Synthesis of sulfide- and disulfide-type bisaporphines from thebaine

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Dedicated to Professor Sándor Antus on his 60th birthday

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Abstract

The rearrangement reaction of thebaine (**1**) with methanesulfonic acid, in the presence of hydrogen sulfide, resulted in a sulfide-type bisaporphine **13**, instead of the expected thiol **12**. The acidic hydrolysis of the thiocyanato derivatives **3, 9, 20** and **21**, obtained from thebaine (**1**), as well as the reduction of **9** and **21** with sodium borohydride yielded disulfide-type bisaporphines **16** and **23**.

Keywords: Morphinandienes, aporphines, bisaporphines, sulfide, disulfide

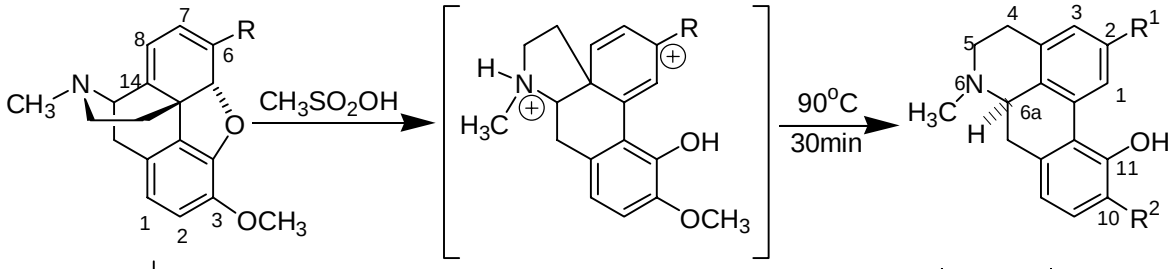
Introduction

The naturally occurring opium alkaloid thebaine (**1**) is a suitable starting material in the synthesis of several 2-substituted dopaminergic aporphines[1]. The key step for the conversion is the rearrangement of thebaine (**1**) with methanesulfonic acid that results in 2,10-dimethoxy-11-hydroxyaporphine (**5**), *via* the formation of a methoxonium ion intermediate (**4**). In the presence of water, the product of the rearrangement is morphothebaine[2] (**6**). With the aim of studying the structure-activity relationships of aporphines, three methods were considered for the formation of compounds containing appropriate functional groups.

According to the first possibility[3], the product **5** of the acid-catalyzed rearrangement of thebaine (**1**) is converted to 2,10,11-trihydroxyaporphine (**7**), or to, for example, 2-fluoroapomorphine (**8**) by protection of the hydroxy groups in the 10- and 11-positions.

According to another method,[4,5] thebaine (**1**) is converted to the appropriately substituted morphinandiene, for example to 6-fluoro-6-demethoxythebaine (**2**) or 6-thiocyanato-6-demethoxythebaine (**3**), followed by acid-catalyzed rearrangement to the corresponding aporphine derivatives **8** and **9**.

The third route, based on our experience[6,7] using the acid-catalyzed rearrangement of thebaine (**1**) in the presence of alcohols and thiols, leads directly to the desired 2-alkoxy- and 2-alkylthioaporphines (for example **10**), which is the result of the nucleophilic substitution of the methoxonium ion intermediate **4**. The excess of thiol results in the cleavage of the 10-methoxy group, where thiols play an important role as methyl acceptors. Thus, from thebaine (**1**) in the presence of ethanethiol, 2-ethylthioapomorphine (**11**) can be obtained in one pot, in high yield (Scheme 1).



