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SOME FLUORO AND NITRO ANALOGUES OF HALLUCINOGENIC AMPHETAMINES

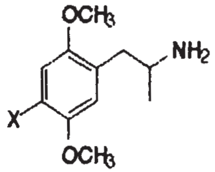
Aida Neira Jara, Milton Aillon Torres,
Bruce Kennedy Cassels [a] and Marcos Caroli Rezende*

Departamento de Química, Universidade Federal de S.Catarina,
Florianópolis, SC 88040-970, Brasil
(a) Departamento de Química, Facultad de Ciencias
Universidad de Chile, Santiago 1, Chile.

Abstract: The preparation of the fluoro and nitro analogues (2)-(5) of the hallucinogens 2,4,5-trimethoxy- and 2-methoxy-4,5-methylenedioxy-amphetamine is described.

Structure-activity studies of psychotomimetic phenethylamines have revealed some structural features which are shared by important members of this family of compounds . [1] These features include the presence of a methyl group at the α- position of the side chain, and the presence of methoxy groups on the ring in a 2,4,5-substitution pattern. These features are incorporated into the model 1-(2,4,5-trimethoxyphenyl)-2-aminopropane (2,4,5-trimethoxyamphetamine, TMA-2, 1, X= OCH_3), which has been the basis of structural variations in QSAR studies .

(*) To whom correspondence should be addressed.



X= OCH_3 (TMA-2)
X= Br (DOB)
X= I (DOI)
X= NO_2 (DON)

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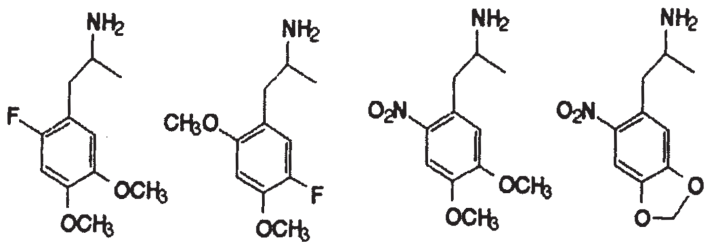
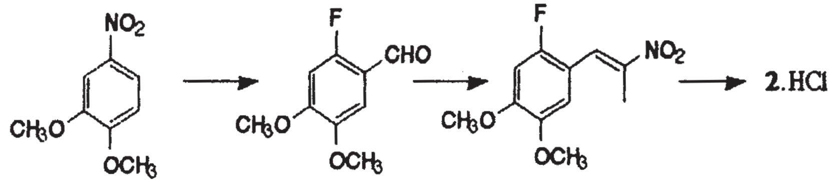
An important variation of the TMA-2 structure is the substitution at the 4-position of the methoxy by other groups.[2,3] The lipophilicity of these groups has been correlated with the potency of the resulting arylaminopropanes.[4] Substitutions at the 2- or 5-positions have yielded less consistent results. Nevertheless, the preparation of other 2- or 5-substituted analogues is necessary for a better understanding of the electronic and steric factors which govern the drug-receptor interactions, responsible for the activity of these compounds.

The 4-nitro analogue of TMA-2 (DON, 1, X= NO_2) has been prepared and found to be a potent hallucinogen in humans.[6] The 4-fluoroamphetamine (1, X=F), just as the other halogenated analogues, DOB and DOI, should be fairly active. Studies on the binding of this fluorinated derivative to 5-HT_2 receptors [3] suggests that this is indeed the case, although no reports are yet available of its potency in humans.

Nothing is known about the fluoro analogues of TMA-2, substituted at the 2- and 5- positions. In the present communication we describe the preparation of these fluorinated compounds (2) and (3), together with the nitro analogue (4) and the nitro derivative (5). This latter compound is in fact an analogue of the known hallucinogen 1-(2-methoxy-4,5-methylenedioxyphenyl)-2-aminopropane (MMDA-2), ten times more potent than mescaline.[7]



The synthesis of compounds (2) and (3) followed a common route which involved the initial introduction of a fluoro substituent into the aromatic ring (Schiemann reaction). The resulting dimethoxyfluorobenzene was then converted into the appropriately substituted benzaldehyde (6) and (7), which underwent condensation with nitroethane to the corresponding 1-aryl-2-nitropropenes (8) and (9), followed by reduction with lithium aluminum hydride.



