A New Efficient Method for the Preparation of 2-Fluoro-*N*-propylnorapomorphine†

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A new synthesis of the highly efficient, selective dopamine D_2 agonist, 2-fluoro-*N*-propylnorapomorphine **1** has been accomplished, involving the transformation of thebaine **13** into 6-fluoro-6-demethoxythebaine **10**, followed by sequential *N*-demethylation, *N*-alkylation, rearrangement with methanesulfonic acid into the apocodeine derivative **17**, and subsequent *O*-demethylation with boron tribromide.

Among the dopaminerg apomorphine derivatives, 2-fluoro-*N*-propylnorapomorphine **1**, prepared by Neumeyer *et al.*,[1] has been shown as the hitherto most efficient and most selective D_2 agonist. However, a significant drawback of the published synthetic procedure to **1** is the conversion of the phenolic hydroxy group of the aporphine skeletone into the desired amino function in a tedious five-step operation.

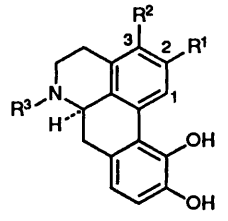
We have recently elaborated[2,3] a simple and efficient procedure for obtaining C-2 and C-3 halogen-substituted (Cl or Br) analogues **3**–**6** of aporphine, by conversion of thebaine **13** into the appropriate halogen-substituted tetradehydromorphinane,[4,5] which—following *N*-demethylation and subsequent *N*-propylation—were subjected to rearrangement induced by methanesulfonic acid into the corresponding apocodeine derivatives. *O*-Demethylation of the latter then readily furnished the desired apomorphines.

Our previous methodology[4] for the preparation compounds **14** and **15** was not applicable to the synthesis of 6-fluoro-6-demethoxythebaine, since the reaction of 14-chlorocodeine tosylate **7** with tetrabutylammonium fluoride gave rise to 6-chloro-6-demethoxythebaine **14**; a similar reaction occurred when **7** was subjected to the same reaction conditions in the absence of external nucleophiles.

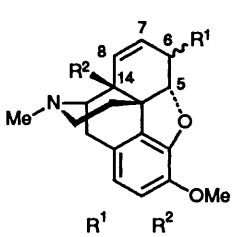
Therefore, 6β-fluoro-14-hydroxy-6-deoxycodeine **8** was selected as the starting material, a compound successfully prepared from thebaine **13** according to our previously developed procedure.[6] The reaction of **8** with phosphorus tribromide resulted in 7β-bromo-6β-fluoro-6-deoxyneopine **9**, which could be converted into 6-fluoro-6-demethoxythebaine **10** on treatment with potassium *tert*-butoxide. The preparation of the diene **10** could be achieved with lower yield by employing the reaction of **8** with thionyl chloride. In this case, the reaction proceeded with racemization[7] to give a mixture of the intermediate 7α- and 7β-chloroderivatives only the latter being capable of being converted into the desired diene.

Rearrangement of the diene **10** with methanesulfonic acid at room temperature (2 h) afforded nearly 50% of the 2-fluoroapocodeine **16**, together with an unisolated by-product.

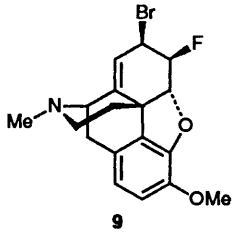
O-Demethylation of 2-fluoroapocodeine **16** with boron tribromide gave 2-fluoroapomorphine **2**.[8] Owing to the allylic amine character, for the *N*-demethylation of the fluorodiene **10** only the diethyl azodicarboxylate method[2] proved to be successful, and the resulting *N*-demethyl derivative **11** was alkylated with propyl bromide to give 6-fluoro-*N*-propyl-6-demethoxynorthebaine **12**. The rearrangement of this latter compound



	R^1	R^2	R^3
1	F	H	Pr
2	F	H	Me
3	Cl	H	Pr
4	Br	H	Pr
5	H	Cl	Pr
6	H	Br	Pr



	R^1	R^2
7	α-OTs	Cl
8	β-F	OH



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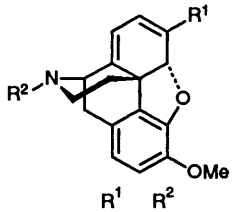
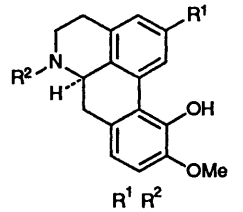


	R^1	R^2
10	F	Me
11	F	H
12	F	Pr
13	OMe	Me
14	Cl	Me
15	Br	Me



	R^1	R^2
16	F	Me
17	F	Pr

with methanesulfonic acid at room temperature furnished 2-fluoro-*N*-propylnorapocodeine **17**, and subsquent cleavage of the phenolic ether function with boron tribromide gave rise to the title compound **1**.

