J. Pharm. Pharmac., 1969, **21**, 9–17 *Received July* 2, 1968

Examination of the hallucinogen 2,5-dimethoxy-4-methylamphetamine

G. F. PHILLIPS* AND R. J. MESLEY†

**Drugs sub-Division and †Physical Methods sub-Division, Laboratory of the Government Chemist, Stamford Street, London, S.E.*1, *England*

Physical characteristics are reported for a tablet form of a new hallucinogenic drug previously circulating in the USA under the name "STP". High resolution mass, nmr, ultraviolet and infrared spectrometric evidence, which identify the extracted base as 2,5-dimethoxy-4-methylamphetamine, and its chromatographic behaviour, are compared with the experimental compound "DOM". Polymorphic modifications exhibiting distinct solid phase infrared spectra have been studied by X-ray diffraction and by differential calorimetry. Animal behavioural tests indicate that the psychotomimetic activity of the base is comparable with mescaline but up to 50 times more potent.

In the summer of 1967, references appeared in the British press to "a new and dangerous drug" circulating under the description "STP" in the U.S.A. and Canada. Some medical reports suggested that this drug, the nature of which was not then known, was significantly more potent and longer acting than lysergide (LSD), and that certain phenothiazines—customarily used as antidotes for LSD—potentiate its action and may cause respiratory collapse. The initials STP were not thought to be chemically significant; some press reports suggested the substance to be 5-methoxy-*NN*-dimethyltryptamine (i.e. the methyl ether of the natural hallucinogen bufotenine) or confused the drug with a military incapacitating agent "BZ".

Only very limited supplies of the drug were believed to have reached this country but the Home Office Drugs Branch was able to obtain a single tablet, thought to be of Californian origin; the tablet was submitted to this Laboratory for examination. A few milligrams of a base hydrochloride were extracted, sufficient to investigate the thin-layer chromatographic behaviour and to record high resolution mass, ultraviolet and infrared spectra; in addition animal behavioural tests with a small portion of the tablet and with aqueous and chloroform extracts were undertaken on our behalf at the Chemical Defence Experimental Establishment. From accurate mass measurement and the spectral characteristics it was possible to deduce with fair certainty the structure to be 1-methyl-2-(2,5-dimethoxy-4-methylphenyl)ethylamine: it is convenient to refer to this structure as 2,5-dimethoxy-4-methylamphetamine.

Concurrently, workers at the U.S. Food and Drug Administration (FDA) had encountered several dosage forms (white, orange or light blue tablets) loosely described as STP and by a similar deductive process had reached an identical conclusion about the structure of the psychotomimetic ingredient (Martin & Alexander, 1968). The weight, dimensions, lactose excipient and well finished appearance were all comparable with the tablet we had examined [U.S. Bureau of Drug Abuse Control (USBDAC), personal communication]. Moreover the FDA identified‡ the base with

‡ Press release 2nd August, 1967; cited, *inter alia*, in *Chem. Engng News*, 14th Aug., 1967, p. 39.

an experimental compound, DOM, developed by the Dow Chemical Co. but for which no information had hitherto been published nor had there been an "Investigational New Drug" application.

Through the courtesy of the US-BDAC a small sample of DOM was supplied to the Home Office. Access to this material permitted a fuller examination of the spectrometric, chromatographic and chemical characteristics of 2,5-dimethoxy-4-methylamphetamine, a refined estimate of its psychotomimetic activity, and comparison with the base extracted from the STP tablet. A preliminary account of the tablet examination was given restricted publication (Maunder, 1967); the more detailed results are now reported as an aid to the identification of this substance should its use become more prevalent in this country. To date, the relatively few samples detected have been either the pale blue tablet or clear gelatin capsules filled with a similarly coloured powder apparently diluted with lactose.

EXPERIMENTAL

Melting points (uncorrected) were determined in sealed evacuated capillaries or with Kofler hot-stage microscope or inferred from calorimetric transitions.

Ultraviolet absorption spectra were recorded as aqueous or acidified solutions using a Unicam SP.800 spectrophotometer.

