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Potential Psychotomimetics. Bromomethoxyamphetamines

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In the study of psychotomimetic amphetamines, 2,5-dimethoxy-4-methylamphetamine (DOM) is the most potent compound yet discovered (50–150 times mescaline).[2] At least part of its potency is related to the nature of the para substituent. In light of Knoll's[3] studies on the psychotomimetic effects of *p*-bromomethamphetamine and its cross-tolerance to LSD, the synthesis and evaluation of bromomethoxyamphetamines appeared to be a logical extension. Br has a comparable size, but different electronic character than Me. Kang and Green[4] have recently demonstrated a correlation between the electronic character of the ring and hallucinogenic potency of methoxylated amphetamines. The substitution of Br into various ring positions of methoxylated amphetamines allows for several electronic arrangements.

Chemistry.—The general synthetic route involved preparation of the appropriately substituted benzaldehydes, condensation with $EtNO_2$, and reduction to the bromomethoxyamphetamines. Tables I and II summarize the compounds which have been prepared.

Attention is called to the report by Pandya and coworkers[5] concerning the bromination of *m*-hydroxybenzaldehyde. The product of this reaction is claimed to be 3-hydroxy-4-bromobenzaldehyde; however, the

(1)

(2) A. T. Shulgin, T. Sargent, and C. Naranjo, *Nature (London)*, **221**, 537 (1969).

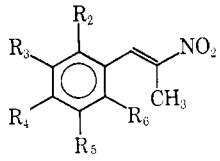
(3) J. Knoll in "Amphetamines and Related Compounds," E. Costa and S. Garattini, Ed., Raven Press, New York, N. Y., 1970, p 761.

(4) S. Kang and J. P. Green, *Nature (London)*, **226**, 645 (1970).

(5) K. C. Pandya, R. B. K. Pandya, and R. N. Singh, *J. Indian Chem. Soc.*, **29**, 363 (1952).

TABLE I

SUBSTITUTED 1-PHENYL-2-NITROPROPENES



R_2	R_3	R_4	R_5	R_6	Mp, °C	Yield, %
Br	H	H	OCH_3	H	73–74.5	61.8
H	Br	OCH_3	H	H	73–74	45
H	OCH_3	Br	H	H	73–74.5	36.8
Br	H	OCH_3	OCH_3	H	105–106	59.4
H	OCH_3	Br	OCH_3	H	121–121.5	46.8
OCH_3	H	Br	OCH_3	H	113.5–115	57

A correlation has been demonstrated between the degree of fluorescence and the psychotomimetic potency for methoxylated amphetamines; no such relationship seems to exist for this series.[10] For example, **2** and **6** have nearly the same degree of fluorescence, but differ widely in their biological effects. A detailed study of the pharmacology is in progress.

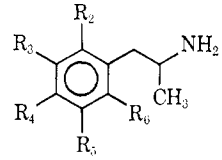
Experimental Section[11]

Bromomethoxybenzaldehydes.—All substituted benzaldehydes have been reported previously with the exception of 2,5-dimethoxy-4-bromobenzaldehyde and 3,5-dimethoxy-4-bromobenzaldehyde, whose syntheses are described below.

3,5-Dimethoxy-4-bromobenzaldehyde.—3,5-Dihydroxy-4-bromobenzoic acid (K & K Laboratories, Inc.) was di-O-methylated with Me_2SO_4 in the usual manner: yield 78% (EtOH-H_2O); mp 248–250° (lit.[12] 249–50°). The acid chloride was obtained by reaction with $SOCl_2$. The crude product (mp 124–128°) was used in the next step without further purification. The aldehyde was obtained by reduction of the acid chloride by $LiAlH(O\text{-}tert\text{-}Bu)_3$ as described by Ho, *et al.*[13] The crude aldehyde was recrystd from MeOH-H_2O; yield 52%; mp 112–114°.

TABLE II

BROMOMETHOXYAMPHETAMINE HYDROCHLORIDES



Compd	R_2	R_3	R_4	R_5	R_6	Mp, °C	Yield, %
1	Br	H	H	OCH_3	H	151.5–153	20
2	H	Br	OCH_3	H	H	210–213	28.8
3	H	OCH_3	Br	H	H	161.5–163	32
4	Br	H	OCH_3	OCH_3	H	214–215.5	42
5	H	OCH_3	Br	OCH_3	H	221–222	36.8
6	OCH_3	H	Br	OCH_3	H	198–199	29.5

product which we isolated proved to be 2-bromo-5-hydroxybenzaldehyde. This assignment was verified by nmr spectroscopy and chemical conversion by O-methylation and permanganate oxidation to 2-bromo-5-methoxybenzoic acid. The physical properties of this material agreed with the literature values.[6]

The LAH reduction of 1-(bromomethoxyphenyl)-2-nitropropenes was complicated by the extreme ease of debromination. Low temperatures and equimolar amounts of reagents prevented debromination, but resulted in poor yields of the bromomethoxyamphetamines.

