepared. Three monethoxy compounds were evaluated in clinical trials. Only the compound with the ethoxy group in the para-position retained biological activity. The appearance of ethoxy groups in either of the other two positions led to a decrease in biological activity.

All this brings into emphasis the substituent that is located in the 4-position. This position could well be sensitive in man to some extent, for it is known in certain animal species to be a principal location for detoxification of amphetamine by hydroxylation. Perhaps these materials display different biological activity due to the substituent in the 4-position. We know that hydrogen in this location provides an active compound, 2,5-dimethoxyamphetamine. A methoxyl group at this position leads to the most active compound mentioned, and this potency is not lost with the ethoxy homolog. It seemed obvious that the blocking of this position with a group that would be biologically unavailable to metabolism, such as a methyl group which cannot be either easily removed or oxidized to a hydroxy group, could grossly change its biological nature. It could be argued that such a compound might

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be more potent because now it cannot be cleared through detoxification. On the other hand, one could argue that the compound could not only be without potency, but also that it might serve as a competitive antagonist to the known potent materials, and so actually serve as a prophylactic agent against them.

The first of these two possibilities proved to be the case. This compound is DOM, and it proved to be about eighty times as potent as mescaline in activity and to be extremely long-lived in activity as well. An obvious departure from this compound was the extension in length of this 4-alkyl chain, leading to the specific compound 4-ethyl-2,5-dimethoxyamphetamine, known as DOET. It was originally called DOE ("E" for ethyl, as "M" was for methyl), but this code name turned out, unfortunately, to be a synonym for methamphetamine, and the "T" was rapidly added to keep confusion and undesirable association from occurring in the literature. This ethyl compound does not have a potency listed in the table. Dr. Snyder will deal at length about it specifically. It has a dual action. At low levels it serves as an energizer, and it is being clinically evaluated from that point of view in his laboratories. It is only at higher levels that there are psychotomimetic effects. Thus, it is more potent in the sense of biological activity, and less potent in terms of mescaline units.

This brings to an end the listing of compounds and their relative activities. In the space I have left I would like to take this body of data and see what can be done from the consideration of structural parameters. In this way, insight could be gained concerning metabolic products that might not normally be present in the organism but whose presence might produce these mental changes artificially.

Chain length has already been mentioned. The column in the table entitled "chain length" lists those effects. These and subsequent data are presented in a recent analysis (Shulgin *et al.*, 1969; see also references contained therein). In TMA, a chain length of three is twice as active as mescaline. Extending the chain to four leads to a decrease in the activity below that found with the chain length of three. This length appears to be optimum. The two-carbon analog of 3,4-dimethoxyamphetamine is the compound DMPEA, dimethoxyphenylethylamine. This is the substance related to the pink spot of schizophrenic urine. It has been shown to be inactive even at levels five times that of mescaline, *i.e.*, it has an activity of  $<0.2$  M.U. Since DMA is less than 1 M.U. no information can be gleaned. When TMA-2 undergoes a change in chain length from three to two, the biological activity of the compound drops down to that of mescaline itself, a full order of magnitude of change. A similar change occurs with 4-methoxy amphetamine. Progressing from a chain length of three to two, the compound decreases from a drug much more potent than mescaline to one distinctly less potent. The one remaining example is with

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DOM itself. Both the two and the four chain compound have been synthesized, both have been evaluated, and both are less active than the three carbon chain. All this evidence tends to affirm that a three carbon chain is indeed an optimum chain length.

Suggestions have been advanced that these materials may show biological activity by virtue of the fact that they may either imitate or form indoles during the course of their metabolism. In the formation of an indole, the nitrogen must have access to the aromatic ring. This can be achieved by attack on the ortho-methoxyl group in a ring with substitution allowing quinone formation or on the ortho-hydrogen of an oxidized ring in a direct nucleophilic attack. This proclivity to form a quinone at a methoxy group would be maximum if the oxygen orientations were such as to allow quinone formation, either ortho or para. A 1,2,4-arrangement of the three oxygens would provide a maximum opportunity for reaction, whereas there would be a minimum possibility if the oxygens were arranged meta to one another, in a 1,3,5-pattern. There are five compounds that have a 1,2,4 orientation of oxygen, and these are indicated by a \* in the table. The compounds that are para, 2,4, or 2,4,6-oriented are indicated by \*\*. Presumably the former would be most able to form a quinone intermediate by methoxy displacement, and the latter least able to form it. Yet these two groups of compounds encompass the same range of biologic activities. On this basis, one can conclude that quinone formation through an ortho methoxy group is not a likely explanation.