Thin-layer chromatography systems. (A), silica gel (30 g) impregnated with NaOH (60 ml 0·1 N), developed with chloroform–methanol (9 : 1) (Genest & Farmilo, 1964); (B), adsorbent as (A) but with methanol as solvent; (C), silica gel, developed with methanol–ammonia (sp. gr.: 0·880) (100 : 1·5) (Sunshine, 1963). Visualization was by spraying with 1% iodine in methanol or by examining the fluorescence under ultraviolet (360 nm) illumination.

Colour reagents. Froehde: sodium molybdate (50 mg) in sulphuric acid (10 ml). Mandelin: ammonium vanadate (1 g) in sulphuric acid (100 ml). Marquis: 40% formalin (8–10 drops) in sulphuric acid (10 ml). Mecke: selenious acid (0·25 g) in sulphuric acid (25 ml).

Infrared absorption spectra were recorded as Nujol mulls using a Grubb Parsons GS 2 grating spectrometer.

X-ray powder diffraction patterns were recorded photographically using a Unicam 9 cm camera and vanadium-filtered chromium Kα radiation. Measurements of I/I_0 were made with a Joyce recording microdensitometer.

Mass spectra were obtained initially with an Associated Electrical Industries MS-9 spectrometer (at the National Physical Laboratory) and subsequently in this Laboratory with an MS-902. Both instruments are double focussing, electron bombardment mass spectrometers with a resolution better than 1 : 10,000. Accurate mass measurements were made with reference to heptacosafluorotributylamine and all fragment formulae assigned agree within 15 ppm (MS9), or 5 ppm (MS-902), with the theoretical values.

100 *MHz proton magnetic resonance spectra* were recorded (at the National Physical Laboratory) with a Varian HA-100 spectrometer using solutions in carbon tetrachloride. Chemical shifts were calculated as τ values using tetramethylsilane as standard.

Differential scanning calorimetry was carried out with a Perkin-Elmer DSC-1B apparatus, using dry nitrogen at 20 ml/min as carrier gas and a heating rate of 8°/min.

RESULTS

Tablet form. The tablet was circular, biconvex and half-scored; the turquoise colour approximately matched G5 in the *Chemist and Druggist* Identification Guide. It weighed 189·6 mg. The maximum thickness was 3·74 mm (almost 5/32 inch) and diameter 7·16 mm (10/32 inch). The physical characteristics were such that expertise in its production could be inferred. The only crystalline component detected by X-ray diffraction was lactose monohydrate.

The tablet was substantially soluble in water and completely soluble in dilute hydrochloric acid. With small quantities (less than 10 mg) dispersed in sodium hydroxide solution the first chloroform extraction preferentially removed small amounts of fatty material; acidification of the alkaline phase, followed by an excess of dilute ammonia or sodium bicarbonate, with chloroform extraction yielded essentially pure base. On a larger scale (upwards of 20 mg) the base was not significantly retained in the initial alkaline phase. It was discovered that the free base is somewhat volatile and isolation as the salt is safer. Altogether approximately 2·0 mg of amorphous base, m.p. 59° (Kofler block), was extracted from 42 mg of the tablet.

The ultraviolet absorption spectrum of an acidified solution of 1 mg of the tablet [λ_{max} 288 nm (E 1%, 1 cm = 7·5) λ_{min} 255, shoulder 220/225 (E 1% 1 cm *ca* 22) and λ_{max} <215] was very similar to that of methoxamine [λ_{max} 291, λ_{min} 253, λ_{max} 226, shoulder 215], which has the structure 2-amino-1-(2,5-dimethoxyphenyl)propan-1-ol. The aqueous extract also included a blue dyestuff, λ_{max} 626 nm, and chloride ion, confirmed conventionally.

