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FORMATION OF A NEW POLYCYCLIC HETERORING SYSTEM BY THE ACID-CATALYZED REARRANGEMENT OF THEBAINE IN THE PRESENCE OF THIOSALICYLIC ACID

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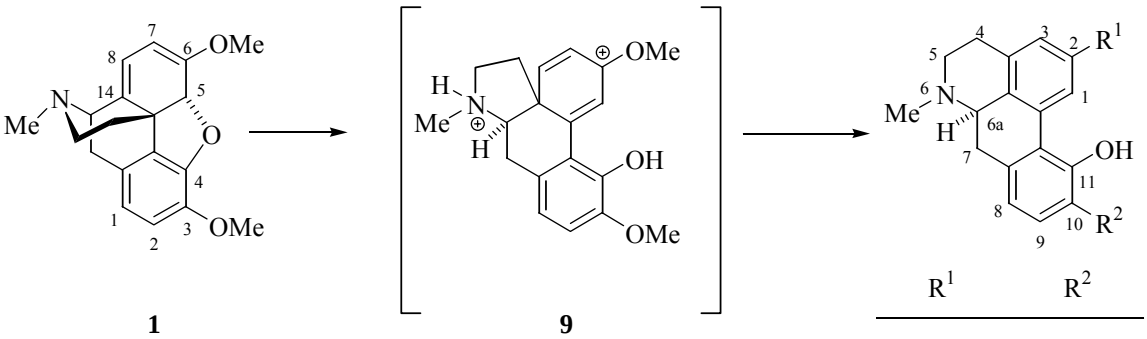
Abstract - The methanesulfonic acid-catalyzed rearrangement of thebaine (**1**) in the presence of thiophenol resulted in 2-phenylthioapocodeine (**7**), whose *O*-demethylation gave 2-phenylthioapomorphine (**8**). An analogous transformation of **1** with thiosalicylic acid furnished the ethers (**6**) and (**11**) together with a polycyclic ketone (**12**) and a polycyclic acetal (**15**). Upon treatment of the acetal (**15**) with acid the thioxanthylium salt (**16**) was prepared.

Recently we have reported[1,2] the conversion of the natural thebaine (**1**) into the dopaminergic alkylthioapocodeines (**2**) and (**3**), and the alkylthioapomorphines (**4**) and (**5**) by means of the application of the methanesulfonic acid/thiol multifunctional reagent system. During this transformation, the ring-rearrangement, introduction of the alkylthio function, and splitting off of the phenolether moiety in three consecutive steps could be realized in a one-pot operation with high yield.



