Rearrangement of Morphinandienes in Methanesulfonic Acid[1]

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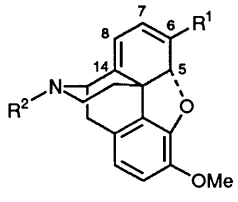
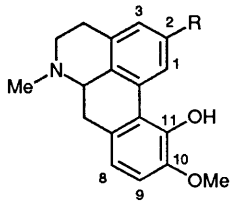
Besides 2-fluoroapocodeine **7**, the methanesulfonic acid-induced rearrangement of 6-fluoro-6-demethoxythebaine **2** gave the C-2 substituted apocodeines **8**, **11** and **20**. Analogous rearrangement of thebaine **1** in the presence of alcohols offers a convenient and high-yielding route to the 2-alkoxymorphothebaine **6**, **11**, **12** and **13**. Formation of the products has been explained in terms of nucleophilic substitution of the cationic intermediates **21** and **22** from the acid-catalysed reaction.

A possible route to dopaminerg apomorphine derivatives is based on the transformations[2,3] of 2-methoxymorphothebaine **6**, available from methanesulfonic acid-induced rearrangement of thebaine **1**. However, a drawback of this methodology is that the required functional groups must be developed on the aporphine skeleton. In our method, the morphinandienes **2**–**5** with the required substitution pattern are initially prepared, and then converted into the corresponding apomorphine analogues. Following this strategy *N*-propyl- **14**,[3] 2-chloro-**15** and 2-bromo-*N*-propyl- **16**[4] and 3-chloro- **17** and 3-bromo-*N*-propyl-norapomorphine **18**[5] have been prepared. These substituted morphinandienes rearranged in methanesulfonic acid in 80–90% yield, no by-products being isolated.

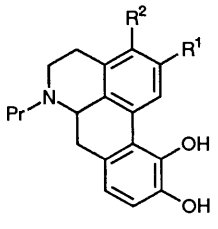
Recently we described[6] the preparation of 2-fluoro-*N*-propylnorapomorphine **19**, hitherto known[7] as the most efficient and selective D_2 agonist, by employing an analogous reaction sequence, in which—most surprisingly—the methanesulfonic acid-induced rearrangement of the fluoro dienes **2** and **3** was the lowest-yielding step (< 50%).





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

	R
6	OMe
7	F
8	OH
9	Cl
10	Br
11	OEt
12	OPr
13	OBu



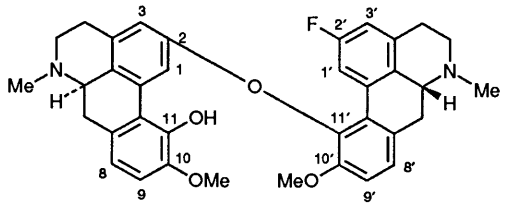
	R^1	R^2
14	H	H
15	Cl	H
16	Br	H
17	H	Cl
18	H	Br
19	F	H

Here we report the isolation of the by-products formed on the rearrangement of 6-fluoro-6-demethoxythebaine **2** in methanesulfonic acid and provide a mechanistic account of the reaction. An analogous rearrangement of thebaine **1** in the presence of alcohols, a convenient and high-yielding route to 2-alkoxymorphothebaine, is also described.

Results and Discussion

The rearrangement of 6-fluoro-6-demethoxythebaine **2**[6] in methanesulfonic acid under standard conditions (90 °C, 30 min) gave a four-component mixture, from which the major products 2-fluoroapocodeine **7** and morphothebaine **8** and the by-products 2-ethoxymorphothebaine **11** and a bisaporphine **20** were isolated by column chromatography. The reaction when conducted at room temperature for 2 h gave a *ca.* 50% yield of 2-fluoroapocodeine **7**, with only traces of the morphothebaine **8**; the amount of the ethyl ether **11** was unchanged, while that of the dimer **20** increased somewhat.

Formation of the unexpected products is explained in terms of substitution of the fluorine-stabilized cation **21** with the *O*-nucleophiles present in the reaction mixture; this mechanism is similar to that suggested[8] for the acid-catalysed rearrangement of thebaine. In order to trigger such reactions to produce the morphothebaine **8** and the ethyl ether **11**, respectively, methanesulfonic acid containing 1% of water and the ethanol of crystallization present in the starting diene **2** are found to be satisfactory. The dimer **20** is most probably formed from the major product with the phenol **7** acting as a nucleophile.