At the ortho-hydrogen, however, a totally different argument presents itself, for an attack at this position would involve an intermediate of quinone form, one amenable to nucleophilic attack. The addition of methoxy groups to the parent molecule would make this style of reaction more probable. These compounds have been compared on the basis of the addition of a methoxy group to a reference material. These references and the consequences of methoxylation are summarized in the next column of the table. The only structural requirement is that there should be an oxygen located para to the displaced hydrogen. The table looks like an unsuccessful football play by Knute Rockne as it is presented. Nonetheless, it is apparent that there is a large number of plusses, implying that the activity has generally gone up with the addition of a methoxy group. Thus, there is some encouragement given to the argument that this type of an intermediate might be involved, reflecting the differences in basicity resulting from the addition of a methoxy group. This analysis is compromised by the fact that methoxy groups are being added at different positions to achieve this overall inductive effect.

It is interesting to go through the same data considering the specific position at which a methoxy group is added. The comparison of compounds

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without an ortho-methoxy group in relationship to counterpart compounds with one is shown in the next column of the table. A large number of plusses is apparent, only one unchanged, and no minusses. In almost every instance, a given compound in comparison with an analogous material that is substituted with an ortho-methoxy group shows the latter to be more active. Quite the opposite is observed with the addition of a group in the meta position. In general, the addition of a meta-methoxy group to a parent compound decreases its activity.

The parallel presentation for para-substitution is not presented, as it is not fair. Almost all of these compounds are para-substituted. There are only a very few instances in which you can compare materials with and without a para group. The one remaining analysis that is given in the table is a comparison between dimethoxy compounds and their methylenedioxy counterparts. In most cases, the methylenedioxy analog was a compound that is slightly more potent.

What can one conclude from all of this? The ultimate purpose of this study is to look at what compounds might be present in the human, not through normal metabolism, but generated through some idiosyncratic or pathologic state. This material might result from some norepinephrine pathway deviation, and might be a biologically active agent. Although it appears that a chain length of three carbons is optimum, this may merely reflect the defense of the amino group to decamination. As three-carbon chains are virtually unknown in animal metabolism, it is probable that the two-carbon chain of the norepinephrine metabolism is a more likely structure for such an agent. An increase in the number of methoxy groups leads to an increase in the potency of a compound, but this must be more carefully analyzed. The addition of ortho groups increases activity, the addition of meta-methoxy groups decreases it, and although the para substituent is not essential, it certainly is of much importance.

Accepting that this abnormal agent is going to be related to the norepinephrine scheme, it is possible that some dimethoxy material, perhaps dimethoxyhydroxyphenethylamine, could be involved. Since 6-hydroxylation can occur *in vivo*, perhaps some 6-hydroxy or 6-methoxy analog of norepinephrine metabolites might be expected. This is a 2,4,5-orientation that has proved to be the most potent of the orientations studied. These materials, dimethoxyphenethanolamine or the 6-hydroxy analogs of the various metabolic intermediates, represent a series of compounds that could be implicated in abnormal metabolism.

How can one challenge these proposals? Paradoxically, the most direct way of challenging this entire group will fail, for if you have a material that is suspected of being an endogenous psychotogen, you cannot assay it in

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normal human subjects because the normal subject is, indeed, normal for the very reason that he has the machinery for disposing of such a compound. Therefore, one must distort such a compound in some way that will make it a valid challenge. One way would be through the introduction of a methyl group  $\alpha$  to the amine function. This would lead to a series of variously substituted ephedrine, presumably less susceptible to MAO attack. Possibly the replacement of the methoxy group in the para position with a methyl group would interfere with metabolic disposition.

A chemical explanation of mental illness is only one of several that are possible, but the fact remains that there are some aspects of mental illness that can be duplicated chemically. A hypothesis of an endogenous psychotogen certainly deserves this type of further investigation, and the compounds which are implicit in these combinations of ring substitutions, of chain length variations and in degrees of oxygenation could very well provide the tools that can challenge this hypothesis.

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## DISCUSSION

DR. BURGER: Thank you, Dr. Shulgin, for an excellent, comprehensive and thought-provoking presentation.

DR. DOMINO: I'd like to ask about the phencyclidines. In your discussion, Dr. Shulgin, you mentioned Sernyl or phencyclidine in relationship to atropine-like compounds, but pharmacologically, of course, they are quite different. Phencyclidine is really a sympathomimetic and in large doses is used as an anesthetic. A lot of people would even argue that it is not a psychoto-

mimetic, but at least the psychiatrists I'm associated with feel that phencyclidine is, indeed, the best drug model of the primary symptoms of schizophrenia of any psychotomimetic we have.

Since this is a phenylmethamphetamine derivative, I wonder if you could comment a little bit further about phencyclidine and where you would place it in your scheme.