Experimental

Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. TLC was performed on Merck 5554 silica gel F_{254} foils using benzene–methanol (8:2, v/v) as developer. The detecting agent was Dragendorff's reagent. Mass spectra were measured with a VG-7035 (GC-MS-DS) instrument. ^1H NMR spectra were recorded on a Bruker WP 200 SY spectro-

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meter, chemical shift are reported in ppm (δ) from internal TMS.

7β-*Bromo*-6β-*fluorodeoxyneopine* **9**.—To a solution of 6β-fluoro-14-hydroxy-6-deoxycodeine **8** (2.0 g, 6.3 mmol) in dry chloroform (20 cm^3) phosphorous tribromide (1.2 cm^3, 12.6 mmol) was added dropwise at 0 °C with stirring. After completion of the addition the mixture was warmed to 50 °C, stirred for 2 h at this temperature, and then cooled to room temperature. Water (20 cm^3) was added dropwise with external cooling on a water-bath, and the mixture adjusted to pH 8, by the addition of ammonium hydroxide, with continuous stirring and cooling. The organic layer was separated and the aqueous phase was extracted with chloroform (3 × 10 cm^3). The combined organic extracts were washed with saturated brine, dried ($MgSO_4$) and concentrated. Crystallization of the residue from ethanol afforded *compound* **9** (1.95 g, 81.2%), m.p. 137–140 °C (Found: Br, 19.85; F, 5.0; N, 3.5. $C_{18}H_{19}FBrNO_2$ requires Br, 21.01; F, 4.99; N, 3.68%); $\delta_H(CDCl_3)$ 2.49 (3 H, s, NMe), 3.9 (3 H, s, OMe), 4.37 (1 H, dd, 6-H), 4.7 (1 H, m, 7-H), 5.11 (1 H, q, 5-H), 5.85 (1 H, q, 8-H), 6.72 (2 H, dd, ArH, $J_{5,6}$ 8.2, $J_{6,7}$ 3.9, $J_{6,6F}$ 51); *m/z* 380 (M^+, 15%); $[\alpha]_D^{24}$ −420 (*c* 0.1, $CHCl_3$).

6-*Fluoro*-6-*demethoxythebaine* **10**.—A mixture of compound **9** (1.0 g, 2.62 mmol) and potassium *tert*-butoxide (1.0 g, 8.9 mmol) in absolute ethanol (50 cm^3) was refluxed for 1 h. The cooled reaction mixture was filtered and the filtrate concentrated to give *compound* **10** (0.67 g, 85%), m.p. 155–157 °C (from EtOH) (Found: F, 6.2; N, 4.5. $C_{18}H_{18}FNO_2$ requires F, 6.34; N, 4.67%), $\delta_H(CDCl_3)$ 2.48 (3 H, s, NMe), 3.88 (3 H, s, OMe), 5.42 (1 H, d, 5-H), 5.46 (1 H, dd, 8-H), 5.65 (1 H, dd, 7 H) and 6.66 (2 H, dd, ArH); *m/z* 299 (M^+, 100%); $[\alpha]_D^{24}$ −110 (*c* 0.5, $CHCl_3$).

2-*Fluoroapocodeine* **16**.—6-Fluoro-6-demethoxythebaine **10** (0.6 g, 2.0 mmol) was dissolved at 0 °C in 99% methanesulfonic acid (6.0 cm^3) and the mixture was kept at room temperature for 2 h. It was then added dropwise to a solution of potassium hydrogen carbonate (12 g) in water (60 cm^3) with stirring. The resulting precipitate was filtered off, dried, dissolved in absolute ethanol (2.0 cm^3) and acidified with hydrochloric acid in ethanol to give 2-fluoroapocodeine hydrochloride (0.34 g, 51%), m.p. 258 °C (decomp.).

Free base **16**, m.p. 189–192 °C (from EtOH) (Found: F, 6.18; N, 4.52. $C_{18}H_{18}FNO_2$ requires F, 6.34; N, 4.67%); $\delta_H(CDCl_3)$ 2.55 (3 H, s, NMe), 3.92 (3 H, s, OMe), 6.77 (1 H, dd, 3-H), 6.8 (2 H, s, 8-H and 9-H) and 8.02 (1 H, dd, 1-H); *m/z* 299 (M^+, 100%); $[\alpha]_D^{24}$ −70 (*c* 0.1, $CHCl_3$).