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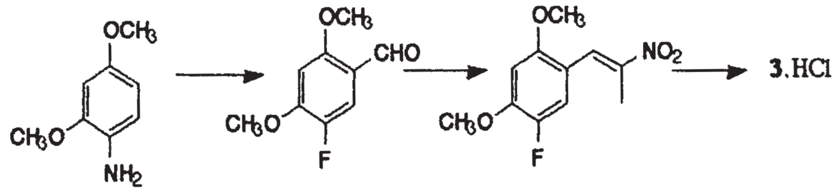

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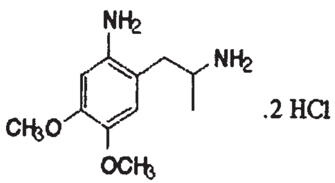
We applied the same strategy to the preparation of 1-(2-fluoro-4,5-methylenedioxyphenyl)-2-aminopropane. However, in contrast to the dimethoxylated aryl diazonium salt, pyrolysis of the crude 3,4-methylenedioxyphenyl diazonium fluoroborate, obtained by treatment of 3,4-methylenedioxyaniline with n-butyl nitrite/HBF_4, did not give the expected fluorobenzene. Instead, only a gum distilled over after prolonged heating of the diazonium fluoroborate.

The basic condensation of the fluorobenzaldehydes (6) and (7) with nitroethane required slightly different reaction conditions, depending on the position of the fluoro substituent. Concurrent formation of a benzonitrile was observed when the 2-fluorobenzaldehyde (6) was heated with nitroethane and ammonium acetate in acetic acid. The formation of nitriles in the reaction of benzaldehydes with nitroethane has been described.[8] The presence of electron-withdrawing substituents at the 2-position of the ring formation of the 2-fluoro-4,5-dimethoxybenzonitrile was indicated by a sharp absorption at 2000 cm^{-1} of the crude product. Reduction with $LiAlH_4$ led to the 2-fluoro-4,5-dimethoxybenzylamine, isolated as the corresponding hydrochloride. This salt exhibited in its nmr spectrum in D_2O two methoxy singlets at 3.9 and 4.7 ppm, a methylene signal at 4.2 ppm, and the characteristic aromatic fluorine-split doublets centered at 6.9 and 7.05 ppm.

The nitroamphetamines (4) and (5) could be obtained by nitration of the corresponding 1-aryl-2-aminopropanes. Catalytic reduction of compound (4) formed in addition 1-(2-amino-4,5-dimethoxyphenyl)-2-aminopropane, isolated as the bis hydrochloride (10).



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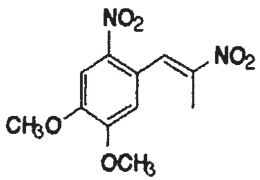

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We also tried to obtain compound (10) by a shorter pathway, which involved the condensation fo 2-nitro-4,5-dimethoxy-benzaldehyde with nitroethane, followed by the reduction of both nitro groups of the resulting 1-aryl-2-nitropropene (11). However, we could not obtain compound (11) by condensation of the nitrobenzaldehyde and nitroethane in the presence of NH_4OAc/ HOAc. Prolonged heating of the reagents at 90-100 °C did not form the nitropropene (11). Unexpectedly, this compound could be obtained by nitration of the 1-(3,4-dimethoxyphenyl)-2-nitropropene. However, reduction of compound (11) with Pd-C/H_2SO_4-HOAc [9,10] led to the formation of only traces of the corresponding 2-aminoamphetamine (10) and this route was finally abandoned.

Experimental:

Melting points were recorded with a digital hot-plate apparatus (Microquimica APF-301) and were not corrected. Ir spectra were

obtained with a Perkin-Elmer 781 spectrometer, analyses were performed with a 2400 Perkin-Elmer apparatus. ^1H nmr spectra were taken on a Varian EM 360 equipment, ^{13}C nmr spectra were recorded on a 90 MHz Bruker instrument. All nmr spectra employed tetramethylsilane as internal reference.