	R
1	OCH_3
2	F
3	SCN

	R^1	R^2
5	OCH_3	OCH_3
6	OH	OCH_3
7	OH	OH
8	F	OH
9	SCN	OCH_3
10	SEt	OCH_3
11	SEt	OH
12	SH	OCH_3

Scheme 1

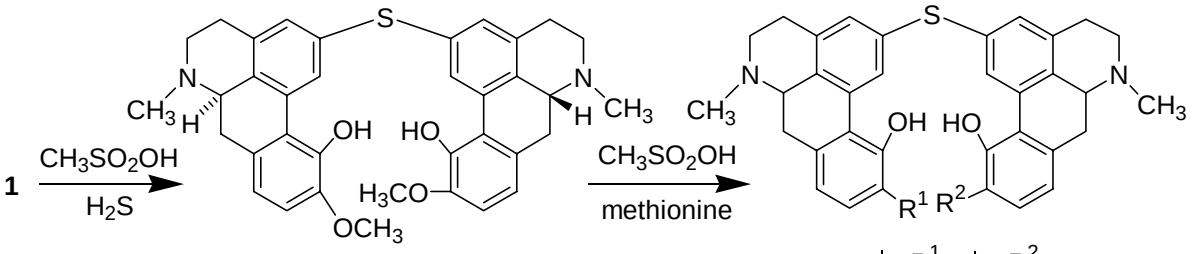
Our recent papers have focused on the synthesis of 2-mercaptoaporphines **(12, 22)**. In the course of our work instead of the desired thiols **12, 22**, sulfide- **14, 15** and disulfide-type **16, 23** bisaporphines were isolated.

Results and Discussion

The acid-catalyzed rearrangement of thebaine (**1**) was carried out with methanesulfonic acid, in the presence of hydrogen sulfide, at 100 °C. Instead of the desired 2-mercaptoapocodeine (**12**), a sulfide-type bisaporphine **13** was isolated.

It is likely that, during the rearrangement, nucleophilic substitution of the 2-methoxy group occurs and the resulting 2-mercaptoapocodeine (**12**), a good nucleophile, reacts immediately with the methoxonium ion intermediate **4** to afford the sulfide **13**. The structure of the product was confirmed by elemental analysis and LC-MS. According to the ^{1}H-NMR spectrum, the

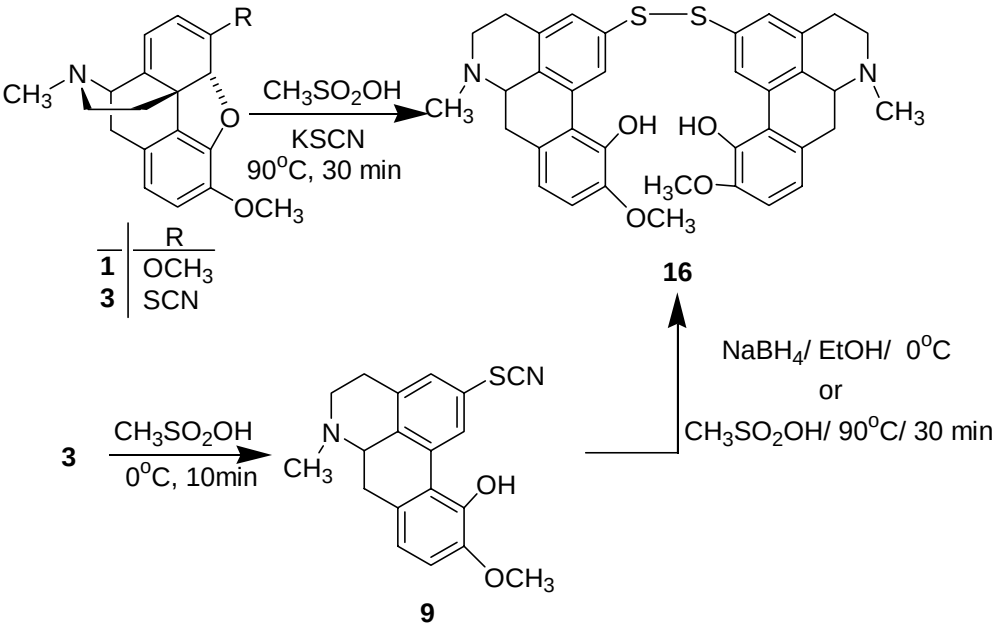
structure of **13** is symmetrical. The O-demethylation of this compound was carried out with methanesulfonic acid, in the presence of methionine, at 100 °C. The reaction proceeded in two steps, and an asymmetrical, partially O-demethylated derivative **14** could be isolated by quenching the process after 30 minutes. The reaction was completed after 2 hours, resulting in the symmetrical bisapomorphine **15** (Scheme 2).



