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THE PREPARATION OF POTENTIALLY PSYCHOACTIVE β-ALKOXYPHENETHYLAMINES

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Abstract The preparation of β-alkoxyphenethylamines 3 is described.

As part of our interest in structure-activity relationships of psychotomimetic phenethylamines [1] and their interactions with serotoninergic receptors [2], we describe in the present communication the preparation of a series of substituted β-alkoxyphenylethylamines.

A few of these compounds had been prepared before [3,4] and their psychotropic properties described with human volunteers. However, no pharmacological studies on these new compounds have been carried out since then, aside from the few instances in which a β-methoxylated derivative has shown a potency similar to or slightly greater than that of the parent compound.

Little is known about the effects of substitution at the β-position of the side chain of hallucinogenic phenethylamines, although it was speculated that their activity might be mediated in part by interactions with adrenergic receptors.

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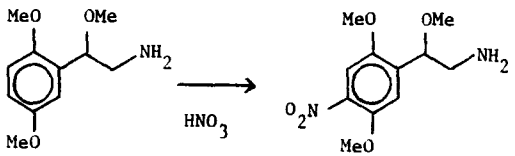
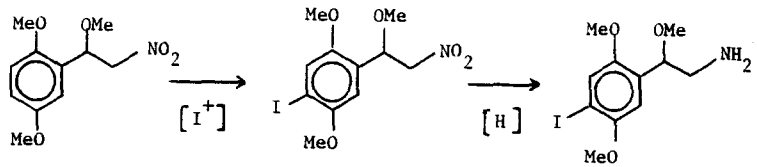
The nitro derivative **3j** was obtained from the phenethylamine **3a**, by nitration of the aromatic ring.



3a **3j**

Iodination of the intermediate **2a** gave the iodo derivative **2k**, which was reduced to form the phenethylamine **3k**.



2a **2k** **3k**

The use of anhydrous benzene as solvent for the nucleophilic addition **1** ⟶ **2** proved to be more convenient than the method previously described, which utilized the alcohol ROH as solvent [3,4], giving nitroethanes **2** in higher yields.

We generally performed the reduction step with AlH_3, generated *in situ* by partial neutralization of $LiAlH_4$ with concentrated sulfuric acid [8]. However, in the case of the 2,4,5-trimethoxyphenyl intermediate **2g**, this procedure led to hydrogenolysis of the β-methoxy substituent. Compound **3g**, as its hydrochloride, could be obtained in 43% yield by reduction of **2g** with lithium aluminum hydride in refluxing THF.

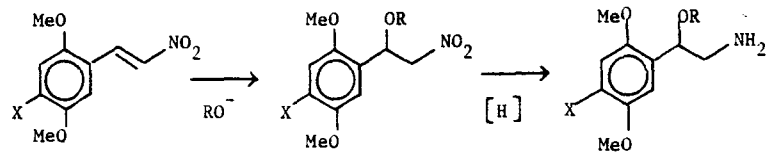
All β-alkoxyphenethylamines were purified and characterized by conversion into the corresponding hydrochloride salts.

The interactions of this series of compounds with 5-$HT_{2A/2C}$ and α_1 receptors are currently under investigation in our laboratories.

A recent paper [5] suggested that the presence of an oxygenated substituent, such as an oxo or a hydroxy group, interposed between the aryl and the amino group of a number of serotoninergic agonists, may enhance ligand selectivity for 5-HT_{2A} versus 5-HT_{2C} receptors. This observation and the scarcity of published data on β-substituted

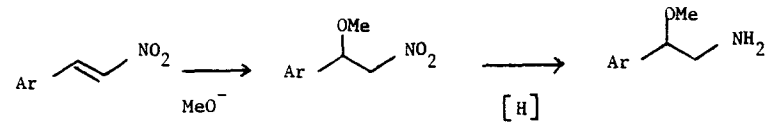
phenethylamines prompted us to prepare a series of new compounds which might prove more discriminating than the traditionally employed 5-$HT_{2A/2C}$ agonists 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) [6] and 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB) [7].

