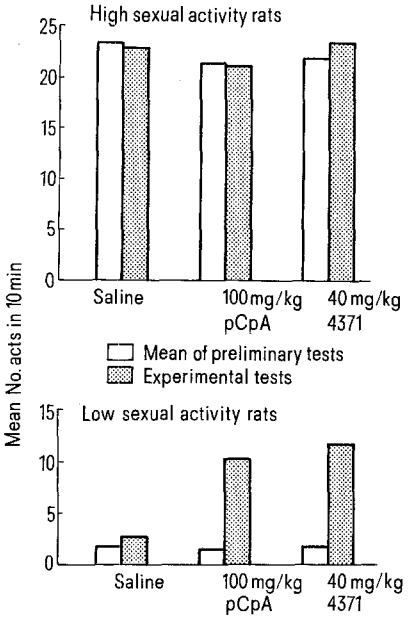

Fig. 4. Effects of 40 mg/kg WB 4371 and 100 mg/kg pCpA given daily for 4 days on male Wistar rats previously selected for 'high' or 'low' sexual activity when tested with female rats. The figure shows the results of the selection and the results after 4 days of drug treatment. In this experiment pCpA was suspended in, and WB 4371 was dissolved in, saline instead of Tween 80. Both WB 4371 and pCpA significantly increased the amount of sexual behaviour towards female rats by the 'low' activity groups ($p < 0.01$ in each case), but had little or no effect on the 'high' activity groups ($n = 14$ per group).

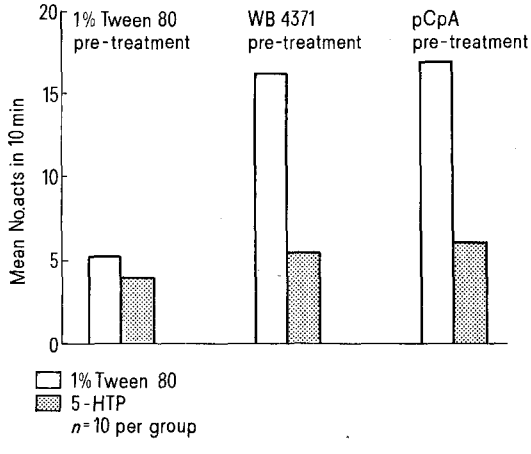

Fig. 5. Effects of 10 mg/kg 5-hydroxytryptophan (5-HTP) or 1% Tween 80 on the sexual behaviour of male Wistar rats pre-treated with either 1% Tween 80, 40 mg/kg WB 4371 or 100 mg/kg pCpA daily for 4 days. The dose of 5-HTP or 1% Tween 80 was administered i.p. 1 h before testing. Both WB 4371 + 1% Tween 80 and pCpA + 1% Tween 80 treated rats gave significantly increased scores ($p < 0.02$ in both cases) but the WB 4371 + 5-HTP and the pCpA + 5-HTP treated animals were not significantly different from controls ($n = 10$ per group).

($p < 0.02$ in both cases) but the WB 4371 + 5-HTP and pCpA + 5-HTP treated animals were not significantly different from controls. There were 10 rats in each group.

The action of pCpA is thought to be related to a decrease of brain 5-HT which results from an inhibition of tryptophan hydroxylase. It has also been suggested that a relative imbalance of cerebral catecholamines and of 5-HT might be involved (TAGLIAMONTE et al.[5]). The case for the paramount importance of lowered cerebral 5-HT levels in the stimulation of sexual behaviour has been vigorously argued by DA PRADA et al.[14,15,2], and it would be especially interesting in view of our last finding to study what, if any, effects WB 4371 has on this amine[16].

Zusammenfassung. Nachweis, dass ein bestimmtes Benzodioxanderivat (WB 4371) eine ausgeprägte Steigerung des Sexualverhaltens männlicher Ratten bewirkt, insbesondere bei Tieren mit geringer sexueller Aktivität. Die stimulierenden Effekte von WB 4371 waren mindestens so stark wie pCpA und wurden wie bei pCpA selbst durch 5-HTP blockiert.

