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Ring-substituted β-methoxyphenethylamines: a new class of psychotomimetic agents active in man

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Four members of a new class of psychotomimetic agents have been synthesized and evaluated in man. These compounds, which incorporate a β-methoxy group onto a β-phenethylamine sidechain, are the first reported psychotomimetics which are structural analogues of the neurotransmitter noradrenaline. These substances are more potent than the corresponding phenethylamines (lacking a β-methoxy group) but less potent than the correspondingly substituted amphetamine derivatives.

Psychotomimetic drugs are of continuing interest as tools for the study of sensory and mental processes. As their action is eventually expressed within the human central nervous system (CNS), there has been much effort to relate them, functionally or structurally, to neurotransmitters (Shulgin 1981; Nichols 1984). The many psychotomimetic indoles are recognizable analogues of 5-hydroxytryptamine. The acetylcholine family includes Ditran, quinuclidinyl benzilate, and related parasympatholytic agents. The largest group, the phenethylamines and their α-methyl homologues, resemble dopamine. There have been no previous reports of any psychotomimetic drugs related to noradrenaline (norepinephrine).

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We have discovered a new class of psychotomimetic drugs (2), the members of which possess a methoxy group in the β-position of the phenethylamine sidechain. In the examples reported here, these β-oxygenated derivatives have a greater CNS potency than their phenethylamine counterparts.

Materials and methods

All new compounds reported here had microanalyses (C,H) that were within 0·4% of the calculated values, and had spectra (infrared, NMR) consistent with the assigned structures. Melting points are uncorrected.

2-Methoxy-2-(2,5-dimethoxy-4-methylphenyl)-ethylamine (2c). A suspension of 2,5-dimethoxy-4-methyl-β-nitrostyrene (Ho et al 1970) (39 g) in warm methanol (300 ml) was treated with a solution of sodium methoxide (9 g sodium in 150 ml methanol). After a few minutes (when the solution was complete and nearly colourless) acetic acid (75 ml) was added followed by water (2000 ml) and the reaction mixture was extracted with methylene chloride (3 × 200 ml). The extracts were pooled, and the solvent removed under vaccum to yield an oil which was diluted with a small amount of

methanol and held for 4 h at 0 °C. The yellow crystals that formed were removed by filtration, and recrystallized from methanol to yield 11·1 g of 2-methoxy-2-(2,5-dimethoxy-4-methylphenyl)-1-nitroethane, m.p. 78–79 °C. This intermediate (in anhydrous tetrahydrofuran) was added to an ice-cold solution of aluminium hydride (prepared from 96 ml of 1 M lithium aluminium hydride in tetrahydrofuran and 2·4 ml 100% sulphuric acid) and brought to reflux for 2 h. The excess hydride was destroyed with isopropanol, and 15% aqueous sodium hydroxide was added until all solids were white and filterable. The filtrate was evaporated to a residual amber oil which was dissolved in methylene chloride and extracted with dilute sulphuric acid. These aqueous extracts were pooled, made basic with 25% sodium hydroxide, and re-extracted with methylene chloride. After removal of the solvent under vacuum, the residue was distilled (0·4 mmHg, 115–128 °C) yielding 5·3 g of a colourless oil. This, in isopropanol (15 ml) was neutralized with conc. HCl and treated with 70 ml diethyl ether to allow the spontaneous crystallization of 2c as the hydrochloride salt, m.p. 171–172 °C.

2-Methoxy-2-(3,4,5-trimethoxyphenyl)-ethylamine (2a) was prepared in a similar manner from 2-methoxy-2-(3,4,5-trimethoxyphenyl)-1-nitroethane (m.p. 143–144 °C) and isolated as the hydrochloride salt, m.p. 198·5–199·5.

2-Methoxy-2-(3,4-methylenedioxyphenyl)-ethylamine (2b) was prepared in a similar manner from 2-methoxy-2-(3,4-methylenedioxyphenyl)-1-nitroethane (m.p. 58–59 °C) and isolated as the hydrochloride salt, m.p. 152–153 °C.

2-Methoxy-2-(4-bromo-2,5-dimethoxyphenyl)-ethylamine (2d) 4-Bromo-2,5-dimethoxy-β-nitrostyrene was prepared from 4-bromo-2,5-dimethoxybenzaldehyde (Barfknecht & Nichols 1971) with ammonium acetate in nitromethane (yellow crystals, m.p. 157–158 °C). This nitrostyrene was converted to 2-methoxy-2-(4-bromo-2,5-dimethoxyphenyl)-1-nitroethane (m.p. 119–120 °C) and reduced to the amine as described for 2c above. 2d·HCl, m.p. 187–188 °C.

Pharmacological evaluation. Compounds 2a–d were evaluated in normal human subjects (for 2c, n = 11, 7 male, 4 female, age range 34–69 years, with 21 trials (T = 21); for the remaining three compounds there were 2 subjects only, with the number of trials and effective dosage range being 2a: 8, 180 mg, 2b: 8, 100–130 mg, and 2d: 5, 10–15 mg) using the double conscious technique (Alles 1959; Shulgin et al 1969). The preliminary screening procedure has been published elsewhere (Jacob & Shulgin 1983), and was conducted on subjects familiar with the effects of psychotropic agents. The experimental protocol employed in this study has been approved by an appropriate human research committee made up of board-certified psychiatrists, and included the statements of informed consent from all subjects.