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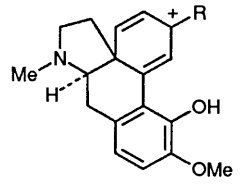

21 R = F
22 R = OMe

Support for the above mechanistic interpretation is provided by rearrangement of the fluoro diene **2** with 16.6% (v/v) aqueous methanesulfonic acid at 90 °C to give the morphothebaine **8** in excellent yield. With ethanol-containing methanesulfonic acid the reaction afforded the 2-ethoxymorphothebaine **11** exclusively under the same conditions. Similarly, in the presence of methanol the methyl ether **6** was isolated. Analogous rearrangement of 6-chloro- **4** and 6-bromo-6-demethoxythebaine **5**[4] in the presence of water or ethanol gave the appropriate 2-halogenoapocodienes **9** and **10** and the by-products **8** and **11**, respectively, (*ca.* 30% yield). These findings

agree with the fact that a fluoro substituent is more effective for cation stabilization than other halogeno substituents.[9]

The methanesulfonic acid-induced rearrangement of thebaine **1** with added alcohols was also investigated.* Rearrangement of thebaine in the absence of alcohols furnished (in *ca.* 60% crude yield) the 2-methoxymorphothebaine **6**,[8] the key intermediate in the syntheses of diversely substituted dopaminerg apomorphine derivatives.[2] The yield of the rearrangement in the presence of methanol was *ca.* 95%, while in the presence of ethanol the crude reaction product contained both the ethyl **11** and methyl ethers **6** (4:1), an observation explained in terms of nucleophilic transetherification of the intermediary methoxonium ion **22**. In the presence of propanol and butanol the corresponding alkyl ethers **12** and **13** were similarly produced, as may be other 2-alkyl ethers with the appropriate alcohols.

Experimental Section

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.[12] Mass spectra were measured with a VG-7035 (GC–MS–DS) instrument. ^{1}H NMR spectra were recorded on a Bruker WP 200 SY spectrometer, chemical shifts are reported in ppm (δ) from internal TMS and coupling constants (J) are measured in Hz.

Rearrangement of the Fluoro Diene **2** *in Methanesulfonic Acid.*—(a) A mixture of compound **2** (1.0 g, 3.34 mmol) and 99% methanesulfonic acid (10.0 cm^3) was heated at 90–95 °C for 30 min, after which it was cooled to room temp., added dropwise to a stirred solution of potassium hydrogen carbonate (20 g) in water (100 cm^3) and extracted with chloroform (3 × 30 cm^3). The combined extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated to give a crude, syrupy mixture of products (0.85 g), which was separated by means of column chromatograhy (Kieselgel 40, benzene–methanol 9:1). The first eluted material was the *2-ethoxymorphothebaine* **11** (0.05 g, 4.6%), m.p. 88–90 °C (from diethyl ether) (Found: C, 74.0; H, 7.15; N, 4.35. $C_{20}H_{23}NO_3$ requires C, 73.8; H, 7.12; N, 4.3%); δ_H($CDCl_3$) 1.4 (3 H, t, J 12, C–Me), 2.52 (3 H, s, N–Me), 3.9 (3 H, s, O–Me), 4.06 (2 H, m, O–CH_2), 6.3 (1 H, s, OH), 6.6 (1 H, d, J 3, 3-H), 6.75 (2 H, s, 8-H and 9-H) and 7.88 (1 H, d, J 3, 1-H); m/z 325 (M^+, 60%); $[\alpha]_D^{22}$ −73.3 (c 0.1, $CHCl_3$). The second eluted compound was 2-fluoroapocodeine **7** (0.25 g, 25%), shown to be identical with an authentic sample.[6]

The third eluted compound was the *bisaporphine* **20** (0.085 g, 8.8%), m.p. 168–170 °C (from diethyl ether) (Found: C, 74.0; H, 6.0; F, 3.25; N, 4.8. $C_{36}H_{35}FN_2O_4$ requires C, 74.66; H, 6.04; F, 3.28; N, 4.83%); δ_H($CDCl_3$) 2.5 (3 H, s, NMe'), 2.58 (3 H, s, NMe), 3.75 (3 H, s, OMe'), 3.85 (3 H, s, OMe), 6.2 (1 H, s, 11-OH), 6.5 (1 H, d, J 3, 3-H), 6.7 (1 H, d, J 12, 3'-H), 6.72 (2 H, s, 8'-H) and 9'-H) 6.9 (1 H, d, J 8, 9-H), 7.1 (1 H, d, J 8, 8-H), 7.75 (1 H, d, J 3, 1-H) and 7.95 (1 H, d, J 12, 1'-H); m/z 578 (M^+, 20%). The fourth eluted compound, morphothebaine **8**, (0.23 g, 23.2%), was identical with an authentic substance prepared from thebaine.[11]

(b) Compound **2** (1.0 g, 3.34 mmol) was dissolved at 0 °C in 99% methanesulfonic acid (10.0 cm^3) and the mixture was kept at room temp. for 2 h; it was then worked up as described above to give the following compounds by column chromatography: 2-ethoxymorphothebaine **11** (0.05 g, 4.6%), 2-fluoroapocodeine **7** (0.42 g, 42%) and the bisaporphine **20** (0.15 g, 15.6%).