The 2-fluoro-4,5-dimethoxybenzaldehyde (6) was prepared by a sequence of reactions described in the literature, starting from 3,4-dimethoxynitrobenzene. [11] Reduction of this nitrobenzene with hydrazine and Pd-C (5%) formed the 3,4-dimethoxyaniline, mp 86 °C, lit. [12] mp 86-87 °C, in 70% yield. This was converted into the corresponding diazonium fluoroborate by treatment with n-butyl nitrite and the resulting crude salt was pyrolysed to give 3,4-dimethoxyfluorobenzene in 20% yield, following the procedure by Furlano and Kirk [13]. Conversion of this fluorobenzene into the 2-fluoro-4,5-dimethoxybenzaldehyde (6) was achieved in 50% yield, by treatment with α, α - dichloromethyl methyl ether [14] and titanium tetrachloride (Aldrich).[13] The product melted at 95 °C, lit.[13] mp 94-96 °C.

The 2,4-dimethoxyfluorobenzene was obtained from 2,4-dimethoxyaniline (Aldrich), bp 207-209 °C, lit. [15] bp 210 °C. The 1-(3,4-dimethoxyphenyl)- and 1-(3,4-methylenedioxyphenyl)-2-aminopropanes were prepared by lithium aluminum hydride reduction[16] of the corresponding 1-aryl-2-nitropropenes, prepared by the method of Gairaud and Lappin [17].

<u>2,4-Dimethoxy-5-fluorobenzaldehyde (7)</u> - A mixture of phosphorus oxychloride (15.3 g, 0.1 mol) and N-methyl formanilide (13.5 g, 0.1 mol) was stirred for 30 minutes at 25 °C. To this mixture was then slowly added 2,4-dimethoxyfluorobenzene (15.6 g, 0.1 mol). After the addition was complete, the resulting mixture was stirred at 35 °C for 3 hours, then left standing overnight and finally poured into ice-water. The white precipitate was filtered and dried to give 17.7 g (96% yield) of the crude <u>fluorobenzaldehyde (7)</u>, crystallized from cyclohexane, mp 76-77 °C. Anal. calc. for $C_9H_9FO_3$ C 58.70, H 4.89; found C 58.93, H 4.94. $\bar{\nu}_{max}$ (KBr) 1700, 1600,

1250, 1200, 1110, 1000, and 820 cm^{-1}. ^{1}H (CDCl3) δ 4.1 (3 H, s, OCH_3), 4.2 (3H, s, OCH_3), 6.8 (1H, d, J = 6 Hz, ArH), 7.9 (1H, d, J = 12 Hz , ArH), 10.3 (1H, s, CHO).

1-(2-Fluoro-4,5-dimethoxyphenyl)-2-nitropropene (8) - A mixture of 2-fluoro-4,5-dimethoxybenzaldehyde (4 g, 0.02 mol) and ammonium acetate (0.38 g, 5 mmol) in nitroethane (21 mL) was heated in a water-bath for 3 hours at 80 ^oC. The excess solvent was then eliminated in a rotary evaporator and the oily residue was scratched with cold ethanol until the solid nitropropene separated. The filtered, dried yellow product (8) weighed 3.6 g (69 % yield), and was crystallized from ethanol, mp 96 ^oC. Anal. calc. for $C_{11}H_{12}FNO_4$ C 54.77 , H 4.98, N 5.81 ; found C 54.98 , H 4.85, N 5.72 . $\bar{\nu}_{max}$ (KBr) 1620, 1600, 1510, 1370, 1240 , 1200 and 900 cm^{-1}. ^{1}H (DMSO-d_6) δ 2.4 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 3.8 (3H, s, OCH_3), 7.0 (1H, d, J= 4Hz, ArH), 7.1 (1H, s, ArH), 8.0 (1H, s, C=CH).

1-(2,4-Dimethoxy-5-fluorophenyl)-2-nitropropene (9)- Prepared in 74% yield by heating 2,4-dimethoxy-5-fluorobenzaldehyde, nitroethane and ammonium acetate in acetic acid.[17] The nitropropene (9) was crystallized from ethanol, mp 102-104 ^oC. Anal. calc. for $C_{11}H_{12}FNO_4$ C 54.77, H 4.98 , N 5.81 ; found C 54.94 , H 5.24 , N 5.90 . $\bar{\nu}_{max}$ (KBr) 1620, 1610, 1500, 1370, 1240, 1200, 1170 and 900 cm^{-1}. ^{1}H (CDCl3) δ 2.3 (3H, s, CH_3) , 3.8 (3H, s, OCH_3) , 3.9 (3H, s, OCH_3), 6.5 (1H, d, J=7 Hz, ArH), 7.1 (1H, d, J= 12 Hz, ArH), 8.1 (1H, s, C=CH).

