AN IMPROVED SYNTHESIS OF 6-HYDROXY-4-[2-(DI-n-PROPYLAMINO)ETHYL]INDOLE

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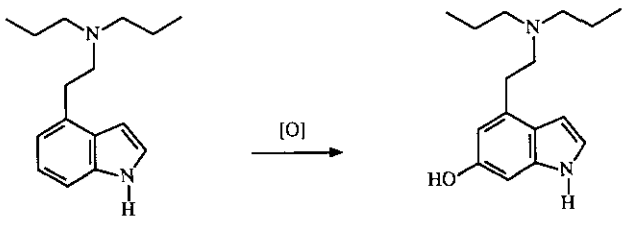
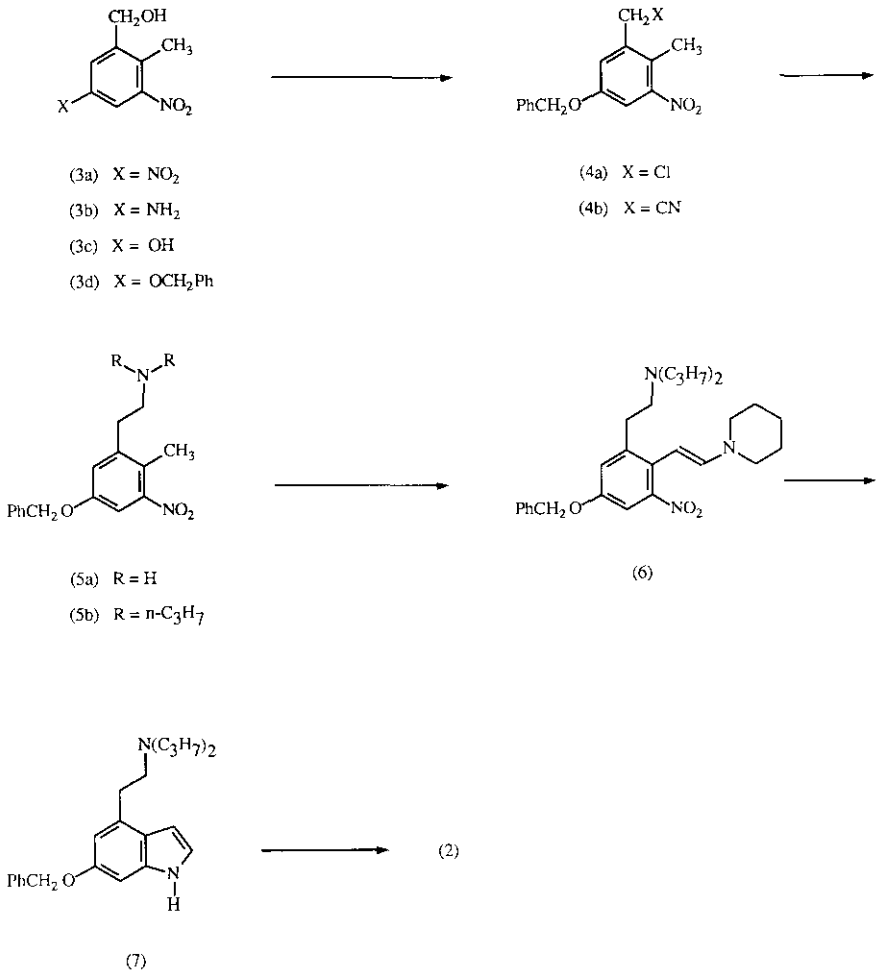
Abstract —— An efficient synthesis is reported for the putative 6-hydroxy metabolite of 4-[2-(di-n-propylamino)ethyl]indole (DPAI), a potent dopaminergic agent.

The partial ergoline derivative 4-[2-(di-n-propylamino)ethyl]indole (DPAI; 1) has been proposed to undergo metabolic hydroxylation in vivo (Scheme 1). In the context of our studies related to DPAI it became necessary to obtain a quantity of the 6-hydroxy metabolite 2. The synthesis of 2, as well as its enhanced biological activity over the parent compound, has been reported by Cannon et al.[1] The length of the original synthesis, as well as the low reported overall yield prompted us to investigate an improved synthetic route (Scheme 2). In the present synthesis the indole formation is delayed until the penultimate step, thereby eliminating the need for two protecting groups, an apparent source of complication in the original synthesis.