Thus, the series of 1-aryl-1-alkoxy-2-aminoethanes **3** were prepared from the corresponding nitroethenes **1** by Michael addition of an alkoxide to the electrophilic double bond, followed by reduction of the resulting 1-alkoxy-2-nitroethanes **2**.



1 **2** **3**

(**a**) R = Me, X = H (**d**) R = Me, X = SPr (**g**) R = Me, X = OMe
(**b**) R = Me, X = Br (**e**) R = Me, X = Et
(**c**) R = Et, X = Br (**f**) R = Me, X = Me



1 **2** **3**

(**h**) Ar = 3,4-methylenedioxyphenyl
(**i**) Ar = 3,4,5-trimethoxyphenyl

Experimental:

Melting points were obtained with a Kofler hot-stage apparatus and were not corrected.

^1H nmr spectra were recorded on a Varian EM-360 60 MHz instrument. All spectra utilized tetramethylsilane as internal reference.

The 1-aryl-2-nitroethenes **1** were prepared by base-catalyzed condensation of the corresponding benzaldehydes with nitromethane. [4,9]

Preparation of 1-Aryl-1-methoxy-2-nitroethanes **2**. General Procedure- To a stirred, cooled (0-5°C) solution of the nitroethene **1** (10 mmol) in the appropriate volume of dry benzene under nitrogen were added 9.0 mL of a 3.3 M solution of sodium methoxide in methanol (prepared by the addition of 4.5 g of sodium to 60 mL of anhydrous methanol). After 5 minutes of reaction, the mixture was acidified with glacial acetic acid (15 mL), stirred for other 5 minutes and enough water was added to duplicate the initial volume.

The organic layer was then washed with water, the aqueous layer extracted with dichloromethane, the organic extracts combined, dried over $CaCl_2$ and evaporated to give the crude product in the form of a dark yellow oil that solidified on standing.

The product was then purified by flash chromatography, recrystallisation or bulb-to-bulb distillation.

The following compounds were prepared by this general procedure:

1-(2,5-Dimethoxyphenyl)-1-methoxy-2-nitroethane (**2a**) - **1a** (8.8 g ,42 mmol) in dry benzene (80 mL) and the MeONa solution (3.3 M, 18 mL) gave, after purification of the crude product by flash chromatography (silica Merck 60H, chloroform as eluent), 9.4 g (93% yield) of **2a**, mp 58-61°C. Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.22 ; N, 5.81. Found : C, 54.87 ; H, 6.43 ; N, 5.77. ^{1}H nmr (CCl_4) δ 3.4 (3 H, s, β-OMe), 3.8 (3 H, s, OMe), 3.9 (3 H, s, OMe), 4.4 (2 H, m, CH_2NO_2), 5.4 (1 H, m, β-CH), 6.9-7.1 (3 H, m, ArH).

1-(2,5-Dimethoxy-4-bromophenyl)-1-methoxy-2-nitroethane (**2b**) - **1b** (5.0 g , 17 mmol) in dry benzene (70 mL) and the MeONa solution (3.3 M, 18 mL) gave, after recrystallisation in methanol, 3.9 g (72% yield) of **2b**, mp 118-120 °C, lit. [3] mp 119-120 °C.

1-(2,5-Dimethoxy-4-bromophenyl)-1-ethoxy-2-nitroethane (**2c**) - **1b** (3.6 g ,12.5 mmol) in dry benzene (50 mL) and an EtONa solution (3.3 M, 11 mL) gave, after recrystallisation in ethanol, 3.3 g (79% yield) of **2c**, mp 98-100 °C. Anal. Calcd. for $C_{12}H_{16}BrNO_5$: C, 43.11; H, 4.79 ; N, 4.19. Found : C, 43.50 ; H, 4.37 ; N, 3.98. ^{1}H nmr ($CDCl_3$) δ 1.2 (3 H, t, J= 7 Hz, Me), 3.5 (2 H, q, J= 7 Hz, OCH_2), 3.8 (3 H, s, OMe), 3.9 (3 H, s, OMe), 4.5 (2 H, m, CH_2NO_2), 5.4 (1 H, m, β-CH), 7.0 (1 H, s, ArH), 7.1 (1 H, s, ArH).