2-*Fluoroapomorphine* **2**.—A solution of 2-fluoroapocodeine **16** (0.15 g, 0.5 mmol) in dry dichloromethane (5 cm^3) was treated with a dichloromethane solution (1 mol dm^{-3}; 1 cm^3) of boron tribromide under a nitrogen atmosphere. After being stirred overnight at room temperature methanol (6.0 cm^3) was added and the reaction mixture was concentrated and the residue crystallized from methanol–ether to give the *hydrobromide* **2**·HBr (0.14 g, 76.5%), m.p. >300 °C (decomp.) (lit.,[8] >300 °C) (decomp.) (Found: Br, 22.0; F, 5.25; N, 3.96. $C_{17}H_{17}FBrNO_2$ requires Br, 21.81; F, 5.18; N, 3.82%); δ_H(DMSO) 3.1 (3 H, s, NMe), 6.65 (1 H, d, 9-H), 6.8 (1 H, d, 8-H), 7.05 (1 H, dd, 3-H) and 8.1 (1 H, dd, 1-H); *m/z* 285 (M^+, 75%).

6-*Fluoro*-6-*demethoxynorthebaine* **11**.—A mixture of 6-fluoro-6-demethoxythebaine **10** (1.5 g, 5.0 mmol) and diethyl azodicarboxylate (1.0 g, 6.0 mmol) in absolute benzene (40 cm^3) was boiled under reflux for 20 h. After removal of the solvent by distillation at reduced pressure, a mixture of the residue and pyridine hydrochloride (1.0 g) in ethanol (30 cm^3) was stirred at room temperature for 24 h. The crystalline product was filtered off and washed with ethanol to give the *hydrochloride* **11**·HCl, m.p. 261–263 °C (decomp.); *free base* **11** (0.8 g, 57%), m.p. 130–132 °C (from EtOH) (Found: F, 6.5; N, 4.8. $C_{17}H_{16}FNO_2$ requires F, 6.65; N, 4.9%); $\delta_H(CDCl_3)$ 3.85 (3 H, m, OMe), 5.4 (1 H, d, 5-H), 5.43 (1 H, dd, 8-H), 5.62 (1 H, dd, 7-H) and 6.65 (2 H, dd, ArH); *m/z* 285 (M^+, 100%).

6-*Fluoro*-N-*propyl*-6-*demethoxynorthebaine* **12**.—A mixture of the *N*-dimethyl derivative **11** (0.62 g, 2.2 mmol), sodium hydrogen carbonate (0.5 g) and propyl bromide (0.31 g, 2.5 mmol) in absolute *N*,*N*-dimethylformamide (30 cm^3) was stirred at 70 °C for 20 h. The inorganic salts were then filtered off and the filtrate was evaporated (5 mmHg, 60 °C), the residue was dissolved in water (50 cm^3) and extracted with chloroform (3 × 30 cm^3). The combined organic extracts were dried and evaporated to give the crude syrupy product (0.75 g), which was purified by means of column chromatography (Kieselgel 40, 9:1 chloroform–methanol) to give *compound* **12** (0.6 g, 84.5%) as oil; $\delta_H(CDCl_3)$ 0.92 (3 H, t, CMe), 3.89 (3 H, s, OMe), 5.4 (1 H, d, 5-H), 5.48 (1 H, dd, 8-H), 5.62 (1 H, dd, 7-H) and 6.65 (2 H, dd, ArH); *m/z* 327 (M^+, 100%).

2-*Fluoro*-N-*propylnorapocodeine* **17**.—Rearrangement of the diene **12** (0.7 g, 2.14 mmol) with methanesulfonic acid, as described for the preparation of **16** gave the *hydrochloride* **17**·HCl (0.35 g, 45%), m.p. 235–238 °C (decomp.) (from EtOH) (Found: F, 5.1; N, 3.7. $C_{20}H_{23}FClNO_2$ requires F, 5.22; N, 3.84%); $\delta_H(D_2O)$ 1.1 (3 H, t, CMe), 3.88 (3 H, s, OMe), 6.8 (3 H, m, CH, 8-H and 9-H) and 7.9 (1 H, dd, 1-H); *m/z* 327 (M^+, 90%); $[\alpha]_D^{24}$ −35 (*c* 0.1, H_2O).

2-*Fluoro*-N-*propylnorapomorphine* **1**.—*O*-Demethylation of 2-fluoro-*N*-propylnorapocodeine **17** (0.15 g, 0.46 mmol) as described for **2**, gave the *hydrobromide* **1**·HBr (0.15 g, 79%), m.p. 198–201 °C (from EtOH–Et_2O) (lit.,[1] 200–202 °C) (Found: F, 4.95; N, 3.65. $C_{19}H_{21}FBrNO_2$ requires F, 4.81; N, 3.55%); $\delta_H(D_2O)$ 1.08 (3 H, t, CMe), 6.78 (2 H, m, 8-H and 9-H), 6.95 (1 H, d, 3-H) and 8.05 (1 H, d, 1-H); *m/z* 312 (M^+, 70%); $[\alpha]_D^{24}$ −25 (*c* 0.1, MeOH) [lit.,[1] −28.8 (*c* 0.13, MeOH)].

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