4-BROMO-2,5-DIMETHOXYAMPHETAMINE: PSYCHOACTIVITY, TOXIC EFFECTS AND ANALYTICAL METHODS

D. DELLIU

Division of Analytical Laboratories of the Health Commission of New South Wales, P.O. Box 162, Lidcombe, N.S.W. 2141 (Australia)

(Received January 16, 1981)
(Revision received August 13, 1982)
(Accepted September 22, 1982)

Summary

4-bromo-2,5-dimethoxyamphetamine (bromo-DMA) is a drug of special interest in Australia as it is available in forms which are seldom seen elsewhere in the world. Data of interest to the Forensic Chemist is summarized. The psychoactivity of bromo-DMA is discussed and a number of case histories involving higher doses are related. A description of dosage forms has been included and variations in drug concentration is discussed. Chemical properties and various methods of quantitative and qualitative analysis, including the use of high performance liquid chromatography, mass spectrometry and infra-red spectroscopy are listed.

Key words: 4-Bromo-2,5-dimethoxyamphetamine; Bromo-DMA; Dosage forms; Analytical methods

Introduction

The street use of the illicit hallucinogen LSD in Australia has to a large extent been replaced by a relatively new psychedelic drug which is sold as LSD. This drug, 4-bromo-2,5-dimethoxyamphetamine (bromo-DMA), (Fig. 1a), may also be named 2,5-dimethoxy-4-bromophenylisopropylamine or 4-bromo-2,5-dimethoxy-α-methylphenethylamine. It is commonly known as DOB or PBR in the United States [1] and as bromo-DMA in Australia. The potency and effects of the drug are discussed and methods of quantitative and qualitative analysis are described.
Background

The most potent psychoactive drugs of the phenethylamine class have been shown to be the ring methoxylated phenylisopropylamines [2], the most active of which are the 2,5-dimethoxy-4-substituted ones [1,3,4].

Many workers have examined this activity in an attempt to explain it. Nichols [5] examined the literature on the relationship between structure and activity of the phenethylamine hallucinogens, and concluded that although empirical structure-activity relationships can be described, there is at present no clear rationale for many of them, and the mechanisms at the receptor level are unknown. The most active compounds possess para-substituents that are resistant to oxidative metabolism and increasing potency generally parallels increasing stability of the para group [5]. Benington et al. [6] found that bromine substitution at the para position increased activity when compared with alkyl substitution in either stereoisomer of 2,5-dimethoxymethamphetamine, but the psychomimetic potency of bromo-DMA is due mainly to the R(-)-isomer. Sargent et al. [7] studied the human pharmacodynamics by incorporating a $^{82}$Br- or $^{77}$Br-label. They showed that bromine was not biologically removed from the benzene ring and the radioactivity appeared to concentrate in normal human brain tissue.

Dosage forms

In all cases where sufficient sample has been received to permit examination by infra-red spectroscopy, the bromo-DMA was present as the hydrochloride salt. The drug is usually absorbed onto paper which is bonded to a thinner non-absorbent, patterned sheet. From 1978 until the end of 1981 the three forms pictured (Figs. 2a-c) were the most common seen in Australia. In 1982 there has been a rapid increase in the number of different designs [8], eight new forms have been seen within a few months. The first form seen in 1978 was the 'tile', with a black and white design, which divides the sheet into doses of approximately 1 cm square (Fig. 2a). The 'Golden Eagle' (Fig. 2b) bears a green outline of a bird on a yellow background. The 1 cm squares are often delineated by red lines. This form has also been seen as a blue bird on a white background. Many thousands of these doses or 'tickets' have been seen by this laboratory [9,10]. Figure 2c shows a complex design of similar 1 cm square dimensions. The design is purple on a pink background. These three forms appear to have been prepared in sheets of 400 squares by spraying with or dipping into a solution of the drug. Apparently, as the sheet dries the drug migrates towards the edges, resulting in a concentration gradient across the sheet. Chemical analysis carried out by this laboratory [10] has shown that the concentration gradient may result in the drug content of the edge doses being two to three times that of those in the centre. Thus, even doses from one source
Fig. 2. (a–c) Street dosage forms or 'tickets' of bromo-DMA. Each square design is 1 cm and each corresponds to one 'ticket' or dosage form.
may vary considerably in potency. The concentration of the drug in a square has been found to range between 1.4 mg and 4.6 mg.

These, and more recent similar dosage forms [8], have been seen in significant numbers only in Australia and New Zealand, which suggests that they may be locally made.

Dose and effects

The effects of bromo-DMA are similar to those of lysergide [5,11], although the onset is slower and the effects are longer lasting [1,4]. The first awareness of change is noted in about 1 h and according to Shulgin [1], full intoxication is rarely achieved until after 3 h or 4 h. During the plateau between the fourth and tenth hours there is rich fantasy but little visual distortion. The effects wear off gradually and may last a total of 24–36 h [1].

