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# 4-Bromo-2,5-Dimethoxyphenylisopropylamine, a New Centrally Active Amphetamine Analog

A. T. SHULGIN, T. SARGENT and C. NARANJO

*Abstract.* A new centrally active halo-amine, 4-bromo-2,5-dimethoxyphenylisopropylamine, is described. In clinical evaluation it proved to enhance effectively both emotional and intellectual perception, without the imagery and perceptual distortions commonly encountered with many of the chemically related psychotomimetics. These properties suggest a potential valuable role in conjunction with psychotherapy.

*Key Words*
Psychotomimetic
Amphetamine
Hallucinogenic
Toxic Psychosis
Psychodysleptic

There has recently been wide documentation of the psychotomimetic or hallucinogenic activity of analogs of the amphetamine molecule. These ring-substituted phenylisopropylamines vary in psychotropic potency depending not only upon the total density and location of the substituents, but upon their specific nature as well.

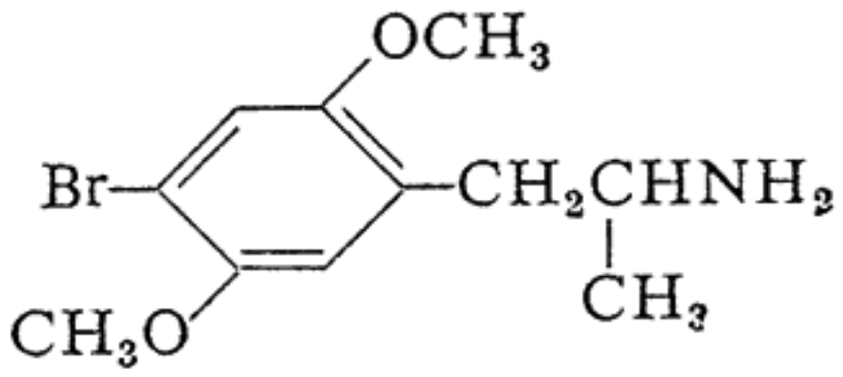
An increase in the number of alkoxy substituents leads to an increase in potency with an apparent maximum at trisubstitution [11]. Although SMYTHIES *et al.* [12] have reported that P-methoxyphenylisopropylamine exhibits 'LSD-like' potency in rats, clinical experiments have shown it to be no more potent than either of the dimethoxylated (2,4- or 2,5-) or the tetramethoxylated analogs; all of these are distinctly less active than several of the trimethoxy counterparts [9, 11].

A number of compounds have been described that differ from one another only in the identity of the substituent in the *para* (4-) position, while retaining the 2,5-dimethoxy substitution pattern. 2,4,5-Trimethoxyphenylisopropylamine (TMA-2), with a methoxyl group in the 4-position, is the most potent of the trimethoxyphenylisopropylamines [11]; the 4-ethoxy

homolog is fully active [10], while a hydrogen at this position halves the potency. On the other hand, *para*-substitution with alkyl groups leads to compounds theoretically more resistant to metabolic degradation. These chemical modifications have led to dramatic increases in potency as shown in human clinical studies of the 4-methyl and the 4-ethyl analogs of TMA-2 (DOM [STP] and DOET, resp.; [13, 14]). The metabolic lability of the methoxy group in the 4-position is experimentally supported by the observed demethylation of 4-$^{14}$C-methoxy labelled 3,4-dimethoxyphenethylamine (DMPEA) in rats [8], a property not shared by the 3-methoxy group in this molecule. These and other reports [1, 4, 15] all focus attention upon the singular importance of the *para*-position.

As a ring substituent, a bromine atom is theoretically even more resistant than an alkyl group to metabolic attack. Its inclusion in N-methylamphetamine has led to compounds that are, in animal studies, more potent than mescaline [5, 6], and a large number of bromo-methoxy analogs of amphetamine have recently been prepared by CASSELS [2]. To further test the concept of metabolic stability at the 4-position, we have studied the compound in which the 4-methoxy group of TMA-2 (the methyl and ethyl groups of DOM and DOET) is replaced by a bromine atom.

## *Methods of Preparation*



The compound, 4-bromo-2,5-dimethoxyphenylisopropylamine, was prepared by the elemental bromination of 2,5-dimethoxyphenyl-isopropylamine in a manner similar to that reported by HARLEY-MASON [3] for 3,4-dimethoxyphenethylamine. The hydrochloride was readily recrystallized from isopropanol (m.p. 207–208). NMR analysis confirmed unique bromination in the *para*-position; ArH (in $D_2O$, as the hydrochloride) appeared at 6.97 and 7.20 ppm downfield from TMS (external standard) without splitting and with correct integration. The remaining proton spectrum was essentially unchanged from that of the starting dimethoxy-compound (Varian; A-60).

