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# Behavioural Effects of some Derivatives of Amphetamine and LSD and their Significance

In attempts to work out possible mechanisms of action of the hallucinogenic drugs, it would be helpful to know which chemical groups modify their activity. In the methoxylated amphetamines, some methoxy groups may act as electrostatic binding sites and some may effect the shape and energy distribution of the $\pi$ cloud. It may also be important to know whether the amino group is necessary for activity. It has been shown that N,N-dimethylmescaline is a less potent compound than mescaline[1,2]. We have now tested further N,N-dimethyl derivatives of hallucinogenic amphetamines using the Bovet-Gatti profiles on the Sidman avoidance schedule[3,4] which we have found to discriminate between hallucinogenic drugs very well. 4-Methoxyamphetamine is a very potent disrupting drug in rats and produces a typical "hallucinogenic" profile at 3 mg/kg (equivalent to mescaline at 25 mg/kg). The N,N-dimethyl derivative was totally inactive at 25 mg/kg. 2,5-Dimethoxy-4-methyl amphetamine (DOM) is the most potent human hallucinogenic amphetamine known (active in rats at 2·5 mg/kg). Its N,N-dimethyl derivative was also quite inactive at 20 mg/kg. These results suggest that, if these compounds bond, they do so using their N atoms, in which case our hypothesis[5] would predict that the 3-compound (not yet tested) would be an active hallucinogen. The relative activity of methoxylated amphetamines seems to correlate more with their quantum chemical properties, such as their Hückel molecular orbital (HMO) energies and degree of native fluorescence[6], than with their steric properties. That is to say, the steric requirements seem to be an unhindered N and an unhindered *ortho* or *para* methoxy group, and the energetic requirement is a high HMO energy.

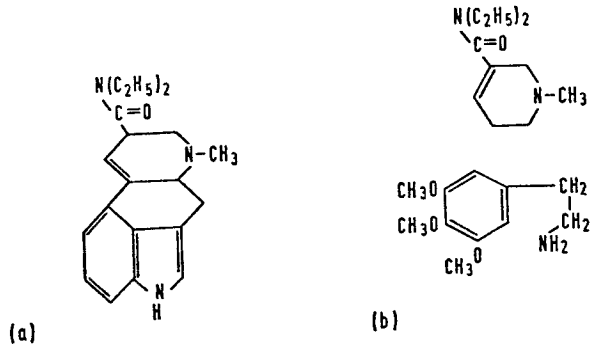


Fig. 1. (*a*) LSD; (*b*) mescaline and 1-methyl-1,2,5,6-tetrahydropyridine-3-(N,N-diethylcarboxamide).

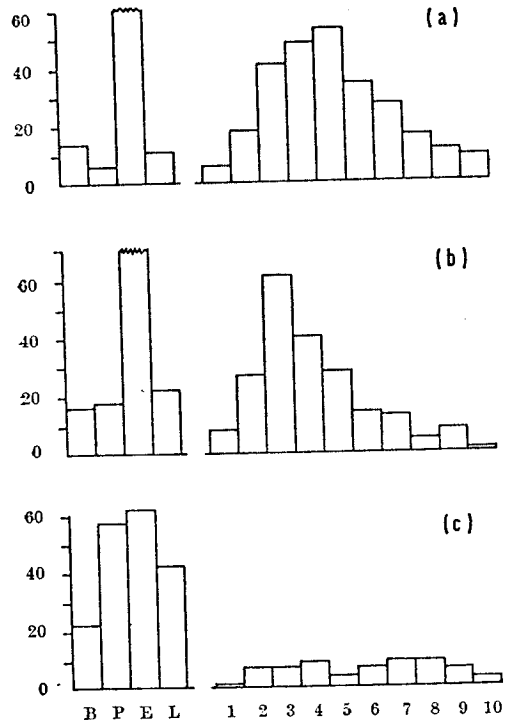


Fig. 2. The Bovet-Gatti profiles of the interaction between THPC and mescaline; (*a*) 15 mg/kg of THPC; (*b*) 12·5 mg/kg of mescaline; (*c*) the same, after treatment with 15 mg/kg of THPC. The latter is similar to the effect normally produced by 25 mg/kg of mescaline. The total number of responses in each category is given. B, Burst responses; P, premature responses; E, efficient responses; L, late responses; on the right the distribution of responses within the 10 s conditioned stimulus (CS) period is given. Hallucinogens increase B, P and L responses and shift the peak of the responses in the CS period to the left. The total number of E responses may be computed as the sum of the columns in the right-hand figure.