1- (2-Fluoro-4,5-dimethoxyphenyl)-2-aminopropane (2) - To a suspension of lithium aluminum hydride (0.8 g, 0.02 mol) in dry THF (10 mL) was added with stirring a solution of 1-(2-fluoro-4,5-dimethoxyphenyl)-2-nitropropene (1 g, 4.1 mmol) in dry THF (15 mL). The resulting mixture was refluxed for 3 hours. It was then cooled and the excess $LiAlH_4$ decomposed by careful addition of water. After filtration and washing the inorganic precipitate with diethyl ether, the combined organic extracts were evaporated and the oily residue redissolved in dilute (0.1 M) sulfuric acid. This aqueous solution was then washed with diethyl ether , then basified with an 0.1 M sodium hydroxide solution and the crude amine extracted with CH_2Cl_2 . After drying and evaporating the solvent, the oil was purified by bulb-to-bulb distillation (140 - 150 ^oC / 0.5 mm Hg). The pure amine, which distilled over as a clear colourless oil, was dissolved in a small amount of isopropanol, the resulting solution was acidified with HCl to pH 1-2 and diluted with twice its volume of dry ether . After stirring this solution overnight, the aminopropane hydrochloride (2).HCl crystallized out to give 0.6 g (58% yield) of the product, mp 226-228 ^oC. Anal. calc. for $C_{11}H_{17}ClFNO_2$ C 52.91, H 6.81, N 5.61 ; found C 52.96 , H 6.81 , N 5.43 . $\bar{\nu}_{max}$ (KBr) 2900 (broad), 1610, 1500, 1240, 1200 and 1000 cm^{-1}. ^{1}H (DMSO-d_6) δ 1.2 (3H, d, J= 7 Hz, CH_3), 2.7-3.0 (2H, m, $ArCH_2$), 3.4 (1H, m, CHN), 3.7 (6H, s, OCH_3), 6.8 (1H,d, J= 12 Hz, ArH) , 6.9 (1H,d,J= 8 Hz, ArH), 8.4 (3H, broad singlet, NH_3^+).

1-(2,4-Dimethoxy-5-fluorophenyl)-2-aminopropane (3)- Prepared from the corresponding nitropropene (9) and purified following the procedure described above for compound (2). The hydrochloride (3).HCl , obtained in 60% yield, melted at 146-148 ^oC. Anal. calc. for $C_{11}H_{17}ClFNO_2$ C 52.91, H 6.81, N 5.61 ; found C 52.56, H 7.12, N 5.40 . $\bar{\nu}_{max}$ (KBr) 2900 (broad), 1610, 1500, 1240, 1200 and 1000 cm^{-1} . ^{1}H (DMSO-d_6) δ 1.2 (2H, d, J= 7 Hz, CH_3), 2.7-3.0 (2H, m, $ArCH_2$), 3.4 (1H,m, CHN), 3.8(3H, s, OCH_3), 3.9 (3H, s, OCH_3), 6.9 (1H, d, J= 7 Hz, ArH), 7.1 (1H, d, J= 12 Hz), 8.4 (3H, broad singlet, NH_3^+).

1-(2-Nitro-4,5-dimethoxyphenyl)-2-aminopropane (4) - A solution of 1-(3,4-dimethoxyphenyl)-2-aminopropane (1.95 g, 10 mmol) in 2 N HNO_3 (10 mL) was added with stirring at 15 ^oC to a concentrated solution of nitric acid (d 1.4, 30 mL) diluted with water (12 mL). The mixture was then stirred at 25 ^oC for 3 hours and then poured into ice-water. The precipitated product was suspended and stirred in a sodium hydroxide solution (0.1 M) and the free amine was extracted with CH_2Cl_2 , the solvent was dried and eliminated in a rotary evaporator. The residue was redissolved in dry diethyl ether and the amine hydrochloride (4).HCl precipitated by passing gaseous HCl through the ethereal solution. The product weighed 1.9 g (69% yield) and was crystallized from methanol - ether, mp 212-213 ^oC, lit. [18] 212-213 ^oC. Anal. calc. for $C_{11}H_{17}ClN_2O_4$ C 47.74 , H 6.15, N 10.13 ; found C 47.62, H 6.05, N 10.25 . $\bar{\nu}_{max}$ (KBr) 2900 (broad) 1580, 1520, 1330 cm^{-1}.