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[16] We thank Drs M. BESSER and D. H. JENKINSON and Professor H. O. SCHILD for helpful comments, and Mr. D. P. BLUNDELL for help with the experiments.

[17] Reprints by Prof. HANNAH STEINBERG, Pharmacology Department, University College London, Gower Street, London, WC1E 6BT (England).

The Behavioral Effects of 2,5-Dimethoxy-4-Alkyl Amphetamines

The hallucinogenic derivatives of tryptamine and phenylalkylamine show cross tolerance with lysergic acid diethylamide (LSD) indicating that they share a common mode of action[1]. The A ring of LSD could correspond to the 6-membered rings of tryptamine and phenethylamine. The N(6) of LSD is probably located at the position of the side-chain nitrogen in the tryptamine and phenethylamine moieties (Figure 1). This hypothesis as propounded by KANG and GREEN[2] has been supported by a variety of experimental findings. As would be predicted from this theory the *trans* isomer of 2-(3,4,5-trimethoxyphenyl) cyclopropylamine appears to have the biological activity of mescaline[3]. The rigid analogues 2-amino-7-hydroxy-

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tetralin[4] and 2-aminotetralin[5] corresponding to the A and C rings of LSD also have mescaline like activity. Another finding which supports this theory of a common hallucinogenic receptor is that if an hallucinogenic tryptamine is substituted in the 2-position it becomes inactive[6] as does LSD, for example if it is converted to 2-Bromo LSD[7]. Of the 4 stereoisomers of LSD the most potent is (5R; 8R)-(+)-LSD. From this fact it would be predicted that the R(−) isomer of an hallucinogenic ring-substituted phenylisopropylamine (amphetamine) would be more active than the S(+) isomer if the structure of these hallucinogens is congruent with the active LSD isomer. This is in fact the case as has been demonstrated by asymmetric synthesis[8] and testing[9] of the R(−) and S(+) isomers of 2 hallucinogenic amphetamines 2, 5-dimethoxy-4-methylamphetamine (DOM) and 2, 5-dimethoxy-4-bromo-amphetamine (DOB).

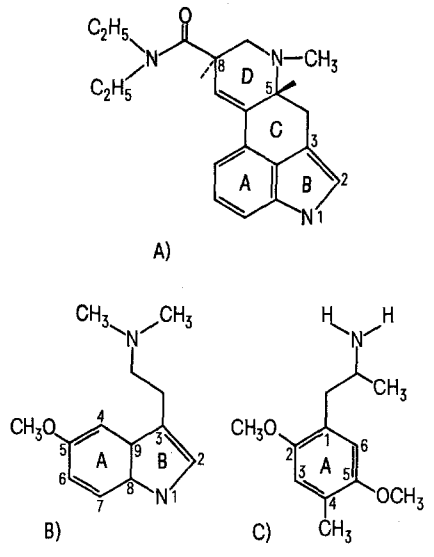

Fig. 1. The chemical structures of: *A*) 5R; 8R-LSD. *B*) N, N-dimethyl-5-methoxytryptamine. *C*) 2, 5-Dimethoxy-4-methylamphetamine.

