[12] Smart, J. S., and Surkan, A. J., *Water Resources Res.*, **3**, 963 (1967).
[13] Wisler, C. O., and Brater, E. F., *Hydrology*, second ed., 225, 230, 328 (John Wiley and Sons, Inc., New York, 1959).
[14] Rouse, H., in *Engineering Hydraulics* (edit. by Rouse, H.), 1 (John Wiley and Sons, Inc., New York, 1950).
[15] Lacey, G., *Minutes Proc. Inst. Civ. Eng.*, **229**, 259 (1930).
[16] Baldwin, R. B., *The Measure of the Moon*, 236, 241, 335 (University of Chicago Press, Chicago, 1963).
[17] Kopal, Z., *Proc. Roy. Soc.*, A, **296**, 254 (1967).
[18] Runcorn, S. K., *Proc. Roy. Soc.*, A, **296**, 270 (1967).
[19] Sverdrup, H. U., Johnson, M. W., and Fleming, R. H., *The Oceans*, 13, 19 (Prentice-Hall, Inc., Englewood Cliffs, 1942).
[20] Gilvarry, J. J., *Icarus*, **3**, 121 (1964).
[21] Gilvarry, J. J., *Icarus*, **5**, 228 (1966).
[22] Bjork, R. L., *J. Geophys. Res.*, **66**, 3379 (1961).
[23] Anders, E., *Science*, **138**, 431 (1962).
[24] Leopole, L. B., and Langbein, W. B., *Prof. Pap.* 500-*A* (US Geological Survey, Washington, 1962).
[25] Langbein, W. B., *J. Hydraulics Div., Proc. Amer. Soc. Civ. Eng.*, **90**, 3846 (1964).

Structure–Activity Relationships of One-Ring Psychotomimetics

by
ALEXANDER T. SHULGIN
1483 Shulgin Road,
Lafayette, California
THORNTON SARGENT
1044 Silver Place,
Berkeley, California
CLAUDIO NARANJO
Centro de Estudios de
Antropologia Medica,
Universidad de Chile,
Santiago, Chile

Human dose-response relationships for psychotomimetic phenethylamines: an isopropylamine side chain and triple methoxy substitution provide optimum activity. Available data suggest possible structures for the hypothetical psychotogen of schizophrenia.

INVESTIGATIONS of the aetiology of psychoses have followed the functional or the biochemical approach. The latter stems from a hypothesis advanced by Osmond and Smythies in 1952 (ref. 1) that an aberration in the metabolism of catecholamines could produce an endogenous psychotogen resembling the well known psychotomimetic mescaline. Our work has stemmed directly from this. The purpose of this article is to examine the structure–activity relationships of related compounds which may reflect the metabolic processes involved in psychosis.

The idea of an endogenous psychotogen finds support in that some aspects of schizophrenia can be produced in healthy subjects by chemical means. This mimicry was initially viewed as the "model psychosis", but subsequent studies have revealed shortcomings[2] and as investigational tools psychotomimetic compounds have recently fallen into disuse and even disrepute[3]. Many of the features characteristic of the induced intoxication are nevertheless frequently observed as symptoms of schizophrenia: distortion of time and space, synaesthesia, occasional hallucinatory experiences, delusional states, depersonalization, changes in effect, and an easy and often uncontrolled access to subconscious material. There is now evidence for a genetic basis of schizophrenia[4,5], and this supports the hypothesis of a biochemical lesion. Possibly the complexity of the syndrome is the result of multiple alleles, and permutations of these may account in some part for this complexity[5]. The diversity in the syndrome, and also in the nature of the chemically induced intoxication produced by phenethylamines, indoles and carbolines[6,7], may imply a multiplicity of metabolic sites of action. Recently there has been a controversy over the presence of 3,4-dimethoxyphenethylamine (DMPEA, XXXVIII) in the urine of schizophrenic patients[8]. Although DMPEA itself has been reported not to be psychotomimetic[9,10], it may nevertheless reflect the metabolism of an endogenous psychotogen.

Rather than systematizing the complex features of the chemically induced psychosis, we have considered this state constant and have investigated the dose-response relationships instead. Some recent studies have shown accord between human effective levels, and both biological (ref. 11 and private communication from H. E. Himwich) and physical[12] properties. Although animal studies have shown a general correlation with human results[13–16], there are some exceptions possibly attributable to metabolic differences between species. Furthermore, the dosage required to obtain behavioural effects in test animals is usually many times the effective human dosage. Because of these difficulties with animal results, we have limited this report to data obtained from human experiments.

Mescaline was selected as the initial compound for this study. Although it is less active than most psychotomimetics, it has the dual virtue of chemical simplicity, allowing many structural permutations, and a close relationship to compounds known to be naturally present in humans.

" Double Conscious " Technique

If the psychotomimetic effect is to be considered constant, ideally the subjects should also be kept constant. To this end the same subjects were used for as many of the different compounds as possible. The use of the double blind method is not applicable to this approach[17,18] and we have preferred to use the "double conscious" technique of Alles[17].