(c) To an ethanolic solution (1 cm^3) of *compound* **2** (1.0 g, 3.34 mmol) was added 99%) methanesulfonic acid (5 cm^3) and the mixture was heated at 90–95 °C for 30 min. After cooling to room temp. it was added dropwise to a stirred solution of potassium hydrogen carbonate (20 g) in water (100 cm^3). The resulting precipitate was filtered off, dried and recrystallized from diethyl ether to afford compound **11** (0.85 g, 78%).

(d) Rearrangement of compound **2** (1.0 g, 3.34 mmol) in methanol (1 cm^3) with methanesulfonic acid, as described above, gave the morphothebaine 2-methyl ether **6** (0.78 g, 75%), m.p. 160–161 °C (from acetone–water 1:1), which was identical with an authentic sample synthesized from thebaine (lit.,[8] m.p. 159–160 °C from acetonitrile).

General Procedure for the Rearrangement of Thebaine **1** *in Alcoholic Methanesulfonic Acid.*—To an alcoholic solution (1 cm^3) of thebaine **1** (1.0 g, 0.31 mmol) was added 99% methanesulfonic acid (5 cm^3). The mixture was heated at 90–95 °C for 30 min, and then, after cooling to room temperature, added dropwise to a stirred solution of potassium hydrogen carbonate (20 g) in water (100 cm^3). When methanol was employed the precipitate was filtered off and dried, but in *all* other cases the mixture was extracted with chloroform (3 × 30 cm^3). The combined organic extracts were dried and evaporated to give a crude syrupy mixture of the methyl ether and alkyl ether, which was separated by means of column chromatography (Kieselgel 40, benzene–methanol 9:1). The following compounds were obtained by employing the above procedure.

(a) In methanolic methanesulfonic acid the crude methyl ether **6** (0.99 g, 95%), m.p. 149–151 °C. The crude product was suitable for further chemical transformations without purification.

(b) In ethanolic methanesulfonic acid the first eluted compound was the ethyl ether **11** (0.51 g, 49%) and the second eluted material was the methyl ether **6** (0.12 g, 12%).

(c) In propanolic methanesulfonic acid the first eluted material was the *2-propoxymorphothebaine* **12** (0.65 g, 59.6%) m.p. 75–76 °C (from diethyl ether) (Found: C, 74.1; H, 7.4; N, 4.2. $C_{21}H_{25}NO_3$ requires C, 74.31; H, 7.42; N, 4.13%); δ_H($CDCl_3$) 1.3 (3 H, t, J 14, C–Me), 1.8 (2 H, q, C–CH_2), 2.53 (3 H, s, NMe), 3.91 (3 H, s, OMe), 3.98 (2 H, q, O–CH_2), 6.25 (1 H, s, OH), 6.61 (1 H, d, J 3, 3-H), 6.76 (2 H, s, 8-H and 9-H) and 7.89 (1 H, d, J 3, 1-H); m/z 339 (M^+, 70%); $[\alpha]_D^{22}$ −105 (c 0.1, $CHCl_3$). The second eluted compound was the *methyl ether* **6** (0.16 g, 16%).

(d) In butanolic methanesulfonic acid the first eluted compound was the *2-butoxymorphothebaine* **13** (0.55 g, 48%), m.p. 99–101 °C (from diethyl ether) (Found: C, 74.0; H, 7.5; N, 3.85. $C_{22}H_{27}NO_3$ requires C, 74.75; H, 7.7; N, 3.96%); δ_H($CDCl_3$) 0.98 (3 H, t, J 13, C–Me), 1.5 (2 H, q, C–CH_2), 1.75 (2 H, m, C–CH_2), 2.52 (3 H, s, NMe), 3.91 (3 H, s, OMe), 4.0 (2 H, m, O–CH_2), 6.3 (1 H, s, OH), 6.6 (1 H, d, J 3, 3-H), 6.75 (2 H, s, 8-H and 9-H) and 7.88 (1 H, d, J 3, 1-H); m/z 353 (M^+, 58%); $[\alpha]_D^{22}$ −95 (c 0.1, $CHCl_3$). The second eluent compound was the methyl ether **6** (0.12 g, 12%).

Acknowledgements

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* Rearrangement of thebaine with hydrochloric acid in the presence of alcohols gave the corresponding alkyl ethers of thebenine.[10]

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