The acetate of (4) was obtained by stirring the hydrochloride (0.3 g, 1.1 mmol), triethylamine (0.23 g, 2.3 mmol) and trichloroacetone [19] (0.21 g, 1.3 mmol) in acetonitrile (10 mL) at 25 ^oC for one hour. The solvent was then rotary evaporated and the residue purified by flash chromatography (ethanol:chloroform: :1:2 as eluent) to give 0.24 g (80% yield) of the product, mp 182-185 ^oC. Anal. calc. for $C_{13}H_{18}N_2O_5$ C 55.32, H 6.38, N 9.93 ; found C 55.04, H 6.50, N 9.75 .

1-(2-Nitro-4,5-methylenedioxyphenyl)-2-aminopropane (5) - Prepared in a similar way as described for compound (4), by nitration of 1-(3,4-methylenedioxyphenyl)-2-aminopropane, in 80% yield. The hydrochloride (5).HCl melted at 189-191 ^oC. Anal. calc. for $C_{10}H_{13}ClN_2O_4$ C 46.06, H 4.99, N 10.75 ; found C 45.71, H 5.04, N 10.74 . $\bar{\nu}_{max}$ (KBr) 2900 (broad), 1590, 1500, 1480, 1320 cm^{-1}. ^1H (D_2O) δ 1.4 (3H,d,J=6 Hz,CH_3), 3.2 (2H,m,ArCH_2), 3.7 (1H,m,CHN), 6.2 (2H,s,OCH_2O), 7.0 (1H,s,ArH), 7.6 (1H, s, ArH). ^{13}C (CD_3OD) δ 18.8, 39.4, 49.6, 105.0, 106.8, 112.6, 129.4, 144.5, 149.2, 153.7 .

The acetate of (5) was prepared as described above for compound (4) in 75% yield, mp 137-139 ^oC. Anal. calc. for $C_{12}H_{14}N_2O_5$ C 54.14, H 5.26, N 10.53 ; found C 53.95, H 5.25, N 10.38 .

1-(2-Amino-4,5-dimethoxyphenyl)-2-aminopropane bis Hydrochloride (10) - 1-(2-nitro-4,5-dimethoxyphenyl)-2-aminopropane hydrochloride (2.8 g, 10 mmol) in a methanolic solution of hydrochloric acid (20 mL of methanol and 2 mL of conc. HCl) was hydrogenated at 25 ^oC over Pd-C (10%, 0.2 g) under an initial pressure of 3 atm. When the theoretical amount of H_2 had been consumed the catalyst was removed by filtration and the filtrate concentrated in a rotary evaporator. The bis hydrochloride (10) separated as a white solid which weighed 1.8 g (65% yield) and was recrystallized from methanol-diethyl ether, mp 235 ^oC, lit. [20] 240-241 ^oC. ν_{max} (KBr) 2900 (broad), 1580, 1500 cm^{-1}. ^1H (D_2O) δ 1.4 (3H, d, J= 6 Hz, CH_3), 3.0 (2H, m, ArCH_2), 3.7 (1H, m, CHN), 4.0 (6H,s,OCH_3), 7.0 (2H,m,ArH) .

1-(2-Nitro-4,5-dimethoxyphenyl)-2-nitropropene (11) - To a mixture of conc. HNO_3 (d 1.4, 32 mL) and water (12 mL) at 15 ^oC was added portionwise 1-(3,4-dimethoxyphenyl)-2-nitropropene [17] (4.5 g, 0.02 mol). The resulting mixture was stirred for 3-4 hours and then poured into ice-water. The precipitate was filtered, washed with water and crystallized from ethanol to give 4.3 g (80% yield) of the yellow nitropropene (11), mp 126-127 ^oC. Anal. calc. for $C_{11}H_{12}N_2O_6$ C 49.25, H 4.48, N 10.45 ; found C 49.26, H 4.48, N 10.35 . $\bar{\nu}_{max}$ (KBr) 1620, 1580, 1530, 1500 and 1320 cm^{-1}. ^1H ($CDCl_3$) δ 2.3 (3H,s, CH_3), 4.0(6H, s, OCH_3), 6.8 (1H, s, ArH), 7.8 (1H,s,ArH), 8.3 (1H, s, ArCH=C)

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