For each new compound for which previous data were not available, chemical identity and purity were established through spectroscopic, microanalytical and extensive physical analyses. The toxic levels were then established in several test animals, and gross behavioural changes noted although these did not usually occur until near-lethal levels were reached. The therapeutic index (LD_{50} mice/ED_{human}) was at least 100 in all compounds tested. The human threshold dose was determined by administering an initial dose of 100 μg orally, followed by successive doses at intervals of no less than 3 and usually at least 7 days, at levels about 1·5 times the previous dose. Estimates of threshold dose among subjects agreed within 25 per cent, and they could recognize the same level when repeated, more than 6 months later. The effective dose was then determined in extensive clinical studies at the University of Chile, and was taken as the mean of the threshold dose (already established) and the dosage that was "maximally effective". The potency of each compound was expressed in mescaline units (MU), defined as the quotient of the effective dose of mescaline divided by the effective dose of the compound, both calculated as the free base[19]. The effective dose of mescaline was taken as 3·75 mg/kg. The MU values

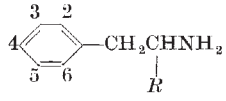
should not be considered accurate to closer than 25 per cent, and those values that are deduced from the literature, established in different subjects and on different criteria, must be held as less reliable.

Data Analysis

All the new, as well as the previously known, human data on psychotomimetic compounds of the phenethylamine type have been assembled in Table 1. These compounds will be discussed with regard to various structural parameters, and listed in subsequent tables. The extent of change in potency is represented by ++, +, 0, − and − −, indicating changes of at least an order of magnitude increase, moderate increase, no change, moderate decrease and an order of magnitude decrease. The symbol < means that the potency is less than the number indicated because the dosage required to calculate this number was ineffective and higher doses were not used.

Length of chain. Early in the study of the analogues of the catecholamines, the highly active sympathomimetic amphetamine was prepared and studied by Alles[20]. Modification of the structure of mescaline by amalgamation of these two structures provided 3,4,5-trimethoxyphenylisopropylamine (VIII)[21]; its psychotomimetic potency has been demonstrated[22] and confirmed[23].

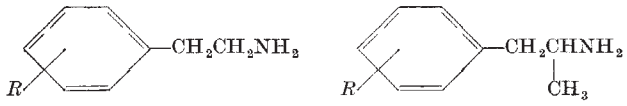
Table 1



Compound No.	2	3	4	5	6	R	Activity MU	Footnotes
I	H	H	OCH_3	H	H	CH_3	5	*a, b*
II	OCH_3	OCH_3	H	H	H	CH_3	—	*c*
III	OCH_3	H	OCH_3	H	H	CH_3	5	*b*
IV	OCH_3	H	H	OCH_3	H	CH_3	8	*b*
V	OCH_3	H	H	H	OCH_3	CH_3	—	*c*
VI	H	OCH_3	OCH_3	H	H	CH_3	<1	*d*
VII	H	OCH_3	H	OCH_3	H	CH_3	—	*c*
VIII	H	OCH_3	OCH_3	OCH_3	H	CH_3	2·2	*e*
IX	OCH_3	H	OCH_3	OCH_3	H	CH_3	17	*f*
X	OCH_3	OCH_3	OCH_3	H	H	CH_3	<2	*f*
XI	OCH_3	OCH_3	H	OCH_3	H	CH_3	4	*b*
XII	OCH_3	OCH_3	H	H	OCH_3	CH_3	13	*b*
XIII	OCH_3	H	OCH_3	H	OCH_3	CH_3	10	*b*
XIV	O—CH_2—O		H	H	H	CH_3	—	*c*
XV	H	O—CH_2—O		H	H	CH_3	3	*d*
XVI	H	OCH_3	O—CH_2—O		H	CH_3	2·7	*g*
XVII	OCH_3	H	O—CH_2—O		H	CH_3	12	*f, h*
XVIII	OCH_3	O—CH_2—O			H	CH_3	10	*f, h*
XIX	O—CH_2—O		OCH_3	H	H	CH_3	3	*b*
XX	O—CH_2—O		H	OCH_3	H	CH_3	—	*c*
XXI	O—CH_2—O		H	H	OCH_3	CH_3	—	*c*
XXII	OCH_3	O—CH_2—O		OCH_3	H	CH_3	12	*i*
XXIII	OCH_3	OCH_3	O—CH_2—O		H	CH_3	5	*i*
XXIV	H	OCH_3	O(CH_2)$_2$—O		H	CH_3	<1	*g*
XXV	OCH_3	OCH_3	OCH_3	OCH_3	H	CH_3	6	*b*
XXVI	OCH_3	OCH_3	OCH_3	H	OCH_3	CH_3	—	*c*
XXVII	OCH_3	OCH_3	H	OCH_3	OCH_3	CH_3	—	*c*
XXVIII	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	CH_3	—	*c*
XXIX	OC_2H_5	H	OCH_3	OCH_3	H	CH_3	<7	*b, j*
XXX	OCH_3	H	OC_2H_5	OCH_3	H	CH_3	15	*b, j*
XXXI	OCH_3	H	OCH_3	OC_2H_5	H	CH_3	<7	*b, j*
XXXII	OC_2H_5	H	OC_2H_5	OCH_3	H	CH_3	—	*j, k*
XXXIII	OC_2H_5	H	OCH_3	OC_2H_5	H	CH_3	—	*j, k*
XXXIV	OCH_3	H	OC_2H_5	OC_2H_5	H	CH_3	—	*j, k*
XXXV	OC_2H_5	H	OC_2H_5	OC_2H_5	H	CH_3	—	*j, k*
XXXVI	OCH_3	H	CH_3	OCH_3	H	CH_3	80	*b, l*
XXXVII	H	H	OCH_3	H	H	H	<1	*m*
XXXVIII	H	OCH_3	OCH_3	H	H	H	<0·2	*n*
XXXIX	H	OCH_3	OCH_3	OCH_3	H	H	1·0	*o*
XL	OCH_3	H	OCH_3	OCH_3	H	H	1	*p*
XLI	OCH_3	O—CH_2—O		H	H	H	<5	*b*
XLII	H	OCH_3	O—CH_2—O		H	H	1	*b*
XLIII	H	OCH_3	OCH_3	OCH_3	H	C_2H_5	<2	*q*
XLIV	OCH_3	O—CH_2—O		H	H	C_2H_5	—	*k*