Briefly, threshold levels were obtained by incremental increases of a given chemical, starting at 0·5 mg taken orally as the hydrochloride salt in water. With a tentative assignment of active levels, the trials were broadened to include adult volunteers who were experienced with a broad range of psychotropic substances. The setting for the studies was informal, and the subjects were allowed to interact with one another or to remain alone, as they desired. At the conclusion of each session, written reports detailing the qualitative nature of the experience were requested.

The potencies given in Table 1 are expressed in mescaline units (Shulgin et al 1969) which are obtained by dividing the effective dose of mescaline (taken as 400 mg of the sulphate salt) by the mean effective dosage for each compound in the present study.

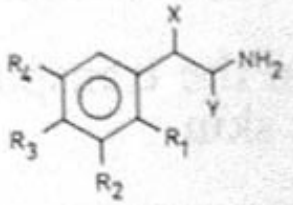
Results and discussion

Table 1 lists the psychotomimetic potencies of the four β-methoxy phenethylamines in this study, with direct comparisons with the known 2-carbon and 3-carbon analogues which lack the β-methoxy group.

One compound, 2c (the two-carbon chain methoxy analogue of DOM, 3c) was carried to full clinical trials. This material, when administered to normal human subjects at dosages of between 15 and 25 mg orally, produced a thoroughly effective alteration of the sensory processes. The chronology of intoxication followed a generally consistent pattern: following an onset at about one half hour after ingestion there was a steady development of responses until the second or third hour (with some body awareness or slight nausea in several subjects); a plateau level was maintained for an additional 6–8 h, and the return to pre-experiment baseline resulted after an additional 4 h or so. The physical aspects of this intoxication included the early body discomfort mentioned above, a generalized anorexia during and following the active period of intoxication, modest sleep disturbance, and with most subjects, a lethargy on the following day. The central effects were largely a consistent enhancement of the visual sense (light and dark contrasts, colour brightening, unexpected shape and pattern interpretation) and an affective disinhibition. There was open humour and easy group conversation.

The remaining three compounds were explored less extensively. Trials with 2a were discontinued at 180 mg, a level at which there was distinct central awareness, but no definable character of action. With 2b, the physical-to-mental distribution of effects was less desirable than with 2c, but the duration of action was much shorter, about one half that of 2c. The DOB analogue 2d showed the highest potency, and had chronology and a sensory enhancement (in the early part of the experiment)

Table 1. The comparative potencies* in man of analogues of noradrenaline.



	R_1	R_2	R_3	R_4	Phenethylamine analogues (1)* X=Y=H	Noradrenaline analogues (2) X=OCH_3 Y=H	Amphetamine analogues (3)† X=H Y=CH_3
(a)	H	OCH_3	OCH_3	OCH_3	'1'	<2‡	2
(b)	H	O–CH_2–O		H	<1	3	3
(c)	OCH_3	H	CH_3	OCH_3	10	20	80
(d)	OCH_3	H	Br	OCH_3	20	30	400

* In mescaline units, comparing potency to that of mescaline. The larger the number, the higher the potency. See experimental.

† Values from the literature (Shulgin 1981).

‡ The '<' sign indicates that no psychotropic activity could be established in man, and if active, the compound would be less potent than implied by the given number.

identical to that described above for 2c. However, between the sixth and eighth hour, there was the development of tinnitus and a neurological hyperreflexia that discouraged further exploration.

The presence of an insubstituted hydroxy group on the β-carbon of a phenethylamine or amphetamine skeleton has usually been associated with peripheral nervous system activity, as in norephedrine, ephedrine, noradrenaline and adrenaline. Presumably, the polar β-hydroxy group inhibits entry to the CNS. One might expect that masking this polar grouping as the *O*-methyl ether might allow entry into the CNS with some consequent expression of central activity. Indeed, the β-*O*-methyl ether of adrenaline (adrenaline methyl ether, AME) has been reported by Page & Hoffer (1964) to produce marked stimulation with depressed patients. Phenmetrazine is another example of a central stimulant in which a β-oxygen is incorporated into an ether linkage. The compounds described in this report are further examples of CNS-active agents with a 'masked' β-hydroxy group, but are the first psychotomimetics with this function. Ease of CNS access may be further enhanced by the replacement of the catechol hydroxyl function with less polar groups (methoxyl, bromo, alkyl) on the aromatic ring.

It is an appealing hypothesis that these compounds are allowed access to the CNS by this blocking of polar functions, and, once there, might be revealed metabolically as close analogues of noradrenaline. We also find it intriguing to speculate that the phenethylamine psychotomimetics (such as 1) might be metabolically activated to noradrenaline analogues by the action of dopamine β-hydroxylase within the CNS. The enzyme dopamine-β-hydroxylase is known to accept a wide range of phenethylamine substrates (Creveling et al 1962).

If some interaction with the noradrenergic receptor is involved in the mechanism of action, significant differences might be expected in the activity of the *R* and *S* enantiomers of these compounds, as naturally occurring adrenaline has the *R*-configuration.

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