1 2

Scheme 1



Scheme 2

Reduction of 2-methyl-3,5-dinitrobenzyl alcohol 3a[2] with sodium hydrosulfide hydrate in MeOH yielded almost exclusively the desired 5-amino isomer 3b in 72% yield. Diazotization of 3b with sodium nitrite, followed by hydrolysis in dilute sulfuric acid afforded a 57% yield of the phenol 3c. This, in turn, was converted to the benzyloxy derivative 3d by treatment with benzyl chloride in *acetone/*K_2CO_3. *Treatment of* 3d with thionyl chloride, giving 4a, followed by treatment with KCN in DMSO furnished 4b in 70% yield from 3d. Selective reduction of the nitrile of 4b was problematic until sodium trifluoroacetoxyborohydride [$NaBH_3(OCOCF_3)$] in THF was used.[3] This cleanly afforded amine 5a in 70% yield. Alkylation of 5a with n-propyl iodide in saturated aqueous K_2CO_3/benzene[4] provided the tertiary amine 5b in 65% yield.

Transformation of the nitrotoluene to the indole was best accomplished using the two-step procedure of Lloyd and Nichols.[5,6] Condensation of 5b with tripiperidinomethane[7] at 110°C under aspirator vacuum for 36 hours gave the enamine 6. This underwent reductive cyclization in the presence of nickel boride and hydrazine hydrate in MeOH[6] to cleanly afford 6-benzyloxy-4-[2-(di-n-propylamino)ethyl]indole 7 in 75% overall yield. Palladium-catalyzed hydrogenation of 7 in EtOH under 1 atmosphere of H_2 pressure resulted in smooth O-debenzylation to give the target compound 2 in 61% yield. Spectral data were entirely consistent with the expected structure and coincided closely with the data reported by Cannon et al.[1] The overall yield for this synthesis (≈ 4%) compared favorably with the reported yield of the original method (0.45%).

EXPERIMENTAL

Ir spectra were recorded using a Beckman 33 instrument with KBr plates. Melting points were determined on a Mel Temp apparatus with open capillary tubes and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian FT-80 or Chemagnetics A-200 spectrometer using tetramethylsilane as an internal reference standard and $CDCl_3$ or acetone-d_6 as solvents. Chemical ionization mass spectra were obtained on a Finnigan 4023 GC/MS, and exact mass measurements were obtained on a Kratos MS-50S spectrometer. Thin layer chromatography was performed using EM Labs silica gel F-254 plates. Preparative silica gel chromatography was performed using either a flash column or Chromatotron apparatus. Tripiperidinomethane was prepared according to the method of Swaringen et al.[7] and nickel boride catalyst according to Lloyd and Nichols.[6]

2-Methyl-3-nitro-5-aminobenzyl Alcohol (3b). To a refluxing solution of 3a (9.0 g, 42 mmol) in 55 ml of methanol was added sodium hydrosulfide hydrate (8.5 g) in 125 ml methanol over 30 min. After reflux for an additional 90 min, the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was suspended in water. The product was recovered by suction filtration, washed several times on the filter with water, and recrystallized from methanol-H_2O to afford 3b (5.5 g, 72%) as a reddish solid: mp 166-167°C; Ir 3400 cm^{-1}; ^1H nmr (acetone-d_6) 2.18 (s, 3H), 4.59 (s, 2H), 6.97, 7.07, (2d, J=3 Hz, 2H); CIMs (m/z) 183 (MH^+); HRMs (Found: M^+, 182.0691, $C_8H_{10}O_3N_2$ requires M^+, 182.0691).

2-Methyl-3-nitro-5-hydroxybenzyl Alcohol (3c). A suspension of 3b (4.5 g, 25 mmol) in 185 ml of 20% sulfuric acid at 5°C was treated with dropwise addition of a solution of $NaNO_2$ (1.9 g, 28 mmol) in 30 ml of water and stirred for an additional 90 min at 0°-5°C. The reaction mixture was then poured into 270 ml of 20% sulfuric acid and heated at 90°C for 2 h. The solution was then cooled to room temperature and extracted with ether. The ether extracts were dried (Na_2SO_4), filtered and concentrated to give 3c (2.6 g, 57%) as a yellow solid which was recrystallized from ether-hexane (mp 110-111°C): Ir 3660 cm^{-1}; ^1H nmr (acetone-d_6) 2.28 (s, 3H), 5.14 (s, 2H), 7.18-7.20 (s, 2H). CIMs (m/z) 184 (MH^+). HRMs (Found M^+, 183.0529, $C_8H_9O_4N$ requires M^+, 183.0532).