	R^1	R^2
2	SMe	OMe
3	SEt	OMe
4	SMe	OH
5	SEt	OH
6	OMe	OMe
7	SPh	OMe
8	SPh	OH

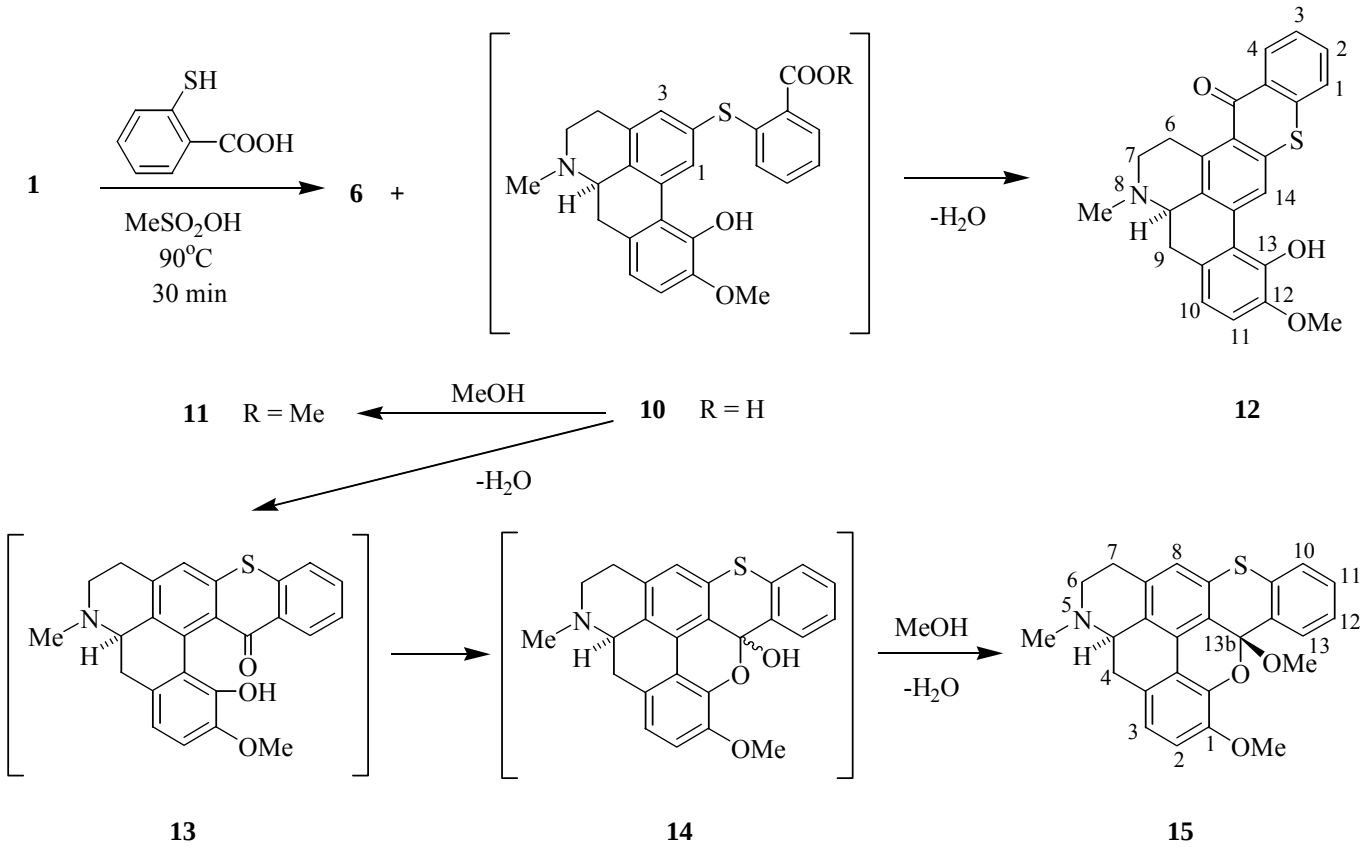
Scheme 1

The key-step of the process is the nucleophilic transetherification of the methoxonium intermediate (**9**) formed[3] from thebaine upon the action of methanesulfonic acid. The primary products (**2** and **3**) of the reaction, carried out at 90°C for 30 min, undergo *O*-demethylation into **4** and **5** upon the action of the alkylthiol during a longer (2 h) reaction time (Scheme 1).

With the goal of synthesizing new arylthioapocodeine and apomorphine derivatives, the methanesulfonic acid-mediated rearrangement of thebaine (**1**) in the presence of thiophenol and thiosalicylic acid was investigated.

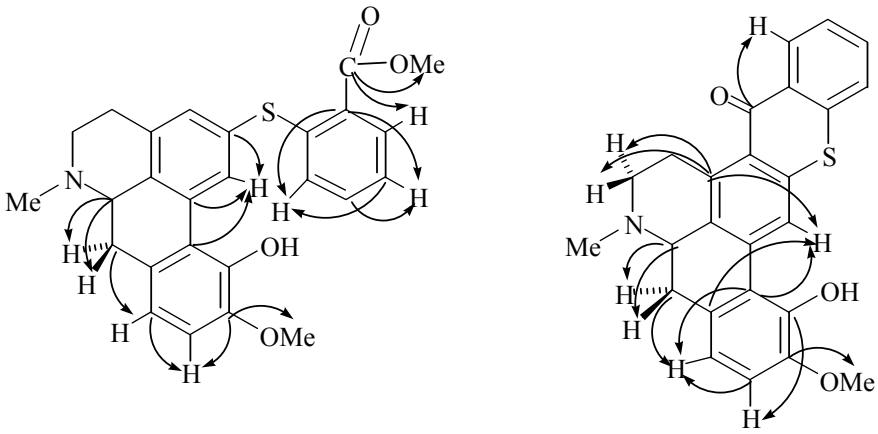
By conducting the acid-catalyzed rearrangement reaction of thebaine (**1**) in the presence of thiophenol at 90°C for 30 min 2-phenylthioapocodeine (**7**) was isolated. Under such conditions *O*-demethylation (i.e. formation of 2-phenylthioapomorphine (**8**)) was not observed even after a longer reaction time (4 h), which indicates the weaker methyl-acceptor properties of thiophenol. Splitting off of the phenol ether moiety was achieved with the methanesulfonic acid/methionine reagent-combination, which was used[4] earlier by us, to furnish **8**.

The rearrangement reaction of thebaine (**1**) with methanesulfonic acid in the presence of thiosalicylic acid resulted in four products (**6**, **11**, **12** and **15**, Scheme 2).