Footnotes: *a*, See ref. 15. *b*, Previously unpublished data. *c*, Chemical synthesis not complete. *d*, Naranjo, C., Shulgin, A. T., and Sargent, T., *Med. Pharmacol. Exp.*, **17**, 359 (1967). *e*, See refs. 22 and 23. *f*, See ref. 19. *g*, Shulgin, A. T., *Nature*, **201**, 1120 (1964). *h*, This MU value is slightly lower than cited in ref. 19. *i*, Shulgin, A. T., and Sargent, T., *Nature*, **215**, 1494 (1967). *j*, Shulgin, A. T., *J. Med. Chem.*, **11**, 186 (1968). *k*, Animal pharmacology not yet complete. *l*, Snyder, S. H., Faillace, L., and Hollister, L., *Science*, **158**, 669 (1967). *m*, Brown, W. T., McGeer, P. L., and Moser, I., *J. Canad. Psychiat. Assoc.*, **13**, 91 (1968). *n*, See refs. 9 and 10, also Vojtechovsky, M., and Krus, D., *Activitas Nervosa Superior* 9.4.67, ninth Ann. Psychopharmacological Meeting, Jesenik, Jan 17–21, 1967. *o*, This is the reference compound mescaline which defines the MU (see text). *p*, Jansen, M. P. J. M., *Rec. Trav. Chim.*, **50**, 291 (1931). *q*, See ref. 24.

Table 2



2-Carbon chain Compound	MU	vs. 3-Carbon chain Compound	MU	Change
XXXVII	<1	I	5	++
XXXVIII	<0·2	VI	<1	?
XXXIX	1	VIII	2·2	+
XL	1	IX	17	++
XLI	<5	XVIII	10	+
XLII	1	XVI	2·7	+

The next immediate homologue was the less active butylamine (XLIII)[24]. Table 2 contains the comparisons of all two and three-carbon chain compounds. In no case was there a decrease in activity with the introduction of the alpha methyl group, while there seems to be a decrease by further extending the chain to four carbons (XLIII).

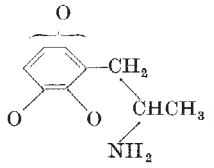
Indole generation. One of the first arguments accompanying the adrenochrome hypothesis was the demonstrated ability of adrenaline to cyclize in oxidative conditions to form an indole ring. Such a cyclized product has been sought but not observed in the living organism. It is nevertheless intriguing to consider the possibility of such an *in vivo* indole synthesis, for many psychotomimetic compounds found in nature are indolic.

There are two reasonable mechanisms by which compounds in Table 1 might be converted to indoles: by the generation of a quinonic intermediate using a pair of oxygen atoms located *ortho* or *para* to one another followed by the abstraction of a molecule of water, or by the nucleophilic attack of the nitrogen atom of the base on one of the *ortho* hydrogens, itself lying *ortho* or *para* to an oxygen atom.

Considering the first mechanism, the probable quinone intermediate that could lead to an indole product is the *para*-quinone structure illustrated. Also possible is the

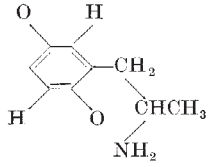
Table 3

Potential for both *ortho* and *para*-quinone; oxygen available



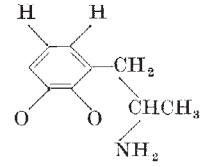
Compound	MU
XI	4
XII	13
XXII	12
XXIII	5
XXV	6
Range	4–13

Potential for *para*-quinone only; oxygen available



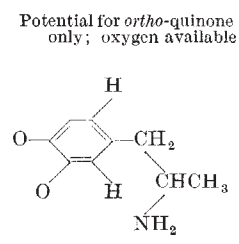
Compound	MU
IV	8
IX	17
XVII	12
XXIX	<7
XXX	15
XXXI	<7
XXXVI	80
Range (with XXXVI)	<7–17 <7–80

Potential for quinone only; oxygen available



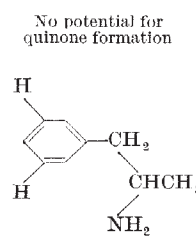
Compound	MU
X	<2
XVIII	10
XIX	3
Range	<2–10