1-(2,5-Dimethoxy-4-thiopropoxyphenyl)-1-methoxy-2-nitroethane (**2d**) - **1d** (3.1 g, 11 mmol) in dry benzene (50 mL) and the MeONa solution (3.3 M, 14 mL) gave, after recrystallisation in methanol, 3.3 g (95% yield) of **2d**, mp 66-67 °C. Anal. Calcd. for $C_{14}H_{21}NO_5S$: C, 53.33; H, 6.67 ; N, 4.44. Found : C, 53.34 ; H, 6.28 ; N, 4.18. ^{1}H nmr ($CDCl_3$) δ 1.0 (3 H, t, J= 7 Hz, Me), 1.7 (2 H, q, J= 7 Hz, CH_2), 2.9 (2 H, t, J= 7 Hz, CH_2S), 3.4 (3 H, s, β-OMe), 3.8 (6 H, s, OMe), 4.4 (2 H, m, CH_2NO_2), 5.3 (1 H, m, β-CH), 6.8 (1 H, s, ArH), 6.9 (1 H, s, ArH).

1-(2,5-Dimethoxy-4-ethylphenyl)-1-methoxy-2-nitroethane (**2e**) - **1e** (1.1 g, 4.6 mmol) in dry benzene (20 mL) and the MeONa solution (3.3 M, 4 mL) gave, after recrystallisation in ethanol, 1.0 g (80% yield) of **2e**, mp 85-86.5 °C. Anal. Calcd. for $C_{13}H_{19}NO_5$: C, 57.99; H, 7.06 ; N, 5.20. Found : C, 57.81 ; H, 6.99 ; N, 5.52. ^{1}H nmr ($CDCl_3$) δ 1.2 (3 H, t, J= 7 Hz, Me), 2.6 (2 H, q, J= 7 Hz, CH_2), 3.3 (3 H, s, β-OMe), 3.8 (6 H, s, OMe), 4.4 (2 H, m, CH_2NO_2), 5.3 (1 H, m, β-CH), 6.6 (1 H, s, ArH), 6.8 (1 H, s, ArH).

1-(2,5-Dimethoxy-4-methylphenyl)-1-methoxy-2-nitroethane (**2f**) - **1f** (1.0 g, 4.5 mmol) in dry benzene (20 mL) and the MeONa solution (3.3 M, 4 mL) gave, after recrystallisation in methanol, 0.8 g (70% yield) of **2f**, mp 75-77 °C, lit. [3] mp 78-79 °C.

1-(2,4,5-Trimethoxyphenyl)-1-methoxy-2-nitroethane (**2g**) - **1g** (3.7 g, 15 mmol) in dry benzene (40 mL) and the MeONa solution (3.3 M, 14 mL) gave, after recrystallisation in methanol, 3.6 g (86% yield) of **2g**, mp 125-126 °C. Anal. Calcd. for $C_{12}H_{17}NO_6$: C, 53.14; H, 6.27 ; N, 5.17. Found : C, 53.09 ; H, 6.47 ; N, 5.51. ^{1}H nmr (CCl_4) δ 3.3 (3 H, s, β-OMe), 3.8 (3 H, s, OMe), 3.9 (6 H, s, OMe), 4.4 (2 H, m, CH_2NO_2), 5.3 (1 H, m, β-CH), 6.7 (1 H, s, ArH), 7.1 (1 H, s, ArH).