Limited examination with the thin-layer system (A) using methanolic iodine visualization suggested that the STP base could be distinguished from methamphetamine but not easily from mescaline, phentermine and amphetamine. In addition a weaker, more mobile, spot, visualized only by its fluorescence in 360 nm illumination, overlapped secondary spots of methoxyphenamine and methoxamine. In general the limited mobility in system (A) is disadvantageous and a more detailed comparison, using several thin-layer systems, was undertaken after the DOM sample was obtained—see below.

Active drug form. The DOM sample was a white powder; it proved to be a hydrochloride salt, m.p. (evacuated capillary) 184–5°. With the Marquis reagent it gave a bright lemon yellow colour slowly turning pink, in contrast to the brown becoming olive green given by amphetamines not substituted in the aromatic ring. Colours were developed with other common alkaloid reagents, including Froehde (yellow turning to lime green), Mandelin (bright green tending to brown), Mecke (varying from brown through green hues back to brown) and sulphuric acid itself (faint pink becoming yellow).

On all three thin-layer systems when visualized with methanolic iodine, DOM gave a single spot comparable with that observed with the base extracted from STP, whereas in 350 nm illumination there was no sign of the latter's weaker more mobile spot. In a detailed study of 31 variously substituted amphetamine, phenethylamine and phenethanolamine salts, using systems (B) and (C) (to be published), only ephedrine, pseudoephedrine, and methamphetamine exhibited mobility overlapping DOM; the first two substances may be distinguished by their bright yellow colour with methanolic iodine spray (DOM gives a pinkish-brown) while methamphetamine may be resolved in the otherwise less favourable system (A).

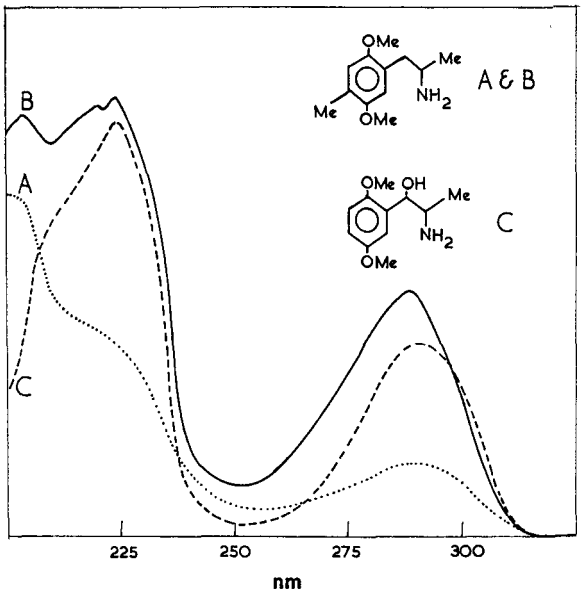

FIG. 1. A = aqueous extract of STP tablet (c = 36 mg %). B = aqueous solution of DOM hydrochloride (c = 6·6 mg %). C = aqueous solution of methoxamine hydrochloride (c = 5·5 mg %).

Note that at wavelengths greater than 220 nm, B and C are virtually superposable, and that from the ratio A/B, the STP tablet must contain about 4·5% DOM base, or 5·3% expressed as the hydrochloride.

An aqueous solution of DOM produced an ultraviolet absorption spectrum [λ_{max} 288 nm (E 1%, 1 cm = 166), λ_{min} 251 (33), λ_{max} 224 (272), λ_{max} 209 (254)] which above 215 nm is in satisfactory agreement with that obtained from the aqueous extract of the STP tablet and moreover is virtually superposable on that previously demonstrated for methoxamine (see Fig. 1); in the latter there is a slight bathochromic shift of the centre of the aromatic band to 291 nm, possibly attributable to interaction of one methoxyl with the side-chain hydroxyl. From the specific absorbance at 288 nm observed for DOM it may be calculated that the STP tablet contained about 4·5% of 2,5-dimethoxy-4-methylamphetamine (that is, 8·6 mg base or 10 mg as the hydrochloride).