Potential for *ortho*-quinone only; oxygen available

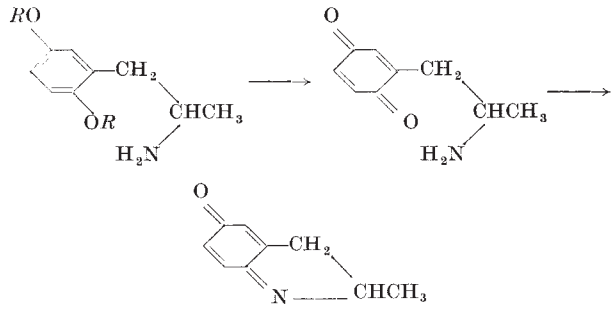


Compound	MU
VI	<1
VIII	2·2
XV	3
XVI	2·7
XXIV	<1
Range	<1–3

No potential for quinone formation

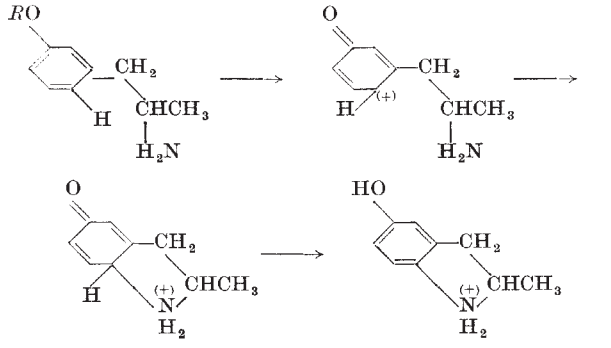


Compound	MU
I	5
III	5
XIII	10
Range	5–10



Oxidative quinone generation

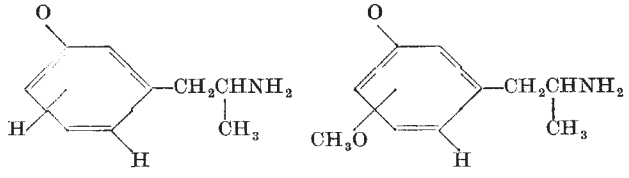
ortho-quinone (not shown), and in either case the interaction of the amino group with the carbonyl oxygen would be necessary. In Table 3 all compounds are arranged into five groupings according to quinone-forming potential. With each group is a skeleton structure that displays the mandatory atomic features; where no substitution is shown, the substituent at that point is not relevant. There appears to be some trend for a decrease of biological activity with the decrease of quinone generation potential. In group E, however, in which no quinone formation is possible, the range of potencies is essentially the same as in group A, where there is theoretically a maximum potential of such formation. Further, group D, which would involve the "adrenochrome" cyclization, contains the least active compounds.



Nucleophilic attack

The second mechanism of conversion to indoles involves the nucleophilic attack of the nitrogen electron pair directly on an unsubstituted position of the ring. The structural requirements are that there be an unsubstituted position *ortho* to the aliphatic chain that carries the nitrogen atom, and that there be an oxygen atom located *para* to this unsubstituted position. This parameter may be evaluated by the addition of alkoxy groups to the system. If the increase in nuclear basicity by such addition increases the susceptibility of the ring to nucleophilic attack, then there should be an increase in potency of the compounds as substitution density is increased. Table 4 compares the compounds which meet these criteria. In virtually every case the addition of a methoxyl group, within the limits stated, has led to an increase in potency. Thus there is support for the possibility of indole formation by this route.

Table 4



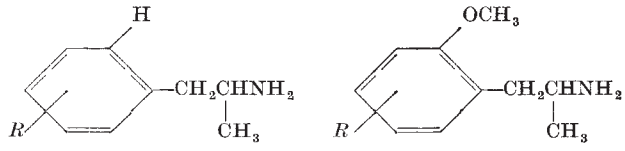
Reference compound	MU	Reference compound plus methoxy group	MU	Change
VI	< 1	VIII	2·2	+
		IX	17	+ +
		X	< 2	?
VIII	2·2	XXV	6	+
X	< 2	XXV	6	+
XI	4	XXV	6	+
XV	3	XVI	2·7	0
		XVII	12	+
		XVIII	10	+
XVI	2·7	XXII	12	+
		XXIII	5	+
XVIII	10	XXII	12	0
XIX	3	XXIII	5	+

In the conversion of adrenaline to adrenochrome and in the oxidative cyclization of demethylated mescaline derivatives[25], both a nucleophilic mechanism and a quinonic intermediate would be required.

Location of Methoxyl Substituent

Varying the specific location of a methoxyl substituent has several effects. (*a*) *Ortho*. Table 5 lists compounds in which an *ortho* methoxyl group has been introduced, and compares resulting changes in activity. In no case has the psychotomimetic activity been decreased, and in most cases there has been a substantial increase resulting from this addition.