1-(3,4-Methylenedioxyphenyl)-1-methoxy-2-nitroethane (**2h**) - **1h** (5.0 g, 26 mmol) in dry benzene (60 mL) and the MeONa solution (3.3 M, 23 mL) gave, after bulb-to-bulb distillation (150 °C/ 0.5 mmHg), 4.8 g (82% yield) of **2h**, as a light yellow oil which slowly solidified, mp 57-58 °C, lit. [3] mp 58-59 °C.

1-(3,4,5-Trimethoxyphenyl)-1-methoxy-2-nitroethane (**2i**) - **1i** (4.0 g, 17 mmol) in dry benzene (40 mL) and the MeONa solution (3.3 M, 15 mL) gave,

after recrystallization in methanol, 2.4 g (53% yield) of **2i**, mp 141-143 °C, lit.[3] mp 143-144 °C.

1-(2,5-Dimethoxy-4-iodophenyl)-1-methoxy-2-nitroethane (**2k**) - To a stirred mixture of silver trifluoroacetate[10] (2.1 g, 9.5 mmol) and 1-(2,5-dimethoxyphenyl)-1-methoxy-2-nitroethane **2a** (2.3 g, 9.5 mmol) in dry chloroform (20 mL) was added dropwise, in the course of 2 hours, a solution of I_2 (2.4 g, 9.5 mmol) in chloroform (30 mL).

The reaction mixture was further stirred for 18 h. The precipitated AgI was then filtered, and washed with chloroform. The organic filtrate was then washed successively with aqueous $NaHSO_3$ (0.1 M), and with water, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 3.4 g of a yellow solid, that was recrystallised in methanol to give 3.0 g (86% yield) of product **2k**, mp 131-133.5 °C. Anal. Calcd. for $C_{11}H_{14}INO_5$: C, 35.97; H, 3.81 ; N, 3.81. Found : C, 36.08 ; H, 3.73 ; N, 3.47. ^1H nmr ($CDCl_3$) δ 3.5 (3 H, s, β-OMe), 4.6 (6 H, s, OMe), 4.7 (2 H, m, CH_2NO_2), 5.6 (1 H, m, β-CH), 7.3 (1 H, s, ArH), 7.7 (1 H, s, ArH).

Reduction of 1-Aryl-1-alkoxy-2-nitroethanes **2**. General Procedure - To a stirred, cooled (0-5 °C) suspension of $LiAlH_4$ (4.6 g, 120 mmol) in dry THF (200 mL) was slowly added concentrated sulfuric acid (5.9 g, 60 mmol). The resulting mixture was stirred for 30 minutes and a solution of the 1-aryl-1-alkoxy-2-nitroethane **2** (24 mmol) in the appropriate volume of dry THF was then added. After stirring for 30 minutes at room temperature, the mixture was gently refluxed for 2 hours. After cooling in an ice-water bath, the excess hydride was decomposed by careful addition of 2-propanol. A sodium hydroxide solution (15%) was then added until a white precipitate was formed. This was filtered off and the filtrate evaporated. The residue was redissolved in dichloromethane, and extracted with dilute sulfuric acid (0.1 M). The aqueous extract was washed with dichloromethane, basified with a sodium hydroxide solution (25%) and the free amine extracted with CH_2Cl_2. After drying and evaporating the solvent, the residue was purified by bulb-to-bulb distillation to give the pure amine in the form of a colorless oil.

The amine was redissolved in a small amount of 2-propanol, and this solution diluted with twice its volume of dry diethyl ether. Acidification with drops of concentrated HCl, followed by overnight stirring of the resulting solution precipitated the pure, crystalline hydrochloride of **3**.

In this way, the following amine salts **3**.HCl were prepared:

1-(2,5-Dimethoxyphenyl)-1-methoxy-2-aminoethane hydrochloride (**3a** HCl) - 65% yield, mp 139-141 °C. Anal. Calcd. for $C_{11}H_{17}NO_3$. HCl : C, 53.33; H, 7.27; N, 5.66. Found: C, 53.38; H, 7.29; N, 5.59. ^1H nmr (D_2O) δ 3.0 (2 H, m, CH_2N^+), 3.1 (3 H, s, β-OMe), 3.6 (6 H, s, OMe), 4.6 (1 H, m, β-CH), 6.7-6.9 (3 H, m, ArH).