	R^1	R^2
14	OH	OCH_3
15	OH	OH

Scheme 2

The hydrolysis or reduction of 2-thiocyanatoapocodeine (**9**), previously synthesized from thebaine in a multi-step process,[5] offered further possibilities for the formation of the thiol function in the 2-position. Hydrolysis with methanesulfonic acid, at 90 °C, gave a low yield product which was shown to be a disulfide-type bisaporphine **16**, instead of the expected thiol **12**. Surprisingly, the reduction of the thiocyanato derivative **9** with sodium borohydride in ethanol afforded also the disulfide **16**.



	R
1	OCH_3
3	SCN

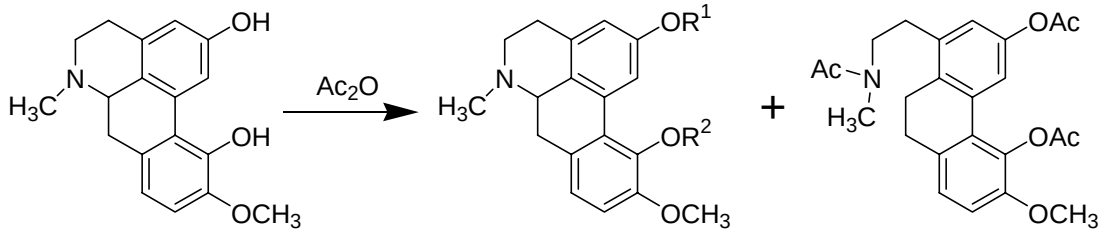
Scheme 3

The disulfide was isolated also in the rearrangement reaction of thebaine with methanesulfonic acid, in the presence of potassium thiocyanate. From the multi-component reaction mixture of the latter one-pot reaction, the disulfide could be isolated in low yield (Scheme 3).

The determination of the structure of disulfide **16** was difficult because, according to the elemental analysis, ^{1}H-NMR and MS spectra, the compound could have a thiol structure **12**. To decide the thiol or disulfide question, the results of an acylation reaction were used.

During the acylation of morphothebaine (**6**), which has a hydroxy-group in the 2-position instead of the mercapto-group of **12**, the formation of various products was described in the literature depending on the reaction conditions. Refluxing with acetic anhydride, in the presence of sodium acetate formed the ring opened phenanthrene[8] **19**, while the product with acetic anhydride, in the presence of pyridine, at room temperature, was diacetylmorphothebaine[9] (**18**).

According to our model experiments, using the selective acylation method of Welsh[10] (20^{o}C , Ac_2O, $NaHCO_3$, H_2O) from morphothebaine, in addition to the diacetyl derivative **18,** the unknown 2-acetoxyapocodeine (**17**) was isolated also, as the main product (Scheme 4).