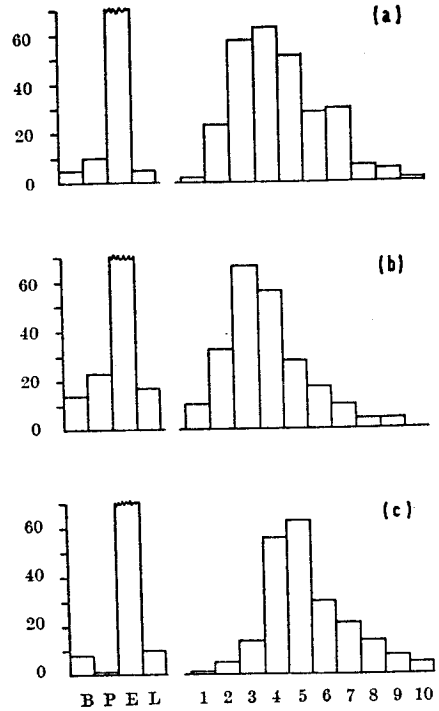


Fig. 3. The same for LSD; (*a*) saline; (*b*) 0·05 mg/kg of LSD; (*c*) 0·1 mg/kg of LSD after 15 mg/kg of THPC.

A second prediction of our hypothesis[5] is that blocking all three active groups on 5-HT (5-hydroxytryptamine) should inactivate the compound. 5-Methoxy-N,N-dimethyltryptamine is a most potent hallucinogen and disrupts rat behaviour at 2·5 mg/kg. We have tested the 1-methyl derivative of this drug and found it to have only a mild "stimulant" (amphetamine-like) profile at 10 mg/kg. This is in contrast to 1-methyl LSD which is an active hallucinogen.

We wished to know whether halving the LSD molecule and giving the bits separately would be effective. An approximation to this procedure can be carried out by determining whether 1-methyl-1,2,5,6-tetrahydropyridine-N,N-diethylcarboxamide (THPC; Fig. 1) potentiates the effect of mescaline. Fig. 2 shows that pre-treatment with 15 mg/kg of THPC, 45 min before treating with 12·5 mg/kg of mescaline, markedly potentiates the effects of the latter. This was confirmed in a second rat, the behaviour of which was completely disrupted for 30 min by the combination. When given before an equivalent dose of LSD (0·1 mg/kg), there was no such potentiation (Fig. 3), but

the effect of LSD was inhibited. This dose of THPC by itself produced no behavioural effect (Figs. 2 and 3).

THPC could potentiate the effect of mescaline by one of two mechanisms: (i) if mescaline occupies only half the LSD site, as Snyder and Richelson have proposed[6], occupation of the other half by THPC might increase its effect, at the same time blocking binding of LSD, or (ii) THPC might affect some other brain mechanism, which, although it might have no direct behavioural effect, would nevertheless potentiate the effect of mescaline on some other system. But because mescaline and LSD are believed to act on the same mechanism, it is difficult to see why such a non-specific action should not potentiate the effect of LSD as well.

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J. R. SMYTHIES

Department of Psychiatry,
University of Edinburgh.

J. BEATON

Department of Psychology,
University of Aberdeen.

F. BENINGTON
R. D. MORIN

Department of Psychiatry,
University of Alabama.

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## Correlation between Activity and Electronic State of Hallucinogenic Amphetamines

THE actions of hallucinogenic agents have been correlated with Hückel molecular orbital calculations of the $\pi$-electrons[1] and with fluorescent properties[2]. The Hückel correlations on three methoxylated amphetamines indicated that hallucinogenic activity correlated with energy of the highest occupied molecular orbital[1].

We calculated the total valence electron charge density, frontier electron density, dipole moment, total energy and all energy levels of thirteen hallucinogenic amphetamines using the INDO method (intermediate neglect of differential overlap)[3] which gives good results in the calculation of dipole moments, molecular geometries, electron nuclear hyperfine coupling constants and force constants[4-7]. Standard bond lengths and bond angles were used to generate cartesian coordinates, and vicinal methoxy groups were regarded as out of plane in a *trans*-configuration. All results were subjected to sequential multiple regression analysis.