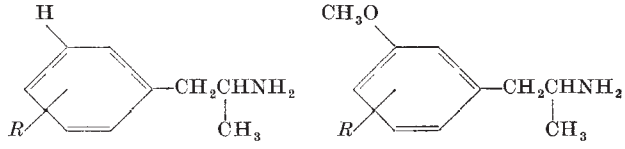
Table 5



Reference compound	MU	*Ortho*-methoxylated product	MU	Change
I	5	III	5	0
III	5	XIII	10	+
IV	8	XII	13	+
VI	< 1	IX	17	+ +
		X	< 2	?
VIII	2·2	XXV	6	+
XV	3	XVII	12	+
		XVIII	10	+
XVI	2·7	XXII	12	+
		XXIII	5	+

(*b*) *Meta*. Table 6 similarly compares compounds with and without a *meta*-methoxyl group. It seems that, with three exceptions, *meta*-methoxylation decreases the psychotomimetic activity. The evaluation of the addition of either an *ortho* or a *meta* methoxyl group is complicated by the necessarily accompanying increase in ring basicity, and the resulting increase in susceptibility to nucleophilic attack.

Table 6



Reference compound	MU	*Meta*-methoxylation product	MU	Change
I	5	VI	< 1	−
III	5	IX	17	−
		X	< 2	−
IV	8	XI	4	−
VI	< 1	VIII	2·2	+
IX	17	XXV	6	−
X	< 2	XXV	6	+
XV	3	XVI	2·7	0
XVII	12	XXIII	5	−
XVIII	10	XXII	12	0

(*c*) *Para*. In considering the effect of *para* substitution, it must be noted that most of the compounds listed in Table 1 are indeed substituted in this position. Although animal evaluations have indicated[15] that *para* substitution is by itself sufficient for psychotomimetic activity, our

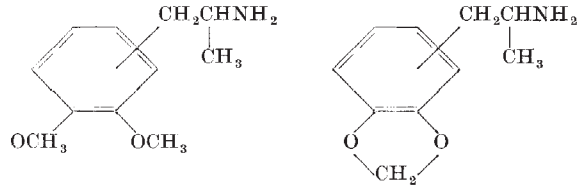
human data show that it is not mandatory (compounds IV and XI). Animal data show that *ortho* and *meta*-methoxy groups alone are not sufficient, but there are no human data on such compounds. The only direct comparisons that can be made with regard to *para* substitution are IV (MU = 8) versus IX (MU = 17) and XI (MU = 4) versus XXV (MU = 6). In both instances the addition of a 4-methoxyl group increases activity, but in both, the 4-unsubstituted isomer was none the less active. In IV, replacement of the methoxyl group at the *para* position with a methyl group leads to XXXVI (MU = 80) with a five-fold further increase in potency.

Nature of the Substituent

Three variations on the methoxy substituent have been reported: replacement with ethoxy groups, replacement of adjacent pairs with a cyclic ether (usually methylenedioxy), and replacement with an alkyl group.

Table 7 lists all the pairs of compounds that can be arranged in accordance with the transformation of two adjacent methoxy groups into a methylenedioxy ring. With one exception there is no loss of potency, and the increase in several cases is noteworthy. In a study in which the heterocycle was the distinctly less strained six-membered ring (XXIV, MU = 1), there is a decrease in activity. Of the seven possible ethoxy homologues of IX, data are available for three. Of these, the *para*-ethoxy isomer (XXX) has activity similar to that of IX. The fact that 4-substitution by ethoxy does not decrease, and the substitution with a methyl group greatly increases, the biological activity over the reference IX draws attention to the importance of the nature of the substituent at this location.

Table 7



Reference compound	MU	vs.	Methylenedioxy counterpart	MU	Change
VI	< 1		XV	3	+
VIII	2·2		XVI	2·7	+
IX	17		XVII	12	−
X	< 2		XVIII	10	+ +
			XIX	3	+
XXV	6		XXII	12	+
			XXIII	5	0

Schizophrenia seems to be a disease unique to humans, so it may well be that a hypothetical endotoxin is unique to human metabolism. The difficulties of interpretation in animal experiment are illustrated by the example of 4-methoxyphenylisopropylamine (I) which shows a potency in rats exceeded only by LSD (ref. 15) yet has an activity of only 5 MU in humans (LSD = 4,600 MU in humans). The structure–activity relationships discussed here have been derived exclusively from human data, and from these several conclusions appear.

The three-carbon side chain seems to provide maximum activity. This is presumably because such molecules are poor substrates for monoamine oxidase (MAO), the enzyme which deaminates the alpha-unsubstituted phenethylamines. Thus an endogenous psychotogen may have a two-carbon chain yet in some way be protected from deamination, for example, by being produced and acting in the synaptic cleft, whereas MAO acts intracellularly[26].

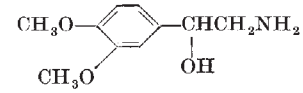
A methoxy group in an *ortho* or *para* position enhances activity, in the *meta* position decreases it. The presence of *ortho* substituents may sterically influence the involvement of the amine group at some biologically effective site. A total of three methoxyl groups seems to be optimum for activity, for both di and tetramethoxylated compounds tend to be less potent. Replacement of the methoxy groups at the 3 and 4-positions with the more strained (and thus more labile) methylenedioxy bridge results in material of increased potency. The replacement of the 4-methoxy group with an ethoxy homologue did not decrease potency, and replacement with a methyl group increased it.