Chloroform extraction of an alkaline solution of DOM yielded a base giving the same infrared spectrum as that normally obtained from the STP tablet. Two polymorphic forms were obtained: material recovered from evaporation of chloroform solution was shown to be substantially form II containing a small proportion of form I, detectable by its infrared absorption at 924 cm^{-1}. On standing for one month this material was wholly converted to form II; form I was obtained in a pure state by crystallization from a melt. Infrared spectra and X-ray diffraction patterns of the hydrochloride as received and of the two forms of the base are shown in Fig. 2 and Table 1 respectively. The melting points of the two forms differ widely: differential scanning calorimetry of form II showed a broad endothermic transition commencing at 55° (melting of form II) followed by an exothermic transition (recrystallization as form I) and a second broad endothermic transition beginning at 110° (melting of form I). The two forms are apparently enantiotropic, since form I slowly reverts to form II at room temperature.

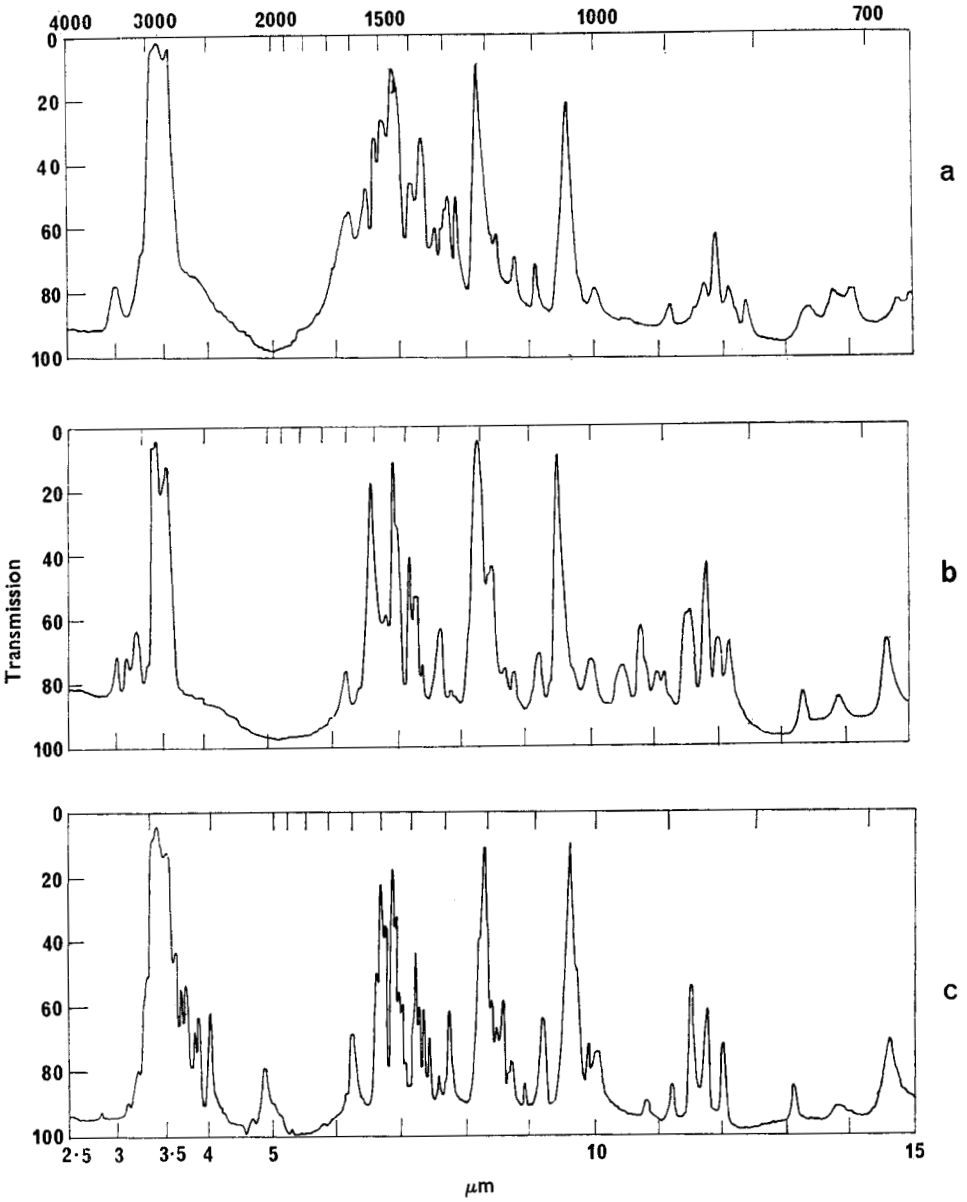

FIG. 2. Infrared spectra (Nujol mulls) of **a**, DOM base form I; **b**, DOM base form II; **c**, DOM hydrochloride.

The high resolution mass spectrum of DOM base was in general agreement with that of the base from the STP tablet and with that given by Bellman (1968). There were, however, some additional peaks in the STP spectrum, most of which were apparently derived from fatty acids used as binders in the tablet, but those at m/e 281, 192 and 116 remain unidentified; accurate mass measurement suggested the formulae $C_{15}H_{23}NO_4$, $C_{12}H_{16}O_2$ and $C_5H_{10}NO_2$ respectively. The high resolution nuclear magnetic resonance spectrum of the DOM base was also recorded.