Bromo-DMA has been shown to cause an increase in systolic blood pressure and temperature, and cause dilation of the pupils in dogs [11]; similar effects are produced by amphetamine. In the same experiments, bromo-DMA also caused an increase in pulse rate and behavioural changes which resembled the effects of L.S.D. Early work with rats and mice involved doses of 1–10 mg/kg [6,12] with an average LD$_{50}$ in mice reported by Benington [6] as 146 ± 168 mg/kg (this being dependent on the isomer). Barfknecht and Nichols [3] have reported that tests on rats gave a mescaline-like effect much more profound than that caused by 2.5 mg/kg of the 4-methyl derivative (STP, Fig. 1b). Shulgin [1] has described bromo-DMA as the most potent phenethylamine psychedelic yet described, with a high potency (approx. 25 mg/kg) and an unusual therapeutic index (approx. 4000, LD$_{50}$ mice/ED$_{50}$ humans). In the same article Shulgin reports that an effective oral dose of the racemic base hydrochloride is 2–3 mg (equivalent to 1.76–2.65 mg calculated as the free base) or 1–2 mg of the ‘R’ isomer. Higher doses may lead to cardiovascular distress and convulsive complication [1] or to disorientation, leading to a panic state and to violent and aggressive behaviour. The following two cases of apparent higher doses were reported by medical practitioners in personal communications. No analyses were carried out but the histories, although incomplete, are of interest: Patient A had ingested four tickets with an unknown quantity of alcohol. The patient collapsed suffering grand mal seizure and a period of semi-consciousness, followed by aggressive, abusive and violent behaviour which required sedation. Patient B had ingested one ticket after consuming an unknown quantity of alcohol. Eight hours later when admitted to hospital, he was distressed, disoriented, very aggressive and uncooperative. After treatment with 10 mg i.v. diazepam the patient became calmer but remained disoriented for several hours longer.

It would appear from a number of reports similar to the above that alcohol may potentiate the effects of the drug. A death from an overdose
has been reported after ingestion of 30--35 mg [13]. A 75-mg dose in a person with a tolerance led to ergotism like complications requiring amputation of the lower legs [3]. A number of anecdotal reports from police and medical practitioners suggest that unpleasant reactions are not uncommon.

Synthetic routes

A clandestine laboratory raided in Victoria in 1980 was synthesizing bromo-DMA from 2,5-dimethoxybenzaldehyde by the following route:

\[
\text{2,5-dimethoxybenzaldehyde} \xrightarrow{\text{C}_2\text{H}_5\text{NO}_2} \text{2,5-dimethoxy-\beta-nitrostyrene}
\]

\[
\text{LiAlH}_4 \xrightarrow{\text{Br}_2} \text{2,5-dimethoxyamphetamine} \xrightarrow{\text{Br}_2} \text{4-bromo-2,5-dimethoxyamphetamine}
\]

A clandestine laboratory detected in Britain in 1981, was producing bromo-DMA by an eight-step method from hydroquinone. A notebook found in the laboratory listed numerous alternative reactions. The phenethylamine analogue was identified amongst the impurities (Fig. 1c).

Properties

Bromo-DMA hydrochloride is a white crystalline powder which is soluble in chloroform, ethanol and methanol, but insoluble in ether. The melting point of the hydrochloride is reported to be between 197°C and 199°C [2,3,14]. It may be recrystallized from ether-ethanol [12] or from isopropanol [1]. Unlike lysergide it is not light or heat sensitive and therefore does not require a foil wrapping or refrigeration.

Analytical methods

Extraction

Under the New South Wales Poisons Act, it is necessary to quantitate bromo-DMA for indictable charges. The following analytical methods have been developed by this laboratory: Bromo-DMA is extracted from the paper using methanol. It has been found that the drug may take up to 5 h to extract completely from the paper, and, for quantitative purposes, the tickets are left overnight in methanol, or alternatively treated with methanol in a sonic bath for about 20 min. When a large number of tickets
(e.g., a whole sheet) is to be extracted, a soxhlet apparatus is used.

**Screening test**

Marquis Reagent (2 drops of formaldehyde solution 40% w/v in 1 ml concentrated sulphuric acid) with bromo-DMA turns deep yellow, then slowly to yellow-green, then very slowly to blue-green [14]. The phenethylamine analogue: 4-bromo-2,5-dimethoxy-phenethylamine (Fig. 3) by contrast reacts to give an orange colour which slowly turns to brown [15].