These general conclusions suggest a variety of possible modes of action. It appears that a substituent at the 4-position affords stability and immunity from chemical attack rather than lability to attack. This is supported by the great increase of activity when the non-labile methyl group is found at this position. A blocking of this position might permit a compound to function as an enzyme inhibitor or a false transmitter. In a study of the metabolism of DMPEA (XXXVIII) the two methoxyl groups were metabolically distinguishable. Using unique ^{14}C labels in each position, fifteen times more of the 4-methoxy group carbon appeared in the expired breath than that derived from the 3-methoxy group[27]. This is evidence for a specific enzyme for the 4-demethylation of 4-methoxy substituted aromatic amines.

On the hypothesis that there is an endogenous psychotogen, to what extent can we deduce its structure? Compounds involved in catecholamine metabolism may be considered with regard to their possible involvement in abnormal function. In the search for a biochemical lesion the more probable expectation will be the loss of an existing enzyme, rather than the appearance of a new one. Thus rather than search for an abnormal methylation process[1] it would seem more fruitful to look for the failure of a demethylation process which would lead to the accumulation of a methylated intermediate.

There have been many methylation and demethylation processes observed that are achieved enzymatically[28,29]. Transmethylation can occur both inter and intramolecularly and selective demethylation has been shown. Although exogenous origins of DMPEA have not been excluded, its appearance as a proven component of human urine[30] supports a process of dimethylation.

One theoretical compound that has a structure compatible with these ideas, and that can be argued as being a metabolic intermediate, is 3,4-dimethoxyphenethanolamine (XLV, DME). This compound was originally proposed by Harley-Mason (see ref. 1) as a possible product of a disordered metabolism of noradrenaline. If, however, it is a normal intermediary in noradrenaline catabolism, it would be rapidly 4-demethylated to the known 4-hydroxy analogue, normetanephrine. An interference with the 4-demethylation enzyme system and the resultant accumulation of DME might produce a psychotic state. Challenges to this hypothesis may encounter difficulties for several reasons. The direct evaluation of DME in human subjects may fail, for this compound can be expected to be deaminated readily. The addition of an alpha-methyl group to DME to produce 3,4-dimethoxynorephedrine would provide protection against deamination.

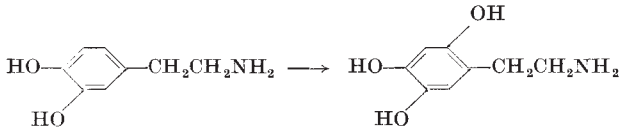


XLV (DME)

Another problem concerns demethylation. If the ability to demethylate is the normal state, then in the normal subject test compounds such as DME will be inactivated by the very process that is assumed to be non-functional in the abnormal state. To circumvent this, the lability of the 4-methoxyl group can be reduced, as in analogues such as 3,4-methylenedioxyethanolamine, or abolished in desoxy analogues such as 3-methoxy-4-methylphenethanolamine.

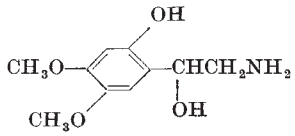
There is a second theoretical structure that is suggested for the hypothetical endogenous psychotogen by

the structure–activity relationships reported here. A feature not considered in the tables is that compounds with the 2,4,5-substitution pattern have consistently high activity. This orientation is known to occur normally in animal metabolism. In the intact rat, labelled dopamine has been shown to be converted to 6-hydroxydopamine (XLVI) (ref. 31), and this product has been shown to be capable of methylation by COMT (ref. 32). Another system that could achieve this orientation is the enzyme complement that converts tyrosine to the 2,5-dihydroxy analogue, homogentisic acid[33]. If this enzyme system could accept DOPA as a substrate, a 2,4,5-trihydroxy product would result.



Dopamine XLVI

Based on this, and by following an argument analogous to that applied to DME, we propose that 2-hydroxy-4,5-dimethoxyphenethanolamine (XLVII) could be a possible endogenous psychotogen. To challenge this possibility, again by analogy to the DME arguments, *ortho* hydroxy or methoxy analogues of these compounds, discussed in reference to DME, warrant synthesis and evaluation.



XLVII

Although a chemical explanation for schizophrenia is only one of several that are possible, the fact remains that some aspects of this state can be reproduced chemically. Thus the hypothesis of an endogenous psychotogen deserves further investigation. The compounds implicit in the combinations of ring and chain variations outlined here may provide the tools that can challenge this hypothesis.

Received September 16; revised December 24, 1968.