2-Methyl-3-nitro-5-benzyloxybenzyl Alcohol (3d). A mixture of 3c (4.6 g, 25 mmol), benzyl chloride (6.3 g, 5.0 mmol) and anhydrous K_2CO_3 (8.8 g) in 100 ml of dry acetone was heated at reflux for 36 h. The suspension was filtered, concentrated and the residue partitioned between water and diethyl ether. The ether extract was washed with dilute aqueous NaOH, water, and was then concentrated. The crude material was chromatographed on a silica gel column eluting with $CHCl_3$/MeOH (10:1) to give 3d (4.8 g, 71%), as a white solid, which was recrystallized from ether-pet ether (mp 59°C): ^1H Nmr ($CDCl_3$) 2.31 (s, 3H), 4.71 (br, 2H) 5.07 (s, 2H), 7.31 (s, 2H), 7.38 (s, 5H). CIMs (m/z) 274 (MH^+). HRMs (Found M^+, 273.0996, $C_{15}H_{15}O_4N$ requires M^+, 273.1001).

2-Methyl-3-nitro-5-benzyloxyphenylacetonitrile (4b). A solution of 3d (2.25 g, 8.2 mmol) in dry benzene (200 ml) was treated with $SOCl_2$ (1.1 g) and stirred at room temperature for 6 h. The solution was washed with water, dried over Na_2SO_4 and concentrated to afford 4a (1.6 g, 5.5 mmol, 66%) which was used in the next step without further purification. This crude chloride was dissolved in 20 ml of freshly distilled DMSO and 0.63 g (9.6 mmol) of KCN was added. The reaction was stirred for 3 h at room temperature, then diluted with water and extracted into ethyl ether. The extract was washed with water, dried (Na_2SO_4) and concentrated. The crude material was chromatographed on a silica gel column eluting with CH_2Cl_2 and the eluate was concentrated to give 4b (1.1 g, 70%) as a white solid which was recrystallized from benzene-hexane (mp 89°C): Ir 2240 cm^{-1}; ^1H nmr ($CDCl_3$) 2.36 (s, 3H), 3.72 (s, 2H), 5.11 (s, 2H), 7.29 (s, 2H), 7.40 (s, 5H). CIMs (m/z) 283 (MH^+), 267 (M^+-CN). HRMs (Found M^+, 282.1005, $C_{16}H_{14}O_3N_2$ requires M^+, 282.1004).

2-(2-Methyl-3-nitro-5-benzyloxyphenyl)aminoethane (5a). To a mixture of $NaBH_4$ (160 mg, 4.2 mmol) and trifluoroacetic acid (485 mg, 4.2 mmol) in dry THF (30 ml) at room temperature was added 4d (240 mg, 0.85 mmol) in 5 ml of THF. The mixture was stirred for 4 h, cooled to 0°-5°C and excess reducing agent was decomposed by dropwise addition of water. The solution was concentrated and the residue was partitioned between CH_2Cl_2 and 2% aqueous citric acid. The aqueous layers were pooled, neutralized with NaOH and extracted with CH_2Cl_2. The organic extract was washed with brine, dried (Na_2SO_4), filtered and concentrated to afford crude 5a (160 mg, 66%) as a tan oil which was purified on a Chromatron using a silica rotor and eluting with CH_2Cl_2 under an NH_3 atmosphere: ^1H Nmr ($CDCl_3$) 2.38 (s, 3H), 3.05 (m, 4H), 4.87 (s, 2H), 7.01 (s, 1H), 7.05 (s, 1H), 7.35 (s, 5H) CIMs (m/z) 257 (M^+-CH_2NH_2), 287 (MH^+); HRMs (Found: M^+, 286.1315, $C_{16}H_{18}O_3N_2$ requires M^+, 286.1317).