6

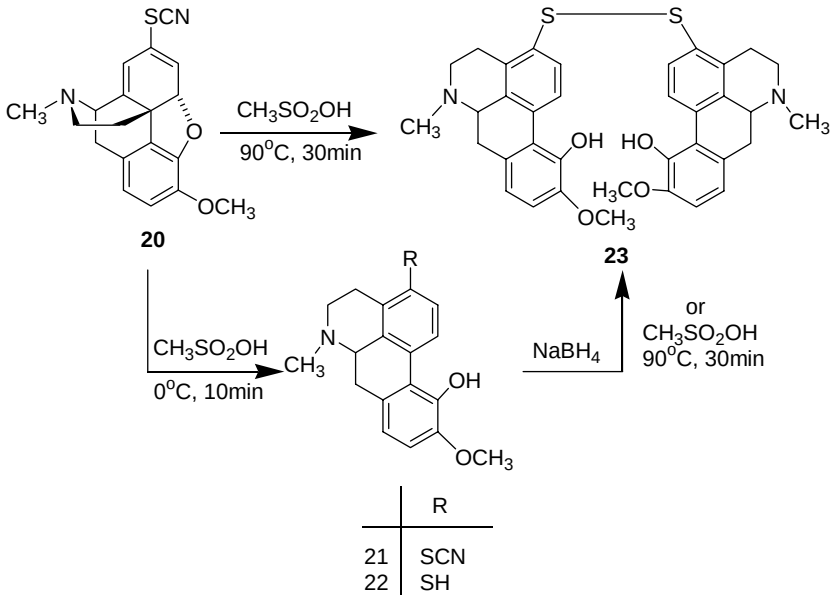
	R^1	R^2
17	Ac	H
18	Ac	Ac

19

Scheme 4

From the Welsh acylation reaction of **16**, unreacted starting material was isolated, which indicated the disulfide structure for our product since there was no formation of the 11-O-acetyl derivative, presumably due to the steric effect of the bisaporphine.

The **9**→**16** transformation requires a revision of our former publication.[5] The product of the acid-catalyzed rearrangement of 7-thiocyanato-6-demethoxythebaine (**20**), followed by acidic hydrolysis, had been identified mistakenly as 3-mercaptoapocodeine (**22**). The product from the reduction of 3-thiocyanatoapocodeine (**21**) with sodium borohydride and the product of the acidic hydrolysis of **21** were found to be identical, and the disulfide structure of the compound **23** was identified similarly to the above-mentioned acylation experiment (Scheme 5).



Scheme 5

Experimental Section

General Procedures. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). Thin layer chromatography was performed on precoated Merck 5554 silica gel 60 F_{254} foils, using a 9:1 dichloromethane/methanol developing system. The spots were visualized with Dragendorff's reagent. Elemental analyses (C, H, N, S) were obtained on a Carlo Erba 1106 analyser. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY spectrometer. Chemical shifts are reported in ppm (δ) from internal $CHCl_3$ (7.26). The coupling constants (*J*) are measured in Hz. Mass spectra were measured with a Finnigan LCQ Classic ion trap mass spectrometer.

Di(apocodeine-2-yl) sulfide (13)

H_2S gas was bubbled through 99% methanesulfonic acid (5 mL) with stirring and external ice cooling, and then to this stirred mixture thebaine (**1**) (1 g, 3.2 mmol) was added. The acidic solution was stirred at 100 °C, for 30 min, with continuous introduction of H_2S into the reaction mixture. After cooling to room temperature, water (50 mL) was added, then the pH was adjusted to 8-9 with 25% ammonia. The reaction mixture was extracted with chloroform/methanol 2:1 (3 x 20 mL), then the organic layer was washed with brine (25 mL), dried with magnesium sulfate, filtered and evaporated in vacuo. The crude product was purified by column chromatography (ethyl acetate/methanol 7:3), to yield pure, solid product 0.49 g (51%), mp 172-175 °C (from diethyl ether), R_f = 0.47 (CH_2Cl_2/MeOH 9:1). ^{1}H NMR: δ_H ($CDCl_3$/CD_3OD 2:1) 8.19 (H-1, H-1',

d, 1.2 Hz), 7.05 (H-3, H-3', d, 1.2 Hz), 6.72 (H-8, H-8', d, 7.5 Hz), 6.67 (H-9, H-9', d, 7.5 Hz), 3.82 (6H, s, O-CH_3), 3.30-2.96 (8H, m, CH_2), 2.73-2.45 (6H, m, CH_2), 2.54 (6H, s, N-CH_3). ^{13}C NMR: δ_C (DMSO) 147.3, 144.0, 133.7, 133.0, 131.7, 129.2, 128.8, 128.2, 126.3, 118.6, 111.5, 60.7, 56.1, 50.8, 40.7, 30.2, 25.4, 18.5. Anal. Calcd. for $C_{36}H_{36}N_2O_4S$ (592.75): C, 72.95; H, 6.12; N, 4.73; S, 5.41. Found: C, 73.14; H, 6.10; N, 4.74; S, 5.40. LC-MS (m/z): 593 (M+1, 100%), 550 (M-42, 20%), 519 (M-73, 12%), 297 (M-295, 40%); $[\alpha]_D^{20}$ = -159.4 (c = 0.22, MeOH).