1 Osmond, H., and Smythies, J. R., *J. Ment. Sci.*, **98**, 309 (1952).
2 Jarvik, M. E., *Psychopharmacology: Pharmacological Effects on Behaviour* (edit. by Pennes, H. H.) (Hoeber, Inc., NY, 1958).
3 Hollister, L. E., *Ann. NY Acad. Sci.*, **96**, 80 (1962).
4 Heston, L. L., *Brit. J. Psychiat.*, **112**, 819 (1962).
5 Karlsson, J. L., *The Biologic Basis of Schizophrenia* (Thomas, Springfield, Illinois, 1966).
6 Szara, S., and Hearst, E., *Ann. NY Acad. Sci.*, **96**, 134 (1962).
7 Naranjo, C., *Ethnopharmacologic Search for Psychoactive Drugs*, 385 *et seq.* (edit. by Efron, D. H.) (US Gov. Printing Office, 1967).
8 Friedhoff, A. J., and van Winkle, E., *Nature*, **194**, 897 (1962).
9 Hollister, L. E., and Friedhoff, A. J., *Nature*, **210**, 1377 (1966).
10 Shulgin, A. T., Sargent, T., and Naranjo, C., *Nature*, **212**, 1606 (1966).
11 Uyeno, E. T., Otis, L. S., and Mitoma, C., *Comm. in Behav. Biol. A*, **1**, 83 (1968).
12 Snyder, S. H., and Merril, C. R., *Proc. US Nat. Acad. Sci.*, **54**, 258 (1965).
13 Smythies, J. R., and Levy, C. K., *J. Ment. Sci.*, **106**, 531 (1960).
14 Corne, S. J., and Pickering, R. W., *Psychopharmacologia*, **11**, 65 (1967).
15 Smythies, J. R., Johnson, V. S., Bradley, R. J., Benington, F., Morin, R. A., and Clark, L. C., *Nature*, **216**, 218 (1967).
16 Dixon, A. K., *Experientia*, **24**, 743 (1968).
17 Alles, G. A., *Neuropharmacology*, Fourth Macy Foundation Conference (edit. by Abrahamson, H. A.), 1959.
18 Snyder, S. H., and Faillace, L., *Science*, **159**, 1492 (1968).
19 Shulgin, A. T., *Experientia*, **20**, 366 (1964).
20 Alles, G. A., *J. Pharmacol. Exp. Therap.*, **47**, 339 (1933).
21 Hey, P., *Quart. J. Pharm. Pharmacol.*, **20**, 129 (1947).
22 Peretz, D. I., Smythies, J. R., and Gibson, W. C., *J. Ment. Sci.*, **101**, 317 (1955).
23 Shulgin, A. T., Bunnell, S., and Sargent, T., *Nature*, **189**, 1011 (1961).
24 Shulgin, A. T., *Experientia*, **17**, 127 (1963).
25 Benington, F., Morin, R. D., and Clark, L. C., *J. Org. Chem.*, **20**, 1292 (1955).
26 Carlsson, A., *Progress in Brain Research*, **8** (edit. by Himwich, H. E., and Himwich, W. A.) (Elsevier, 1964).
27 Sargent, T., Israelstam, D. M., Shulgin, A. T., Landaw, S. A., and Finley, N. N., *Biochem. Biophys. Res. Commun.*, **29**, 126 (1967).
28 Daly, J. W., Axelrod, J., and Witkop, B., *J. Biol. Chem.*, **235**, 1155 (1960).
29 Kuehl, F. A., Hichens, M., Ormond, E., Meisinger, M. A. P., Gale, P. H., Cirillo, V. J., and Brink, N. G., *Nature*, **203**, 154 (1964).
30 Creveling, C. R., and Daly, J. W., *Nature*, **216**, 190 (1967).
31 Senoh, S., Creveling, C. R., Udenfriend, S., and Witkop, B., *J. Amer. Chem. Soc.*, **81**, 6236 (1959).
32 Daly, J., Horner, L., and Witkop, B., *J. Amer. Chem. Soc.*, **83**, 4787 (1961).
33 Meister, A., *Biochemistry of the Amino Acids*, **2**, 899 (Academic Press, New York, 1965).

Effects associated with Permeability Changes caused by Gramicidin *A* in Electroplax Membrane

by
THOMAS PODLESKI
JEAN-PIERRE CHANGEUX
Service de Biochimie Cellulaire,
Institut Pasteur,
Paris

In the membrane of the electroplax from the electric organ of *Electrophorus electricus*, gramicidin *A* causes an increase of permeability to sodium ions. Cooperative effects are associated with the development of this long lasting change in permeability.

Polypeptide antibiotics such as gramicidin, valinomycin, nigericin and several others have been shown to promote permeability changes in several artificial[1] and biological membranes[2]. We are concerned here with the effects of one of them, gramicidin *A*, on the excitable membrane of the electroplax of the electric eel[3–5]. This antibiotic has been shown to cause an increase in the permeability of the membrane, which (1) develops with time according to high order kinetics; (2) proceeds always to the same maximum extent independently of the concentration of gramicidin *A* used; and (3) lasts for several hours at least. We discuss these results in terms of a cooperative reorganization of membrane structure[6–8].

Action of Gramicidin *A* on Electroplax Membrane

Fig. 1 shows a recording of a typical experiment when the innervated membrane of an isolated electroplax is exposed to a solution of 1 μg/ml. of gramicidin *A* (about 5×10^{-7} M). In a few minutes the membrane potential decreases from its resting value of about −80 mV almost to zero (in a few cases positive potentials up to +10 mV have been recorded). Simultaneously, and with the same time course, the membrane conductance increases about 25-fold and reaches a steady value which is significantly smaller than the conductance of the physiological solution. The general features of the steady state voltage–current relationship of the innervated membrane are also modified.

"hiving-off" operation, we think the ministry should first exercise some "accountable management" as proposed by Fulton. It is only too clear to us that they have ignored the needs of the inspectorate and British archaeology.

Yours faithfully,

T. H. PROFITT

The Institution of Professional
Civil Servants,
Northumberland Street,
London WC2.