N,N-Di-n-propyl-2-(2-methyl-3-nitro-5-benzyloxyphenyl)aminoethane (5b). To a mixture of 50 ml of a saturated aqueous K_2CO_3 solution, 1-iodopropane (1.42 g, 7.0 mmol) and 25 ml of benzene was added 5a (400 mg, 1.13 mmol). The reaction mixture was heated at reflux for 96 h, allowed to cool, and the aqueous layer was extracted with benzene. The combined benzene layers were washed with water, dried (Na_2SO_4) and concentrated. Purification was achieved using a 2 mm thick silica rotor on a Chromatotron apparatus and eluting with $CHCl_3$/MeOH 10:1 (satd with NH_3 vapor) to afford 5b (270 mg,

64%) as a clear oil: ^{1}H Nmr ($CDCl_3$); 0.79-0.96 (t, J=7.3 Hz, 6H), 1.32-1.59 (m, 4H), 2.34 (s, 3H), 2.41-2.66 (m, 8H), 5.06 (s, 2H), 7.03 (s, 1H), 7.06 (s, 1H), 7.37 (s, 5H). CIMs (m/z) 371 (MH^+). HRMs (Found: M^+, 370.2215. $C_{22}H_{30}O_3N_2$ requires M^+, 370.2256).

4-[2-(Di-n-propylamino)ethyl]-6-benzyloxyindole (7). Tripiperidinomethane (107 mg, 0.4 mmol) and **5b** (100 mg, 0.27 mmol) were fused at 110°C and stirred under aspirator vacuum (16 mm Hg) for 36 h. The resulting enamine **6** was used directly in the next step without purification. The residue was taken up in a small amount of ethanol and added to a suspension of nickel boride (freshly prepared from 248 mg (1.0 mmol) of nickel II acetate and 76 mg (2.0 mmol) of $NaBH_4$ according to reference 6) in 20 ml of ethanol. Hydrazine hydrate (150 mg, 3 mmol) was added dropwise with stirring. When gas evolution had ceased, the reaction mixture was heated at reflux for an additional 2 h. The mixture was allowed to cool, was filtered through Celite and concentrated. Purification as described above for **5b** yielded **7** (70 mg, 75% from **5b**) as a clear glassy solid: ^{1}H Nmr ($CDCl_3$) 0.85 (t, J=7.1 Hz, 6H), 1.10-1.40 (m, 4H) 2.28-2.48 (m, 8H), 4.90 (s, 2H), 6.50 (d, J=3 Hz, 1H), 6.70 (s, 1H), 6.80 (s, 1H), 7.10 (s, 1H), 7.20-7.26 (m, 5H). CIMs (m/z) 351 (MH^+), 407 (M^+ · isobutane) HRMs (Found: M^+, 350.2355, $C_{23}H_{30}N_2O$ requires M^+, 350.2358).

4-[2-(Di-n-propylamino)ethyl]-6-hydroxyindole (2). To a solution of **7** (70 mg, 0.20 mmol) in 30 ml of ethanol was added 50 mg of 10% Pd/C catalyst. The suspension was stirred under 1 atmosphere of hydrogen pressure for 1 h. The suspension was filtered through Celite, concentrated and purified as described for **7** to yield **2** (32 mg, 61%) of a glass-like solid: ^{1}H Nmr 0.85 (t, J=7.3 Hz, 6H), 1.55 (m, 4H), 2.60 (m, 4H), 2.90-3.10 (m, 4H), 6.50 (s, 1H), 6.70 (s, 1H), 6.80 (s, 1H), 7.10 (s, 1H), 8.05 (br, 1H); CIMs (m/z) 261 (MH^+). Agrees with data published by Cannon et al.[1]

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REFERENCES

1. J. Cannon, T. Lee, M. Ilhan, J. Koons, and J. P. Long, J. Med. Chem., 1984, 27, 386.
2. Available from Aldrich Chemical Co.
3. N. Umino, T. Iwabuma, and N. Itoh, Tetrahedron Lett., 1976, 33, 2875.
4. J. D. McDermed and R. J. Miller, J. Med. Chem., 1976, **19**, 547.
5. D. H. Lloyd and D. E. Nichols, Tetrahedron Lett., 1983, 24, 4561.
6. D. H. Lloyd and D. E. Nichols, J. Org. Chem., 1986, 51, 4294.
7. R. A. Swaringen, J. F. Eaddy, and T. R. Henderson, J. Org. Chem., 1980, 45, 3986.

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