O-Demethylation of 13

Methionine (1 g, 6.7 mmol) was added to a stirred solution of **13** (1 g, 1.7 mmol) in methanesulfonic acid (10 mL). The reaction mixture was kept at 100 ^{o}C, for 90 min. The work up and separation of the two-component reaction mixture were carried out as described in the synthesis of **13**. The column chromatographic purification was accomplished in chloroform/methanol 8:2 eluent system.

The first eluted product is **apocodeine-2-yl(apomorphine-2-yl) sulfide 14** (oil, 0.3 g), R_f = 0.29 (CH_2Cl_2/MeOH 9:1).). ^{1}H NMR: δ_H ($CDCl_3$/CD_3OD 2:1) 8.19 (H-1, H-1', d, 1.2 Hz), 7.05 (H-3, H-3', d, 1.2 Hz), 6.72 (H-8, d, 7.5 Hz), 6.67 (H-9, d, 7.5 Hz), 6.65 (H-8', d, 8.0 Hz), 6.58 (H-9', d, 8.0 Hz), 3.82 (6H, s, O-CH_3), 3.30-2.96 (8H, m, CH_2), 2.73-2.45 (6H, m, CH_2), 2.54 (6H, s, N-CH_3).

The second eluted product is **di(apomorphine-2-yl) sulfide 15** (oil, 0.1 g), R_f = 0.16 (CH_2Cl_2/MeOH 9:1). ^{1}H NMR: δ_H ($CDCl_3$/CD_3OD 2:1) 8.19 (H-1, H-1', d, 1.2 Hz), 7.05 (H-3, H-3', d, 1.2 Hz), 6.65 (H-8, H-8', d, 8.0 Hz), 6.58 (H-9, H-9', d, 8.0 Hz), 3.30-2.96 (8H, m, CH_2), 2.73-2.45 (6H, m, CH_2), 2.54 (6H, s, N-CH_3). ^{13}C NMR: δ_C (DMSO) 144.9, 143.3, 133.7, 133.4, 131.5, 129.2, 128.9, 128.1, 124.6, 118.6, 114.8, 61.0, 50.9, 40.8, 30.2, 25.4, 18.5; LC-MS (m/z): 565 (M+1, 75%), 522 (M-42, 10%), 491 (M-73, 12%), 283 (M-281, 100%).

Di(apocodeine-2-yl) disulfide (16). (a) $NaBH_4$ (0.7 g, 18.5 mmol) was added gradually to a stirred solution of 2-thiocyanatoapocodeine[5] (**9**) (1 g, 3.0 mmol) in abs. methanol (45 mL). After refluxing for 30 min, the reaction mixture was diluted with water (120 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine (50 mL), filtered and evaporated in vacuo. The crude product was purified by column chromatography (ethyl acetate/methanol 7:3), to afford pure **16** (0.35 g, 38%), mp 162-165 ^{o}C (from diethyl ether), R_f = 0.5 (CH_2Cl_2/MeOH 9:1). ^{1}H NMR: δ_H ($CDCl_3$) 8.49 (H-1, H-1', d, 1.2), 7.24 (H-3, H-3', d, 1.2 Hz), 6.75 (H-8, H-9, H-8', H-9', s), 6.57 (11-OH, 11'-OH), 3.90 (6H, s, O-CH_3), 3.26-2.95 (8H, m, CH_2), 2.76-2.41 (6H, m, CH_2), 2.53 (6H, s, N-CH_3). Anal. Calcd. for $C_{36}H_{36}N_2O_4S_2$ (624.81): C, 69.20; H, 5.81; N, 4.48; S, 10.26. Found: C, 69.22; H, 5.81; N, 4.50; S, 10.25.