**Thin layer chromatography**

Thin layer chromatography is used only for screening purposes by this Laboratory. Ammoniacal methanol, the Tl system of Clark [16] is used. The \( R_F \) value of this system is 0.30. As no other isomers were available, this TLC system may not provide unequivocal identification of bromo-DMA. Bromo-DMA is a primary amine and when sprayed with fluorescamine, reacts to give a bright fluorescent spot under long wave-length ultraviolet light. The spot is then further visualized with an acidified iodoplatinate reagent to give a brown spot. Bailey *et al.* [17] list \( R_F \)s of a number of close analogues on two different TLC systems and report that it was difficult to distinguish between them.

**Gas chromatography**

This laboratory makes use of 3% OV 17 and 3% OV 101 columns (both 5 feet long) with flame ionization detectors. The Kovats Index on the OV 101 is 1787 and on the OV 17, 2170 (0.66 relative to caffeine). Bailey *et al.* [17] report retention times of close analogues on four different columns: 3% OV 17, 2.5% OV 225, 5% OV 7 and 3% SE 30. On all columns 2-bromo-4,5-DMA was the isomer which had the closest retention time to 4-bromo-2,5-DMA. The two isomers were separated most successfully by reducing the oven temperature on the OV 17 column from 200°C to 175°C. At this temperature 4-bromo-DMA eluted in 17.4 min and 2-bromo-DMA in 13.5 min.

**High performance liquid chromatography**

Bromo-DMA is determined quantitatively in this laboratory by high performance liquid chromatography. A 30 cm column of 10 \( \mu \)m Porasil (Waters) is used and the following solvent systems give sharp symmetrical peaks.

(i) Methanol/2 N ammonia/0.1 N ammonium nitrate in the ratio 27:2:1 at a flow rate of 1.5 ml/min. Bromo-DMA elutes in 5.4 min.
(ii) Methanol/water/ethanolamine in the ratio 700:300:2 at a flow rate of 1.5 ml/min. Bromo-DMA elutes in 8.5 min.

The optimum detection wavelength is 293 nm.

**Ultra-violet spectroscopy**

Bromo-DMA in 0.1 N sulphuric acid gave a maximum at 293 nm in agreement with published data [14,17]. The molar extinction coefficient \( \epsilon \) is reported as 5412 [18]. Bailey *et al.* [17] showed that 4-bromo-DMA may be distinguished from its isomeric bromo-dimethoxy-amphetamines by ultra-violet spectroscopy. 4-bromo-2,5-DMA has its maximum at the longest wavelength and has the highest molar extinction coefficient of all these isomers.

**Infra-red spectroscopy**

4-bromo-2,5-dimethoxyamphetamine hydrochloride gives a distinctive infra-red spectrum which allows identification and differentiation from the other isomers [14,17].

The region 700–900 cm\(^{-1}\) is the most useful region for distinguishing this compound from its isomeric bromo-dimethoxyamphetamines. There are sharp peaks at 710, 740, 795, 835, 860 and 900 cm\(^{-1}\).

**Proton magnetic resonance spectroscopy**

The splitting pattern of the PMR spectrum of bromo-DMA in deuterated chloroform enabled the 2,4,5-ring substitution pattern to be verified and distinguished the aliphatic protons in the isopropylamine side-chain. Bailey *et al.* [17] warn that care must be exercised in the differentiation of 4-bromo-2,5-DMA from 5-bromo-2,4-DMA and 2-bromo-4,5-DMA, as their respective PMR spectra differ only by very small amounts in their chemical shifts.

**Mass spectrometry**

Mass spectrometry allows the presence of bromine to be readily confirmed [14] due to the bromine doublet and a molecular ion is also obtained. Mass spectrometry alone does not allow identification of the substitution pattern. Bailey *et al.* [17] have shown that the mass spectra of the isomeric bromo-dimethoxyamphetamines vary significantly only in the intensity of the molecular ion relative to the base peak.

**Conclusion**

Although thin layer chromatography and gas chromatography are ex-
cellent as screening tests for bromo-DMA and mass spectrometry is useful for identifying the presence of bromine and giving a molecular weight, these techniques will not distinguish bromo-DMA from its isomeric bromo-dimethoxyamphetamines or from close analogues. Ultra-violet spectroscopy is a useful technique to distinguish between bromo-DMA analogues but infra-red spectroscopy gives the most conclusive differentiation between bromo-DMA and other closely related compounds.

Acknowledgements

I would like to extend my thanks and appreciation to a number of people for their assistance in the preparation of this article: Dr. G. Chesher, Pharmacology Department, the University of Sydney, Mr. G. Cook and Dr. A. Archer both of the Division of Analytical Laboratories of the Health Commission of New South Wales, Dr. A.T. Shulgin, Lafayette, U.S.A. and Dr. J. Metcalf, The Metropolitan Police Laboratory, U.K. My thanks also to the New South Wales Institute of Technology, Sydney, Australia, for running the PMR spectrum of bromo-DMA.

References

14 Microgram V, (11), 125-127.
15 Microgram Xii (1) (1979) 4.