1-(2,5-Dimethoxy-4-bromophenyl)-1-methoxy-2-aminoethane hydrochloride (**3b** HCl) - 69% yield, mp 186-187 °C, lit.[3] mp 187-188 °C. Anal. Calcd. for $C_{11}H_{16}BrNO_3$.HCl : C, 40.43; H,5.21; N, 4.29. Found: C, 40.79; H, 5.13; N, 4.25.

1-(2,5-Dimethoxy-4-bromophenyl)-1-ethoxy-2-aminoethane hydrochloride (**3c** HCl) - 38% yield, mp 205-207 °C. Anal. Calcd. for $C_{12}H_{18}BrNO_3$. HCl : C, 42.29; H, 5.58; N, 4.11. Found: C, 42.05; H, 5.26; N, 4.04. ^1H nmr (D_2O) δ 1.2 (3 H, t, J= 7 Hz, Me), 3.2 (2 H, m, CH_2N^+), 3.5 (2 H, q, J= 7 Hz, OCH_2), 3.8 (3 H, s, OMe), 3.9 (3 H, s, OMe), 5.0 (1 H, m, β-CH), 7.1 (1 H, s, ArH), 7.3 (1 H, s, ArH).

1-(2,5-Dimethoxy-4-thiopropoxyphenyl)-1-methoxy-2-aminoethane hydrochloride (**3d** HCl) - 35% yield, mp 151-153 °C. Anal. Calcd. for $C_{14}H_{23}NO_3S$. HCl : C, 52.25; H, 7.46; N, 4.35. Found: C, 52.05; H, 7.07; N, 4.51. ^1H nmr (D_2O) δ 0.9 (3 H, t, J= 7 Hz, Me), 1.6 (2 H, q, J= 7 Hz, CH_2), 2.9 (2 H, q, J= 7 Hz, CH_2S), 3.0 (2 H, m, CH_2N^+), 3.1 (3 H, s, β-OMe), 3.7 (6 H, s, OMe), 4.6 (1 H, m, β-CH), 6.8 (1 H, s, ArH), 6.9 (1 H, s, ArH).

1-(2,5-Dimethoxy-4-ethylphenyl)-1-methoxy-2-aminoethane hydrochloride (**3e** HCl) - 31% yield, mp 181.5-183 °C. Anal. Calcd. for $C_{13}H_{21}NO_3$. HCl : C, 56.62; H, 7.99; N, 5.08. Found: C, 56.38; H, 7.64; N, 5.15. ^1H nmr (D_2O) δ 0.9 (3 H, t, J=7 Hz, Me), 2.4 (2 H, q, J=7 Hz, CH_2), 3.0 (2 H, m, CH_2N^+), 3.1 (3 H, s, β-OMe), 3.7(6 H, s, OMe), 4.6 (1 H, m, β-CH), 6.8 (2 H, s, ArH).

1-(2,5-Dimethoxy-4-methylphenyl)-1-methoxy-2-aminoethane hydrochloride (**3f** HCl) - 40% yield, mp 170-172 °C, lit.[3] mp 171-172 °C. ^1H nmr (D_2O) δ 2.0 (3H, s, Me), 3.0 (2 H, m, CH_2N^+), 3.1 (3H, s, β-OMe), 3.7 (6H, s, OMe), 4.6 (1 H, m, β-CH), 6.8 (2H, s, ArH)