Table 1. *X-Ray powder diffraction patterns*

Base form II		Base form I		Hydrochloride	
d (Å)	I/I_0	d (Å)	I/I_0	d (Å)	I/I_0
13·9	5	8·59	6	9·97	25
10·8	15	7·81	100	7·28	4
8·59	47	7·43	72	6·64	6
7·76	22	7·18	5	6·17	20
7·08	100	5·67	5	5·77	28
6·64	8	5·21	44	5·59	100
5·71	14	4·49	18	5·34	77
5·50	15	4·24	66	5·04	46
5·18	11	4·02	19	4·70	10
4·77	5	3·89	5	4·35	35
4·63	5	3·79	37	4·24	42
4·47	8	3·73	23	4·11	3
4·31	16	3·62	72	3·94	76
4·24	20	3·43	6	3·80	14
4·13	38	3·18	15	3·66	17
3·89	8	3·11	5	3·54	37
3·79	4	2·99	3	3·46	35
3·69	4	2·77	10	3·37	37
3·56	38	2·61	4	3·31	36
3·49	16	2·59	5	3·08	5
3·33	10	2·50	5	3·02	5
3·04	11	2·42	3	2·91	22
2·38	6	2·39	3	2·81	4
		2·27	2	2·73	3
		2·24	4	2·66	4
		2·19	2	2·57	14
				2·51	7
				2·45	6
				2·40	3
				2·33	10
				2·18	5

Elucidation of structure

The structure 2,5-dimethoxy-4-methylamphetamine was deduced from the spectrometric investigation of the base extracted from the STP tablet and from the subsequently supplied sample of DOM hydrochloride.

Accurate measurement of the parent ion peak gave a mass of 209·1415($C_{12}H_{19}NO_2$ requires 209·1416). The fragment peaks at m/e 166 ($C_{10}H_{14}O_2$) and 44 (C_2H_6N) are both consistent with the parent molecule being a primary amine with a methyl group attached to the α-carbon atom. The presence of an isopropylamine side-chain was confirmed by the 100 MHz nmr spectrum (see Fig. 3). This showed a doublet centred at τ 9·0 due to the CH_3 group adjacent to the CH group in the propyl chain, and a series of eight bands centred at τ 7·56 due to the inequivalent *gem* hydrogens adjacent to the asymmetric carbon atom (AB part of an ABX spin system), while the CH proton itself gave a complex broad signal at τ 7·02 and the NH_2 protons a broad band at τ 8·66.

