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Regioselective O-Demethylation of Aporphines with Methanesulfonic Acid / Methionine: An Efficient One-Pot Transformation of Thebaine to (R)(-)-2-Methoxyapomorphine

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REGIOSELECTIVE O-DEMETHYLATION OF APORPHINES WITH METHANESULFONIC ACID / METHIONINE: AN EFFICIENT ONE-POT TRANSFORMATION OF THEBAINE TO (R)(-)-2-METHOXYAPOMORPHINE

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Abstract: 2-Methoxyapomorphine (**4**) was obtained by the rearrangement of thebaine (**1**) with methanesulfonic acid in the presence of methionine, a reagent system suitable for the regioselective O-demethylation of aporphine derivatives.

In a recent paper Andre et al [1] described that the methanesulfonic acid / methionine reagent system is quite suitable for the O-demethylation of opioid alkaloids, and most particularly, for the preparation of the analogues of Naloxone. By applying this reagent for the O-demethylation of thebaine (**1**) a morphinane → aporphine rearrangement was observed, to result in

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the morphothebaine (2). These authors have claimed that the same compound produced upon the action of methanesulfonic acid in the absence of methionine. However, these findings have not been supported by the description of the reaction conditions, and the isolated products have not been characterized.

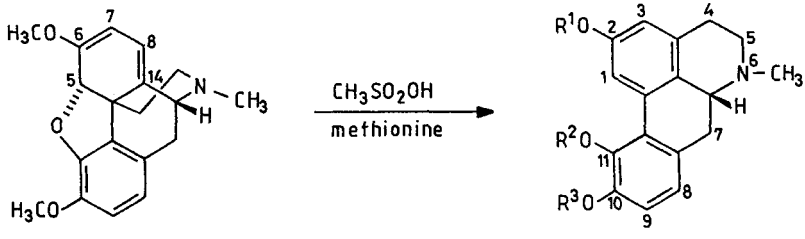
It is well-known that the rearrangement of thebaine with methanesulfonic acid gives[2] 2,10-dimethoxy-11-hydroxyaporphine (3), and thus when the formation of morphothebaine (2) is observed, O-demethylation at position C-2 has also occurred.

We repeated the above reaction under the conditions claimed as optimal[1] for another substrates (30 equivalents of methanesulfonic acid, 1.5 equivalents of methionine, 40 °C, 24 hrs). Column chromatographic separation of the two-component reaction mixture resulted in 2,10-dimethoxy-11-hydroxyaporphine (3) and 2-methoxyapomorphine (4) in a 3:7 ratio. Thus, under the applied reaction conditions the rearrangement is accompanied, primarily, by O-demethylation at C-10. Similar results were obtained when thebaine (1) was first converted with methanesulfonic acid (90 °C, 30 min.) into 2,10-dimethoxy-11-hydroxyaporphine (3), followed by treatment of the cooled reaction mixture with 1.5 equivalents of methionine at 40 °C for 24 hrs. Morphothebaine (2) could not be isolated in either of the two cases.

When the reaction was accomplished in the presence of 2.5 equivalents of methionine (90 °C, 30 min.) a 1:1 mixture of 2-methoxyapomorphine (4) and trihydroxyaporphine (5) was obtained. By conducting the reaction for 6 hrs at the same temperature the

Table The reaction of thebaine (1) with methanesulfonic acid in the presence of methionine

Time (h)	Temp (°C)	Methionine equivalents	Product ratio			
			2	3	4	5
24	40	1.5	-	3	7	-
20	40	1.7	-	2	8	-
0.5	90	2.5	-	-	1	1
6	90	2.5	-	-	1	3



1

	R^1	R^2	R^3
2	H	H	CH_3
3	CH_3	H	CH_3
4	CH_3	H	H
5	H	H	H

product-ratio changed to 1:3 and trihydroxyaporphine (5) was isolated in a yield of 55 %. By treating thebaine (1) in the presence of 1.7 equivalents of methionine at 40 °C for 20 hrs the hydrochloride salt of 2-methoxyapomorphine could be isolated with 60 % yield without column chromatographic purification. This finding is quite attractive since Neumeyer et al[3] prepared this efficient D_2-agonist compound from thebaine in a five-step reaction sequence with an 18 % overall yield.

It is thus established that, by the variation of the reaction conditions, the methanesulfonic acid / methionine reagent system is an effective and selective reagent for the O-demethylation of aporphine derivatives, as well. Investigation of the effectiveness of this reagent for the regio and chemoselective transformation of another alkalolid derivatives, including morphothebaine-2-alkyl ethers[4], is now in progress.

EXPERIMENTAL

99 % $MeSO_3H$ was purchased from Aldrich-Chemie, DL-methionine and Kieselgel 60 were purchased from Reanal (Budapest). Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin layer chromatography was performed on precoated Merck 5554 Kieselgel 60 F_{254} foils using a 8:2 benzene-methanol developing system. The spots were visualized with Draggendorf's reagent. ^1H 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.

(R)(-)-2-Methoxyapomorphine Hydrochloride (**4**.HCl)

A mixture of thebaine (**1**; 1.0 g, 3.2 mmol) and DL-methionine (0.81 g, 5.44 mmol) in methanesulfonic acid (9.2 g, 96 mmol) was stirred at 40 °C for 20 h under N_2. After cooling to room temperature, the reaction mixture was diluted with 30 mL of water and the pH was adjusted to 8 with concentrated aqueous ammonia. The mixture was extracted with AcOEt (4 x 20 mL). The combined organic layer was washed with water and dried over anhydrous $MgSO_4$, filtered and then evaporated to dryness. The product was converted to the HCl salt with HCl/ethanol to yield 0.64 g (60 %) of 4.HCl Mp: 249-251 °C dec., $[\alpha]_D^{25}$-112 (C = 0.2 MeOH) [Lit.[3] Mp: 248-250 °C dec., $[\alpha]_D^{25}$-115 (C = 0.2 MeOH)] ^{1}H NMR (CD_3OD, TMS): δ 2.7 (t, 1H); 2.8-3.0 (m, 1H); 3.0 (s, 3H, NCH_3); 3,2-3.4 (m, 5H); 3.6 (m, 1H); 3.9 (s, 3H, OCH_3); 6.5 (d, J = 2 Hz, 1H, 3-H); 6.3 (dd, 2H, Ar-H); 7.9 (d, J = 2 Hz, 1H, 1-H).

(R)(-)-2,10,11-Trihydroxyaporphine Hydrobromide (**5**.HBr)

A mixture of thebaine (**1**; 1.0 g, 3.2 mmol) and DL-methionine (1.2 g, 8 mmol) in methanesulfonic acid (9.2 g, 96 mmol) was stirred at 90 °C for 6 h under N_2, it was then worked up as described above for **4**.HCl. The two-component crude product was separated by means of column chromatography (Kieselgel 60, benzene-methanol 9:1). The first eluted material was 2-methoxy-apomorphine (**4**, 0.16 g 17 %). The second eluted compound was trihydroxyaporhine which was converted to the HBr salt with 48 % aqueous HBr to yield 0.64 g (55 %) of 5.HBr. Mp: 251-253 °C [Lit.[5] Mp: 253-254 °C) ^{1}H NMR (CD_3OD, TMS): δ 2.3-2,7 (m, 3H);

2.5 (s, 3H, N-CH_3); 3.0-3.2 (m, 4H); 6.5 (d, J = 2 Hz, 1H, 3-H); 6.6 (dd, 2H, Ar-H); 7.8 (d, J = 2 Hz, 1H, 1-H).

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