Biological Results.—The compounds were tested for an effect on a conditioned avoidance response in male rats. The detailed procedure has been reported previously.[7] The effects were compared with those produced by mescaline, 3,4-dimethoxyamphetamine, DOM, and the CNS-stimulant dextroamphetamine. This assay gives an indication whether a compound possesses stimulant action or one more like that of mescaline, 3,4-DMA, and DOM. Table III summarizes the biological data. All compounds which exhibited an effect similar to mescaline-type compounds have the *p*-Br substituent.[8] The data on the 2-bromo-5-methoxy analog (**3**) must be considered tentative, since 2,5-dimethoxyamphetamine which does not have a para substituent is active in humans but inactive in rats.[9]

TABLE III

BIOLOGICAL RESULTS

Compd	Threshold[a] dose, mg/kg	Action
1	25	Inactive
2	9	CNS stimulation; onset of amphetamine-type toxicity at 18 mg/kg
3	7.5	Mescaline-like
4	25	Inactive
5	<10	Mescaline-like with some deaths at 10; inactive at 5 mg/kg
6	<2.5	Mescaline-like; effect much more profound than that caused by 2.5 mg/kg of DOM

[a] Dose at which action was observed; any compd which does not show a mescaline-like effect at 25 mg/kg (the "effective" dose of mescaline) is considered inactive. The threshold dose of 3,4-dimethoxyamphetamine·HCl and DOM·HCl are 12.5 and 2.5, resp.

(6) P. H. Beyer, *Recl. Trav. Chim. Pays-Bas*, **40**, 621 (1921).

(7) C. F. Barfknecht, J. M. Miles, and J. L. Leseney, *J. Pharm. Sci.*, **59**, 1842 (1970).

(8) During the revision of this manuscript, Dr. A. T. Shulgin informed us that 4-bromo-2,5-dimethoxyamphetamine has a potency in humans greater than DOM and an effect similar to 3,4-methylenedioxyamphetamine; *Pharmacology*, in press.

(9) J. R. Smythies, *Neurosci. Res. Program Bull.*, **8**, 79 (1970).

(10) F. Antun, J. R. Smythies, F. Benington, R. D. Morin, C. F. Barfknecht, and D. E. Nichols, *Experientia*, in press.

(11) Melting points were taken on a Hoover Uni-Melt apparatus and are corrected. Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra for all compounds were obtained on a Varian Associates T-60 and are consistent with the assigned structures.

(12) H. Erdtman and B. Leopold, *Acta Chem. Scand.*, **2**, 34 (1948).

(13) B. T. Ho, W. M. McIssac, R. An, L. W. Tansey, K. E. Walker, L. F. Englert, Jr., and M. B. Noel, *J. Med. Chem.*, **13**, 26 (1970).

2,5-Dimethoxy-4-bromobenzaldehyde.—2,5-Dimethoxybenzaldehyde (66.5 g, 0.4 mole) was dissolved in 300 ml of CH_2Cl_2. Anhyd $SnCl_4$ (115 g, 0.44 mole) was added, followed by 64 g of Br_2 over a 1-hr period. The resulting soln was refluxed for 2 hr and stirred overnight at room temp. The orange suspension was poured over 500 g of ice, and the layers were sepd. The CH_2Cl_2 layer was washed with 10% $NaHCO_3$ and H_2O and dried (Na_2SO_4). After filtration the solvent was removed *in vacuo*, and the solid residue recrystd from MeOH–H_2O to yield 64 g (66%) of the aldehyde, mp 132–3°.

The structure was confirmed by oxidation with MnO_4^- to 2,5-dimethoxy-4-brombenzoic acid, mp 170° (lit.[14] mp 170°).

Substituted-1-phenyl-2-nitropropenes.—The substituted benzaldehydes were refluxed with $EtNO_2$ and NH_4OAc in AcOH as described by Gairaud and Lappin.[15]

Bromomethoxyamphetamine Hydrochlorides.—All amphetamines were prepared from the corresponding 1-phenyl-2-nitropropenes by LAH reduction.[16]

(14) A. Luttringhaus and H. Gralheer, *Justus Liebigs Ann. Chem.*, **550**, 67 (1941).

(15) C. B. Gairaud and G. R. Lappin, *J. Org. Chem.*, **18**, 1 (1953).

(16) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 581.