## *Methods of Examination*

Animal toxicology studies were performed with LAF female mice, and indicated an $LD_{50}$ of 100 mg/kg with intraperitoneal administration of the hydrochloride salt in isotonic aqueous solution. This, together with the establishment of a human thresh-

old of 0.004 mg/kg (by methods previously described [11]) suggested an eventual therapeutic index ($LD_{50}$ mice/$ED_{human}$) of over 10,000. It was decided that clinical trials were justified, and these were conducted at the University of Chile.

The clinical trials were conducted in a psychotherapeutic setting, using subjects interested in their own personality development, but who did not have incapacitating psychiatric problems. The compound was administered orally as the hydrochloride in dosages between 0.2 mg and 2 mg, acutely. The time from the administration to the subjects' noting of the first effects was recorded (latency) and also the duration of these effects. The latter were arranged in four groupings: (1) intellectual stimulation; increased thought processes of an intellectual, as compared to an emotional, nature; (2) emotional stimulation; an increased concern with, and enhancement of, affectual and personal relationships; (3) perceptual enhancement; an increase intensity or awareness of color and form, auditory, or tactile perception, and (4) perceptual distortion; wavering of line, alteration of perspective, distortion of objects in the visual field, synaesthesia, eyes-closed imagery, or hallucinations. These parameters, based on both the psychiatrists' observations and the subjects own reports, were scored on the basis of O: not present, +: present, and ++: strongly present.

## *Results*

The results obtained with 4-bromo-2,5-dimethoxyphenylisopropylamine are tabulated in table I. It can be seen that the duration of effect appears to reach a plateau as the dose is increased (table I is arranged in order of increased dosages) with, to a lesser degree, a decrease in latency period. It is apparent from table I that there is an increase of both intellectual and emotional stimulation with dosages up to 2 mg, whereas perceptual enhancement seemed not to be dose dependant. Perceptual distortion did not occur at any dose level.

In general the effects of 4-bromo-2,5-dimethoxyphenylisopropylamine were the enhancement of intellectual and emotional thinking together with an increase in the level of fluency and attention while maintaining full communication capabilities. This compound is therefore similar to 3,4-methylenedioxyamphetamine (MDA) [7] except that here the subjects were more active and had greater contact with the environment. The sense of added significance in ordinary events and motivation toward introspection were similar to that of the hallucinogens such as mescaline, but with a complete lack of imagery or perceptual distortion. This compound on the basis of these preliminary trials would appear to be potentially as useful an adjunct to psychotherapy as MDA [7].

The relationship between biogenic amines and psychosis is still poorly understood, and it was with the intention of possibly clarifying the problem

*Table I*

| Dose, mg | Subject | Latency, h | Duration, h | Intellectual stimulation | Emotional stimulation | Perceptual enhancement | Perceptual distortion |
|---|---|---|---|---|---|---|---|
| 0.2 | A | 1 | 1 | + | 0 | + | 0 |
| 0.2 | B | 1.5 | 3 | 0 | 0 | + | 0 |
| 0.2 | C | – | 0 | 0 | 0 | 0 | 0 |
| 0.2 | D | – | 0 | 0 | 0 | 0 | 0 |
| 0.3 | D | 4 | 6 | + | + | 0 | 0 (1) |
| 0.3 | E | 3 | 6 | 0 | + | + | 0 (2) |
| 0.3 | F | 1.5 | 6 | + | + | 0 | 0 |
| 0.4 | C | (12) | (1) | 0 | + | 0 | 0 (3) |
| 0.4 | G | 2 | 4 | 0 | + | + | 0 |
| 0.8 | D | 2.5 | 10 | + | ++ | + | 0 (1) (4) |
| 1.0 | H | 1 | 24 | ++ | 0 | 0 | 0 |
| 1.0 | I | 1 | 11 | + | ++ | + | 0 |
| 2.0 | J | 1 | 15 | + | ++ | + | 0 (1) |
| 2.0 | K | 1 | 12 | ++ | ++ | 0 | 0 (1) |
| 2.0 | L | 1 | 17 | ++ | ++ | + | 0 (1) |
| 2.0 | M | 1 | 24 | + | ++ | 0 | 0 (1) |

(1) A period of insomnia followed the experiment, but was not included in the duration value.
(2) Only auditory sensory enhancement was noted.
(3) The subject slept throughout the 12-hour latency period.
(4) Only tactile sensory enhancement was noted.

that this compound was made. The high activity of the compound reported here, with a 4-position substituent resistant to metabolic attack, lends support to the concept of a defect of metabolism at the 4-position of the catecholamines being associated with psychotic disorders. A number of analogs of this 4-substituted-2,5-dimethoxyphenylisopropylamine system (4-Cl, 4-F, and 4-$SCH_3$) are being studied, and chemical and pharmacological details will be reported shortly.

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