Synthetic Foodstuffs

SIR,—I wish to clarify the reference to the work of the Tropical Products Institute in the summary of the Parliamentary Question which appeared in your issue of December 28 (220, 1271; 1968).

This institute is not, in fact, currently carrying out any work on novel marine sources of proteins. However, one of our projects (Tropical Products Institute, Annual Report 1967) does concern East African freshwater fish and involves study of means of preservation and improvement of quality.

Yours faithfully,

P. C. SPENSLEY

Tropical Products Institute,
56–62 Gray's Inn Road,
London WC1.

Probability and Prejudice

SIR,—Professor Lindley (*Nature*, 221, 594; 1969) is, like Matthew, entitled to his opinion, but I do not see that his comments in any way dispose of my criticisms. First of all, perhaps I could protest at the irrelevant remarks in his first paragraph, which includes an inaccurate reporting of what I quoted Professor Maynard Smith as saying, namely, that the problem "yields at once to common sense or to Bayes's theorem". By omitting the phrase "to common sense or" Professor Lindley distorts, quite unfairly, the implication in my own remarks.

To come now to the problem, this is unsatisfactory partly because of the third-person reporting in it of Matthew's opinions as data to be used in any numerical evaluations. These data included Matthew's assessments of his own probability of execution as changing from 2/3 to 1/2, so that he had a right to feel happier, in particular if it could be shown that he was being consistent. Professors Maynard Smith and Lindley apparently think he had no such right, but my claim that this view "may legitimately be questioned" was illustrated by my demonstrating how Matthew could be consistent in his assessments. Lindley introduces the further assumption that $r = 1/3$ "as a reasonable value", and concludes that P, the probability of the jailer naming Mark if both Mark and Luke are to be executed, would then have to be 1. Dismissing this possibility, Lindley rejects the consistency of Matthew's assessments. Even if I accept Lindley's value $r = 1/3$ (which Matthew may not have done), Matthew has, however, still a "right to feel happier" on the weaker basis that his second assessment should be at any rate $< 2/3$, which leads to the condition $P > 1/2$. I see nothing extraordinary in such a belief by Matthew about P, especially if he recalls the order of precedence of Mark and Luke in the New Testament. (The jailer may not be a Christian, but Matthew may be unaware of this.)

Yours sincerely,

M. S. BARTLETT

Department of Biomathematics,
Pusey Street,
Oxford.

Mr Short's Shibboleth

SIR,—Your editorial "Mr Short's Shibboleth" (*Nature*, 221, 298; 1969) criticizing arrangements to teach religion in schools is in part based on the relevance of the Old Testament to contemporary situations. The useful supplement to this document which was later issued has a more up-to-date approach.

Yours faithfully,

PATRICK FALLON

4 Worcester Road,
London SW19.

University News

Dr F. P. Lisowaki, University of Birmingham, has been appointed professor of anatomy at the **University of Hong Kong.**

Dr A. Donnachie, University of Glasgow, has been appointed to an additional chair of theoretical physics at the **University of Manchester.**

Announcements

Sir Alexander Haddow is to retire on March 31 from his directorship of the Chester Beatty Research Institute. He will continue his researches as professor of experimental pathology.

The **Scientific Medal,** awarded by the **Zoological Society of London,** has been won by **Dr G. A. Horridge,** director of the Gatty Marine Laboratory, University of St Andrews, in recognition of his work in zoology; a second Scientific Medal has been awarded to **Dr M. Wells** of the University of Cambridge. The **Clough Award** of the Edinburgh Geological Society has been awarded to **Dr M. J. O'Hara,** Grant Institute of Geology, University of Edinburgh, in recognition of his mineralogical and petrological studies in the rocks of the Scottish Highlands.

The **Macromolecular Research Centre** has recently been established at the University of Michigan. Its objectives are to provide intensive graduate and postdoctoral research and education training in the field of macromolecular science, with emphasis on chemical and physical studies of natural and synthetic macromolecules.

ERRATUM. In the article "Stomatal Closure and Inhibition of Transpiration induced by (RS)-Abscisic Acid" by Cathryn J. Mittelheuser and R. F. M. Van Steveninck (*Nature*, 221, 281; 1969) the contents title unfortunately contradicted the authors' findings. It should have read "Abscisic acid induces stomatal closure and inhibits transpiration".

ERRATUM. In the introductory paragraph to the article "Structure–Activity Relationships of One-Ring Psychotomimetics" by Alexander T. Shulgin, Thornton Sargent and Claudio Naranjo (*Nature*, 221, 537; 1969) "triple methoxy substitution" should have read "trisubstitution". In Table 3 "Potential for *ortho*-quinone only; oxygen available" should have read "Potential for *ortho*-quinone only; oxygen not available". On p. 540, twenty-three lines down (XXIV, MU = 1) should have read (XXIV, MU < 1).

ERRATUM. In the article "Bark Beetle Attractants: Identification, Synthesis and Field Bioassay of a New Compound isolated from *Dendroctonus*" by G. W. Kinzer *et al.* (*Nature*, 221, 477; 1969) the first sentence of the fifth paragraph should read "The activity of the synthesized compound was tested in field conditions in the Boyce Thompson Institute's experimental forest near Beaumont, Texas, using tree trunk simulating olfactometers[8]".