The presence of two methoxy groups attached to the ring was indicated by the pair of singlets at τ 6·32 and 6·34 in the nmr spectrum, the successive mass differences between the fragments at m/e 166, 135 ($C_9H_{11}O$) and 105 (C_8H_9), the strong infrared absorptions due to aryl ether groups at 1212 and 1045 cm^{-1} (with no evidence of any other oxygen functions) and the ultraviolet correlation with methoxamine. Similarly the aryl methyl group was indicated by the nmr singlet at τ 7·90 and the mass difference between the fragments of m/e 166 and 151 ($C_9H_{11}O_2$), the latter suggesting that a methyl group can be lost without destroying the stable tropylium structure. The two

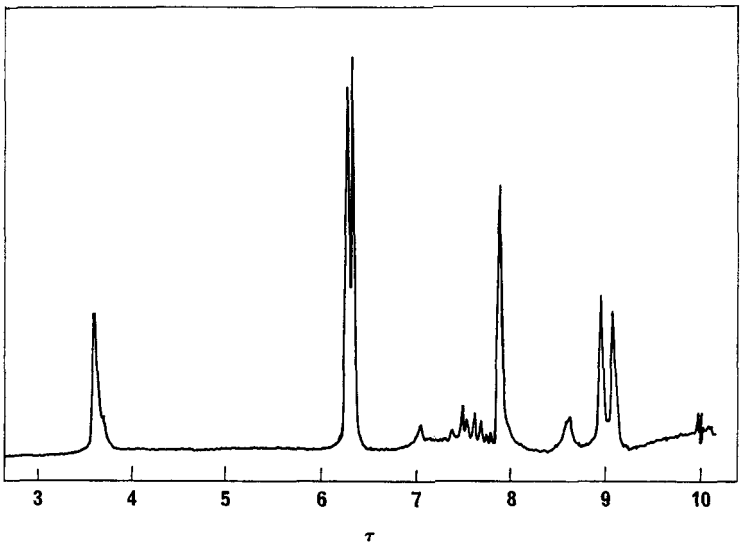

FIG. 3. The 100 MHz nuclear magnetic resonance spectrum of DOM base. For convenience of illustration, the separation of the signals at τ 6·32 and 6·34 has been exaggerated.

aromatic protons gave a single nmr absorption at τ 3·54 with no resolvable fine structure (Martin & Alexander, 1968, reported a rather complex signal); the lack of coupling between these protons, and the absence of strong infrared absorption at 800–830 cm^{-1}, confirm that the two ring protons cannot be adjacent to each other. The *para* relationship of the two methoxy groups is demonstrated by reference to comparison spectra: thus, in the ultraviolet, the position of the π–π^* transition band centred at 288 nm is consistent with, for example, hydroquinone dimethyl ether (λ_{max} 292, 288, 282, λ_{min} 250) rather than the 1,3-dimethoxy derivatives of benzene and toluene (λ_{max} 283, 279, 274, λ_{min} 244) or the 1,2-dimethoxy system in veratrole (λ_{max} 282, 277, 272, λ_{min} 245). A similar inference may be drawn from the position of the C–O stretching absorption in the infrared spectrum at 1212 cm^{-1} (cf. methoxamine 1220 cm^{-1}); *ortho* substitution would give absorption near 1250 cm^{-1} and *meta* substitution near 1150 cm^{-1}. Moreover the fact that the two methoxy groups give a single absorption in the infrared and the very close signals τ 6·32 and 6·34 in the nmr spectrum shows that their environments are very similar, leaving 2,5-dimethoxy-4-methylamphetamine as the only possible structure.

Psychotropic function

By courtesy of their Director, the Chemical Defence Experimental Establishment undertook rodent behavioural tests with the STP tablet and, subsequently, with the DOM salt. Hall's "Open Field" test with rats (Brimblecombe, 1964), and a "Head Twitch" count method (Corne & Pickering, 1967) for groups of 10 mice, were selected as convenient means of broadly distinguishing between amphetamine-like (analeptic) and mescaline-like (psychotomimetic) activity. In preliminary tests, residues of chloroformic and aqueous extracts of 10 mg STP tablet, and 10 mg of tablet dissolved in dimethyl sulphoxide, were compared with mescaline hydrochloride and (±)-amphetamine sulphate; the solutions were administered by subcutaneous injection.