(b) Hydrolysis of **9** in methanesulfonic acid: 2-thiocyanatoapocodeine[5] (**9**) (1 g, 3.0 mmol) was dissolved in 99% methanesulfonic acid (5 mL), and the solution was stirred at 100 ^{o}C, for 30 min. The work up and purification were carried out as described in the synthesis of **13** to yield pure **16** (0.15 g, 16%).

c) Rearrangement of **1** in the presence of KSCN: A mixture of thebaine (**1**) (1 g, 3.2 mmol) and potassium thiocyanate (1 g, 10.3 mmol) was added to 99% methanesulfonic acid (10 mL), with ice-cooling. After stirring for 15 min with external ice-cooling, the reaction mixture was kept at 100°C, for 30 min. The work up was carried out as described in the synthesis of **13**. The crude product was purified by column chromatography (acetone/hexane 8:2, following by chloroform/methanol 9:1), to afford pure **16** (0.1 g, 10%).

Di(apocodeine-3-yl) disulfide (23). (a) $NaBH_4$ (0.7 g, 18.5 mmol) was added gradually to a stirred solution of 3-thiocyanatoapocodeine[5] (**21**) (1 g, 3.0 mmol) in ethanol (45 mL). After refluxing for 30 min, the reaction mixture was diluted with water (120 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine (50 mL), filtered and evaporated in vacuo. The crude product was purified by column chromatography (ethyl acetate/methanol 7:3), to afford pure **23** (0.38 g, 41%), mp 162-165 °C (from diethyl ether), R_f = 0.5 (CH_2Cl_2/MeOH 9:1). ^{1}H NMR: δ_H ($CDCl_3$) 8.19 (H-1, H-1', d, 8.0 Hz), 7.54 (H-2, H-2', d, 8.0 Hz), 6.75 (H-8, H-9, H-8', H-9', s), 6.20 (11-OH, 11'-OH), 3.91 (6H, s, O-CH_3), 3.18-2.90 (8H, m, CH_2), 2.62-2.43 (6H, m, CH_2), 2.55 (6H, s, N-CH_3). Anal. Calcd. for $C_{36}H_{36}N_2O_4S_2$ (624.81): C, 69.20; H, 5.81; N, 4.48; S, 10.26. Found: C, 69.18; H, 5.79; N, 4.47; S, 10.27.
(b) **21** (1 g, 3.0 mmol) was dissolved in methanesulfonic acid (5 mL) then the reaction mixture was stirred at 100 °C, for 30 min. The work up and purification were carried out as described in the synthesis of **13** to obtain pure **23** (0.29 g, 32%).

2-Acetoxyapocodeine (17). To a stirred suspension of morphothebaine **6** (1 g, 3.2 mmol) and sodium hydrogen carbonate (20 g) in water (200 mL) was added gradually acetic anhydride (10 g, 97.9 mmol). The reaction mixture was stirred at room temperature for 30 min, then extracted with dichloromethane (3x50 mL). The organic layer was washed with brine (50 mL), dried with magnesium sulfate, filtered and evaporated in vacuo. The crude product was purified by column chromatography (dichloromethane/methanol 9:1) to afford pure **17** (0.21 g, 18%), mp 155-156 °C (from diethyl ether), R_f = 0.61 ($CHCl_3$/MeOH 8:2). ^{1}H NMR: δ_H ($CDCl_3$) 8.01 (H-1, d, 1.2 Hz), 6.82 (H-2, d, 1.2 Hz), 6.75 (H-8, H-9, s), 6.57 (11-OH), 3.88 (3H, s, O-CH_3), 3.26-2.95 (4H, m, CH_2), 2.76-2.41 (3H, m, CH_2), 2.54 (3H, s, N-CH_3), 2.29 (3H, s, CO-CH_3). ^{13}C NMR: δ_C ($CDCl_3$) 169.7, 150.0, 143.3, 134.1, 133.0, 132.2, 130.0, 119.9, 119.7, 119.2, 118.6, 109.5, 62.3, 56.3, 53.0, 44.0, 34.6, 29.4, 21.2. Anal. Calcd. for $C_{20}H_{21}NO_4$ (339.39): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.60; H, 6.22; N, 4.13. $[\alpha]_D^{20}$ = -111.2 (c = 0.12, $CHCl_3$).

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