Table 1 shows the correlation between hallucinogenic activities in man[8] and the energy of the highest occupied molecular orbital ($E_H$). For this correlation, the linear regression equation, $\log A = a + bx_1 + cx_2 \ldots$, may be expressed by the following equation, where $A$ is hallucinogenic activity

$$\log A = 19{\cdot}07 + 35{\cdot}65\, E_H \qquad (1)$$

The equation for equimolar activity is

$$\log A = 18{\cdot}7 + 35{\cdot}1\, E_H \qquad (2)$$

For equation (1), $r = 0{\cdot}753$, $F = 14{\cdot}36$ and $P < 0{\cdot}005$; for equation (2), $r = 0{\cdot}756$, $F = 14{\cdot}62$ and $P < 0{\cdot}005$. This correlation suggests that the ease of perturbability of the $\pi$-electrons of the amphetamines is a determinant of hallucinogenic activity, the amphetamines presumably forming with the brain receptor a low energy, reversible $\pi$-molecular complex that gives rise to hallucinations.

Table 1. HALLUCINOGENIC ACTIVITIES OF AMPHETAMINE DERIVATIVES IN MAN AND ENERGY OF THE HIGHEST OCCUPIED MOLECULAR ORBITAL ($E_H$)

| Derivative of amphetamine | Hallucinogenic activity | $E_H$ (atomic units) |
|---|---|---|
| 2,5-$(OCH_3)_2$-4-$CH_3$ | 80–100* | −0·4929 |
| 2,4,5-$(OCH_3)_3$ | 17 | −0·5001 |
| 2,3,6-$(OCH_3)_3$ | 13 | −0·5112 |
| 2,4,6-$(OCH_3)_3$ | 10 | −0·5217 |
| 2,5-$(OCH_3)_2$ | 8 | −0·5012 |
| 2,3,4,5-$(OCH_3)_4$ | 6 | −0·5126 |
| 2,4-$(OCH_3)_2$ | 5 | −0·5194 |
| 4-$OCH_3$ | 5 | −0·5262 |
| 2,3,5-$(OCH_3)_3$† | 4 | −0·5026 |
| 3,4,5-$(OCH_3)_3$ | 2 | −0·5218 |
| 2,3,4-$(OCH_3)_3$ | <2 | −0·5274 |
| 3,4-$(OCH_3)_2$ | <1 | −0·5238 |
| (Mescaline)‡ | 1 | −0·5226 |
| (Amphetamine) | 0 | −0·5885 |

* The activity has been reported as 80 and 100[2,8].
† Limited number of tests.
‡ Mescaline, 3,4,5-trimethoxyphenylethylamine, is not an amphetamine derivative but is used as a standard of hallucinogenic activity[8]. Amphetamine is not hallucinogenic and is not considered in the statistical analysis.

Table 2. $E_H$ OF SOME UNTESTED AMPHETAMINE DERIVATIVES AND THEIR PREDICTED HALLUCINOGENIC ACTIVITIES

| Derivative of amphetamine | $E_H$ (atomic units) | Predicted activity |
|---|---|---|
| 2,3,4,6-$(OCH_3)_4$ | −0·5067 | 10·0 |
| 3,5-$(OCH_3)_2$ | −0·5240 | 2·4 |
| 4-OH | −0·5296 | 1·5 |
| 3-$OCH_3$ | −0·5316 | 1·3 |
| 2,6-$(OCH_3)_2$ | −0·5334 | 1·1 |
| 2,3-$(OCH_3)_2$ | −0·5346 | 1·0 |
| 2-$OCH_3$ | −0·5371 | 0·9 |

Equation (1) was used for the predictions; equation (2) gives very similar results.

Although the correlation is significant ($r = 0{\cdot}753$, $F = 14{\cdot}36$, $P < 0{\cdot}005$), $E_H$ does not account for the activities of all the compounds. The 2,3,6-trimethoxy and 2,4,6-trimethoxy derivatives and the 4-methoxy derivative are more active than expected if $E_H$ is the only determinant of activity; and the 2,3,5-trimethoxy is less active. Other electronic or steric characteristics not revealed by this work could contribute to the activity. A better correlation cannot be expected. Drugs are involved in numerous interactions[9] before they induce hallucinations. Also, the error in measuring relative hallucinogenic activity in man is about 20 per cent (personal communication from A. T. Shulgin). Assuming that $E_H$ is the only correlate of activity, we calculated the expected hallucinogenic activity of some untested amphetamines (Table 2). Of these, the 2,3,4,6-tetramethoxy derivative is the only one that should be significantly more potent than amphetamine. Shulgin states in a personal communication that the 2,3,4-trimethoxy derivative has measureable activity, but it is less than two[8]; our calculations predict that it has about the same activity as mescaline.

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SUNGZONG KANG
JACK PETER GREEN

Department of Pharmacology,
Mount Sinai School of Medicine,
New York, New York 10029.

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