DR. SHULGIN: Generally I had placed it much closer to the atropine group, not so much on chemical structure or pharmacological structure, as in the use and misuse of it. There's been quite a flurry of what has been called synthetic THC in and around the West Coast, and probably in the East Coast markets, too. I have assayed several samples of this material, and with one exception they have been phencyclidine. Apparently this has enough of a psychopharmacologic similarity to the tetrahydrocannabinol type of psychotomimetic that it can be sold and disguised verbally as being that, and this is believed. On the other hand, as you mentioned, the excessive usage of it leads to an anesthetic state, and in this way it is very much like the use of twilight sleep in the atropine group. So, in general, I have tended to put it along with the other synthetics related to the *Datura* group, but this is quite arbitrary. Primarily one observes behavioral changes rather than pharmacological ones.

DR. MANDELL: Dr. Shulgin turned me on about an idea that never occurred to me until hearing his talk. His work suggests that we may be able to get rid of the indole concept in LSD and other indole containing hallucinogens. If what Dr. Shulgin is saying about mescaline is true, then we might conceive of the benzene ring in an indole getting electron donor effects from the pyrrole ring.

If what he said was true about the 3-carbon ring structure being the essential link to an active amine nitrogen, in the structure of LSD we can get to the 6-nitrogen in two ways. This structural concept may join together the mescaline and the indole bag by throwing them together with just three very simple and economical structural requirements: (1) the possibility of a high molecular energy level in a single aromatic system; (2) a three carbon chain and (3) a nitrogen. This kind of concept is clear for the phenylethylamine hallucinogens; perhaps it is true for LSD as well. Perhaps the very high potency of LSD is due to the rigidity of holding the 6-nitrogen in place while still maintaining the 3-carbon chain. The 6-nitrogen may be activated by non-bonded resonance with its methyl group.

It never occurred to me until you started playing around with the mescaline story. But, as you know, the pyrrole ring donates electrons, perhaps very much like the methoxy group in mescaline would. This line of thought could marry then in one model, the mescaline theorizing with the indole theorizing. That's off the top of my head. What do you want to do with it?

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DR. SHULGIN: It's certainly appealing to think that you have two sites of basicity in the molecule, one a diffuse  $\pi$ -system with its molecular-orbital definition, and perhaps a somewhat more localized base in the form of a lone nitrogen pair. If you do have these two sites, they may define the successful attachment to some reaction site somewhere. If there is an optimum separation as well as an optimum localization, then a rigid configuration, if it were the right one, would produce a more effective approach to this site.

DR. MANDELL: And the sigma bonds would hold that tight?

DR. SHULGIN: You might make a birdcage structure that would be very specific by adding a third methylene branch in some way.

DR. CRAIG: Perhaps I should tell Dr. Mandell how much I agree with him, because we have already made substantial progress on the syntheses of both of these.

Now if, in addition to leaving out the pyrrole, you change the 6-membered ring to the indene structure, a 5-membered ring, then the substance becomes a phenylethylamine in both directions, as well as being rigid. We have almost completed the syntheses on both of these LSD compounds. I don't know if they will be any good, but it seemed something that ought to be done.

DR. LEHRER: I wonder if you could comment on the question of transport of these substances into the brain. It's known that indoles and catechols are more easily transported into the brain as the corresponding amino acids; and I wonder whether some of the mescaline series of drugs might not get into the brain more easily as the amino acids, and then become decarboxylated?

DR. SHULGIN: The only one I know that's been studied that way is the actual analog of mescaline itself, trimethoxyphenylalanine. It was synthesized in England and reported in the J.C.S., where it was stated that, "Pharmacology will follow." And about two years later, not having found it, I wrote, and was told, oh, yes, there was absolutely nothing of interest. Other than that, I know of no amino acid studies in this area that would challenge that. It would be a fairly simple series to make, I would think.

DR. BIEL: I don't know if they get decarboxylated.

The question I had was in regard to bufotenine. You ascribed rather low activity to it.

DR. SHULGIN: As far as being a psychotomimetic. There is no question but that it's biologically active, however.

DR. BIEL: Himwich recently published the correlation between the appearance of bufotenine in the urine of schizophrenics and a gradual improvement as urinary bufotenine levels went down or disappeared altogether. Does this alter the picture at all?

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DR. SHULGIN: No. There's no question that bufotenine is a metabolite. It's been found not as an artifact but as a genuine component of urine.

I would mention that in the human trial with it (I think it was given intravenously), a whole series of symptoms was observed, but I would hardly call any of them psychotomimetic in nature. That's my only reason for downgrading it. It's not the potency but the nature of the action. It's a highly potent compound.

DR. DOMINO: People turn blue. There are marked cardiovascular effects.

DR. GESSNER: We do have some preliminary data which make us believe that the reason bufotenine is not found to be active is because it simply does not get into the brain. If you put an O-acetyl group on it, it gets into the brain, and then it's hydrolyzed back to bufotenine. It's quite active.

DR. SHULGIN: You haven't done it in humans yet?

DR. GESSNER: No.

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