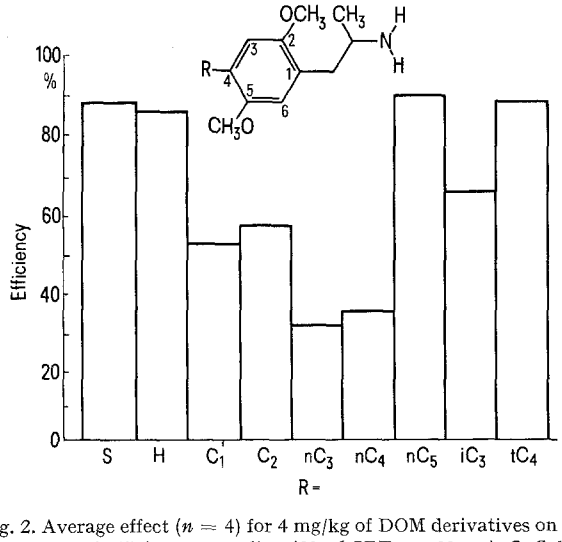

Fig. 2. Average effect ($n = 4$) for 4 mg/kg of DOM derivatives on the percentage of efficient responding ($20 \leqq$ IRTs < 30 sec). S, Saline control; H, R = H; C_1, R = CH_3; C_2, R = C_2H_5; nC_3, R = normal-C_3H_7; nC_4, R = normal-C_4H_9; nC_5, R = normal C_5H_{11}; iC_3, R = iso-C_3H_7; tC_4, R = tertiary-C_4H_9.

In order to understand the critical function of 4-substitution in DOM we now report the effects of a new series of analogues in the rat.

Methods. Synthesis of the DOM analogues. The straight-chain DL-DOM analogs were synthesized from commercially available 2, 5-dimethoxybenzaldehyde via the corresponding carbinol, alkyl-dimethoxybenzene, alkyl-dimethoxybenzaldehyde and the nitropropene, which was reduced with lithium aluminum hydride to the substituted amphetamine. In a similar manner, DL-2, 5-dimethoxy-4-isopropylamphetamine was synthesized from 2, 5-dimethoxyacetophenone. 2, 5-Dimethoxy-4-t-butylamphetamine was obtained from available t-butyl-hydroquinone via the dimethyl ether, aldehyde and nitropropene.

All of the substituted amphetamines were converted to hydrochloride salts and purified in that form. The Table lists the properties of the DL-DOM analogs and literature references to those which have been reported previously. All compounds not previously reported in the literature were characterized by physical and chemical properties IR-spectra, and elemental analysis.

Procedure. 4 adult, male hooded rats weighing between 300 and 350 g at the beginning of the study served as subjects. The paradigm used is based on a modified Discriminated Sidman Avoidance Schedule[13]. Using this test SMYTHIES et al.[14] classified certain drugs on the basis of their disruptive effects, finding that hallucinogenic compounds consistently induced effects different from those induced by stimulant compounds. The subjects were trained until they emitted a minimum of 80% efficient responses, with very little variation in response distribution ($\pm 3\%$) between 5 successive sessions. This stability required approximately 75 daily training sessions. All injections were given after a 15 min warm-up period. The data were then collected for the following 100 min. The 6 compounds shown in the Table were dissolved in saline and injected s.c. in a volume of 0.1 ml/100 g body weight at a dose of 1, 2, and 4 mg/kg.

Results. The results indicate that the most potent 4-substituents are n-propyl and n-butyl which are closely followed by methyl (DOM) and ethyl (DOET). The isopropyl derivative is next in potency but the t-butyl and n-amyl derivatives are inactive (Figure 2). There is a cut-off in activity after the 4 carbon chain in butyl, although there is little difference between the normal butyl and normal propyl. At the doses used 4-methyl was

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slightly more potent than 4-ethyl. Isopropyl was the least active of the derivatives tested causing only slight disruption at 4 mg/kg. It is noteworthy that the anti-5-hydroxytryptamine activity of the diisopropylamide of lysergic acid is much less than the dipropylamide[7]. In the case of both propyl and butyl derivatives a branched chain must not be complementary to the binding site for these compounds because iso-propyl is the least potent derivative in the series and tertiary butyl is inactive.