It appeared that the chloroform extract and the original tablet both produced behavioural changes very similar to those evoked by mescaline and quite distinct from the amphetamine effect on motor activity; the aqueous extract was devoid of activity. From this limited single dose experiment one may only cautiously infer a broadly equipotent response between 10 mg of this tablet and 10 mg of pure mescaline hydrochloride. Similar tests were subsequently undertaken with the DOM salt and it was confirmed that 2,5-dimethoxy-4-methylamphetamine has a psychotomimetic activity qualitatively similar to mescaline and that a dosage of 0·2–0·4 mg/kg has a potency in mice comparable with 10 mg/kg mescaline, i.e. 25 to 50 times more potent.

Two independent studies of the effect of DOM on human volunteers in the U.S.A. were reported by Snyder, Faillace & Hollister (1967); of 16 adults of either sex, those receiving more than 5 mg drug suffered "marked" hallucination. Assuming the minimum adult human hallucinogenic doses of mescaline and lysergide to be 300 and 0·1 mg, it would appear that in man 2,5-dimethoxy-4-methylamphetamine is about 60 times more potent than mescaline but has only one fiftieth the activity of lysergide. It is also of interest to compare this result with Shulgin's (1964) value of 17 times the hallucinogenic potency of mescaline for 2,4,5-trimethoxyamphetamine.

Thus, on the basis of the clinical report of Snyder and his colleagues, and the limited rodent studies with DOM and the STP tablet undertaken by Brimblecombe for us, it appears that early press accounts of a psychotomimetic potency in excess of that of lysergide were unjustified. The clinical study also discounts reference to longer lasting (up to 72 h) effects and moreover no adverse reaction on concomitant administration of chlorpromazine was found. However, this—as was recognized—still leaves open the possibility that several drugs may have been circulating under the description STP. Alternatively the alleged effects may have been due to variable impurities in illicit preparations, or more potent homologues, or even compound dosage forms. With the single tablet available to us it was not possible to investigate further the material of mass 281 ($C_{15}H_{23}NO_4$) but its presence did not appear to enhance the potency relative to DOM. Nevertheless the presence of this substance may be of diagnostic value in comparing different illicit preparations of 2,5-dimethoxy-4-methylamphetamine; it was certainly absent in the mass spectrum of DOM.

Legal status

Possession of both mescaline and amphetamine (α-methylphenethylamine) is controlled by regulations made under the Drugs (Prevention of Misuse) Act, 1964 but the generic description in the Schedule to that Act, and in Schedule 4B to the 1967 Poisons Rules, cannot be held to subsume aromatic ring substituted derivatives of "β-aminopropylbenzene" (see discussion in Phillips, 1967). Thus it was held that 2,5-dimethoxy-4-methylamphetamine was not regulated in Great Britain in 1967; a similar situation prevailed in the U.S.A. until April 2, 1968. No steps have since been taken explicitly to control this substance under the 1964 Act but revision of the generic entries in the Poisons List and Poisons Rules made October 23, 1968 should ensure restriction of supply of a variety of aromatic ring substituted analogues of mescaline (phenethylamines) and amphetamine (α-methylphenethylamines).

Acknowledgements

This investigation was essentially a team effort. The assistance is gratefully acknowledged of Mr. R. W. Brimblecombe of the Chemical Defence Experimental

Establishment, of Dr. R. R. Dean and Mr. H. M. Paisley of the National Physical Laboratory, of Dr. W. H. Evans, Dr. B. Flaherty, Mr. K. Goodhead, Mr. E. E. Houghton and Mr. R. W. Martindale of the Research Division of this Laboratory, and of Mr. M. J. de F. Maunder and Mrs. Jane Gardiner of the Drugs sub-Division. We thank the U.S. Bureau of Drug Abuse Control for the sample of DOM (Dow Chemical Co.) and the Pharmaceutical Society for the sample of methoxamine hydrochloride (manufactured by Burroughs Wellcome and Co.).

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