1-(2,4,5-Trimethoxyphenyl)-1-methoxy-2-aminoethane hydrochloride (**3g**.HCl) - The above reduction, performed with $LiAlH_4/H_2SO_4$, led to the loss of the β-MeO group. The same procedure, employing 1.0 g (3.7 mmol) of the nitro compound **2g** and $LiAlH_4$ (0.7 g, 1.8 mmol) in dry THF (60 mL) gave, after the usual work-up, 0.4 g (45% yield) of the pure amine. The hydrochloride melted at 163-165 °C. Anal. Calcd. for $C_{12}H_{19}NO_4$.HCl: C, 51.89; H, 7.21; N, 5.04. Found: C, 51.60; H, 6.87; N, 5.23. ^{1}H nmr (D_2O) δ 3.0 (2 H, m, CH_2N^+), 3.1 (3 H, s, β-OMe), 3.6-3.7 (9 H, 3 s, OMe), 4.6 (1 H, m, β-CH), 6.6 (1 H, s, ArH), 6.8 (1 H, s, ArH).

1-(3,4-Methylenedioxyphenyl)-1-methoxy-2-aminoethane hydrochloride (**3h**.HCl) - 21% yield, mp 103-105 °C (hydrated form), mp 150 °C , lit [3] mp 152-153 °C. Anal. Calcd. for $C_{10}H_{13}NO_3$.HCl.H_2O : C, 48.10, H, 6.41; N, 5.61. Found: C, 48.26; H, 6.19; N, 5.67.

1-(3,4,5-Trimethoxyphenyl)-1-methoxy-2-aminoethane hydrochloride (**3i**.HCl) - 37% yield, mp 196-197 °C , lit [3] mp 198.5-199.5 °C. Anal. Calcd. for $C_{12}H_{19}NO_4$.HCl : C, 51.89; H, 7.21; N, 5.04. Found: C, 52.14; H, 7.21; N, 5.04.

1-(2,5-Dimethoxy-4-iodophenyl)-1-methoxy-2-aminoethane hydrochloride (**3k**.HCl) - 38% yield, mp 215-217 °C. Anal. Calcd. for $C_{11}H_{16}INO_3$.HCl : C, 35.34; H, 4.55; N, 3.75. Found: C, 35.74; H, 4.20; N, 3.70. ^{1}H nmr (D_2O) δ 3.2 (2 H, m, CH_2N^+), 3.4 (3 H, s, β-OMe), 3.9 (3 H, s, OMe), 4.0 (3 H, s, OMe), 4.9 (1 H, m, β-CH), 7.0 (1 H, s, ArH), 7.6 (1 H, s, ArH).

1-(2,5-Dimethoxy-4-nitrophenyl)-1-methoxy-2-aminoethane hydrochloride (**3j**.HCl) - A solution of the hydrochloride of 1-(2,5-dimethoxyphenyl)-1-methoxy-2-aminoethane (0.5 g, 2 mmol) in water (9 mL) was added with stirring and cooling (0-5 °C) to HNO_3 (65 %, 7 mL). After 5 minutes of stirring, the precipitated product nitrate was filtered and washed with water. The suspended salt in water (15 mL) was then treated with NaOH 5 M and the free base was extracted with dichloromethane (50 mL). After drying and evaporating the organic solvent, the residual yellow oil was purified in a bulb-to-bulb distillation apparatus (160 °C/ 0.4 mmHg). The pure amine was converted into its hydrochloride by addition of drops of concentrated HCl to a solution of the base in 2-propanol/diethyl ether, forming 0.55 g (93% yield) of the product **3j**.HCl, mp 212-214 °C. Anal. Calcd. for $C_{11}H_{16}N_2O_5$.HCl : C, 45.13; H, 5.81; N, 9.57. Found: C, 44.70; H, 5.46; N, 9.31. ^{1}H nmr (D_2O) δ 3.2 (2 H, m, CH_2N^+), 3.4 (3 H, s, β-OMe), 3.9 (3 H, s, OMe), 4.0 (3 H, s, OMe), 5.0 (1 H, m, β-CH), 7.3 (1 H, s, ArH), 7.7 (1 H, s, ArH).

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