Discussion. The peripheral pharmacology of these substances is obviously quite different from their CNS properties perhaps suggesting a unique 5-HT receptor in the brain. The glaring example of this is 2-Bromo-LSD (BOL) which is a powerful uterine 5-HT antagonist[7] but has almost no hallucinogenic activity. Our results are in marked distinction to the effects reported by KULKARNI[12] on the behavior of mice. He reported that the 4-isopropyl analog was much more potent than the 4-ethyl or 4-methyl analog. We find that 4-isopropyl substitution gives rise to the least potent compound of the series. Given the comparison of the 6-membered rings of DOM and the hallucinogenic tryptamine moiety, it might be predicted that 4-methoxy-7-methyl-N,N-dimethyl tryptamine would be the hallucinogenic tryptamine analogue of DOM. If it can be shown that addition of a 7-methyl group to 5-methoxy-N,N-dimethyltryptamine results in a significant increase in hallucinogenic potency then this would be more proof of a common receptor mechanism. It will also be interesting to see if the effects of 4-substitution as reported in this paper would show the same relationship if substituted at C^7 in the tryptamine series.

Properties of 2,5-Dimethoxy-4-alkyl-amphetamines

Alkyl group	m.p.[a] HCl salt (°C)	Lit. m.p.[a] (°C)	Lit. reference
4-Ethyl	192–193	195	10
4-n-Propyl	181–182	182.5–183	11
4-Isopropyl	182–183	[b]	12
4-n-Butyl	145–147	—	[c]
4-t-Butyl	162–163	168	11
4-n-Amyl	139–140	—	[c]

[a] m.p., melting point. [b] Kulkarni[12] reported behavioral effects of this compound but no chemical properties or method of synthesis. [c] New compound.

Résumé. Le comportement des rats a été fortement influencé par des dérivés de la 2, 5-diméthoxyamphétamine Le mécanisme possible de l'action des hallucinogènes est discuté.

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Isoprotenerol Induction of Pineal Serotonin N-Acetyltransferase in Normotensive and Spontaneously Hypertensive Rats

Administration of β-adrenergic blockers during the development period of hypertension in spontaneously hypertensive rats delays the onset of the hypertension and prevents the development of pathological lesions[1]. Our preliminary studies have shown that the β-adrenergic stimulator isoprotenerol has a higher necrogenic effect on the myocardium of spontaneously hypertensive (SH) than of normotensive (N) controls. The common denominator of both observations might well be an altered reactivity of the beta receptor system to catecholamines in SH rats. Suppression of manifestations of this altered reactivity by beta-blockers would prevent the development of pathological lesions.

To test this hypothesis, we have chosen as a model system the enzyme forming the precursor of melatonin in the rat epiphysis, serotonin N-acetyltransferase[2]. β-adrenergic agonists induce more than a 10-fold increase in the activity of this enzyme, both in vitro in epiphyses maintained in tissue culture[3] and in vivo[4]. Administration of β-blockers suppresses this induction. We administered isoprotenerol to SH and N rats and followed the degree of induction of serotonin N-acetyl transferase in the epiphyses of both groups of animals.

Table I. Dependence of the degree of induction of serotonin N-acetyltransferase on the dosage of isoprotenerol

Dosage of isoprotenerol (mg/100 g b.w.)	Activity of serotonin N-acetyltransferase (pmoles of products per h/mg)
0	160 ± 15
0.2	1840 ± 360
0.5	1767 ± 272
1.0	1961 ± 40

Values presented are means from 5 animals ± SE. There were no significant differences between the experimental groups.

Materials and methods. Wistar-Konárovice normotensive and Wistar-Kyoto (the Okamoto-Aoki strain) spontaneously hypertensive rats were used. At least 1 week before the experiment, the animals were maintained on a standard regime of 6–18 h light and 18–6 h darkness. Isoprotenerol (Isuprel hydrochloride, Winthrop Products Co.) was administered s.c. at 10 h, and again at 12 h to experimental animals in a dose of 0.2 mg/100 g b.w. A control group received the same volume of physiological saline. At 14 h, both experimental and control animals were killed, the epiphyses were rapidly removed, weighed and placed on dry ice. Within 20 h of killing, the activity of serotonin N-acetyltransferase was determined by a modification of the method of KLEIN and WELLER[5]

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