Scheme 2

The first product (5%) of the reaction is 2-methoxyapocodeine (**6**) which is the major product[3] of the acid-catalyzed rearrangement of thebaine in the absence of nucleophiles. The second product (15%) is the ester (**11**), formed from the thiosalicylic acid ether (**10**) with methanol split from the methoxonium ion (**9**) upon transetherification. The structure of the ester (**11**) was unequivocally established by NMR spectral studies. Full ^{1}H- and ^{13}C- resonance assignments were obtained from COSY, TOCSY, HSQC and HMBC spectra. An unambiguos proof is provided by HMBC correlations of the C=O carbon to the protons of one of the methoxy groups as well as to 3'-H aromatic proton. Important HMBC correlation are indicated in Figure 1.



11 **12**

Figure 1

Formation of the ketone (**12**), as the crystalline major product (39%), is explained by the dehydration of the intermediary thiosalicylic acid ether (**10**) followed by ring-closure incorporating carbon C-3. This ring-closure is closely related to the transformation[5] of phenylthiosalicylic acid into thioxanthone. A similar ring-closure involving C-1 and leading to the isomeric ketone (**13**) was also anticipated, however, the structure of the major product (**12**) was unequivocally established by NMR spectral studies. The downfield shift of the 14-H (8.43 ppm), unambigously designated by HMBC correlations C-13a/14-H and C-13a/10-H, supports annelation of the thiochromane ring to the ring of aporphine as shown in Figure 1. The alternative annelation (C-1 ring-closure) would expose the only singlet aromatic proton at a much higher field (cf. 3-H in **11** resonates at 7.29 ppm.). The isomeric ketone (**13**) could not be isolated from the reaction mixture, but an experimental proof for its formation was obtained by the isolation of the cyclic acetal (**15**). This by-product (8%) is supposed to form from the ketone (**13**) *via* the cyclohemiacetal (**14**) (as the primary product), which is then transformed into the cyclic acetal (**15**) with methanol split from the methoxonium ion (**9**) upon transetherification.

Besides NMR and MS spectrometric investigations, the structure of the cyclic acetal (**15**) was also substantiated by means of X-Ray measurements (Figure 2), which demonstrated that the acetalic methoxy group is located above the plain of the ring (i.e. linked at β-position).

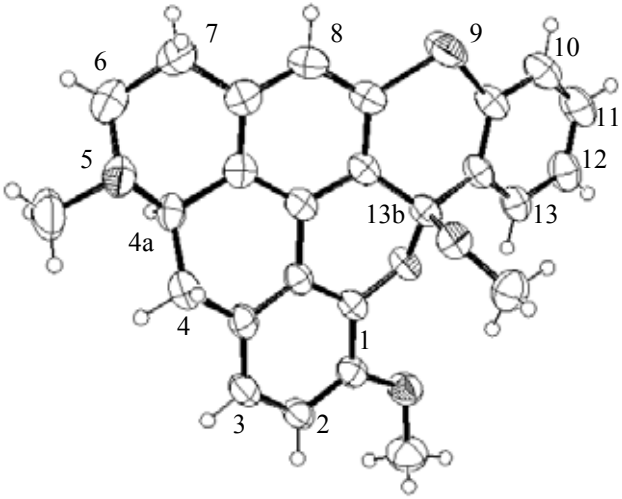
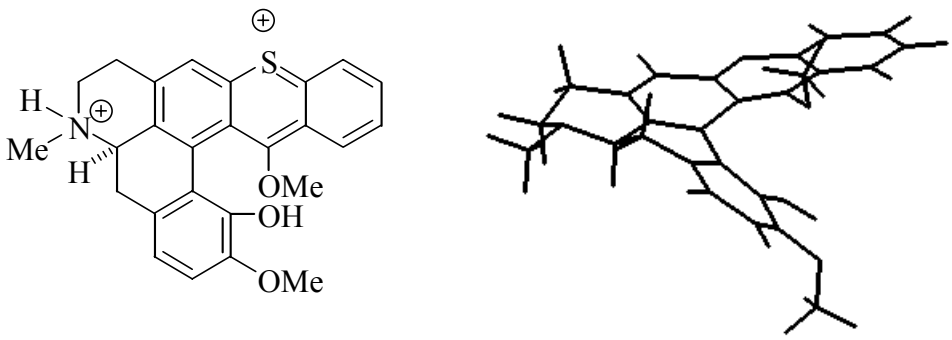


Figure 2

Formation of the α-acetal from the cyclohemiacetal (**14**) is believed also possible. However, from the thioxanthylium ion (**16**), formed from the acetal in the acidic medium, only the β-acetal produced upon the alkaline work-up conditions. This is clearly because the ring carrying the phenolic hydroxyl group hangs below the plain of the rigid ring-system of the thioxanthylium skeleton in **16**, thus permitting the formation of a β-OMe function exclusively, as it is shown in the energy-minimized model calculated by PCMOD v. 6.0 programm (Scheme 3).



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Scheme 3.

This acid-mediated reversible transformation of the acetal (**15**) also proceeds upon treatment with hydrochloric acid, and the red thioxanthylium chloride (**16**) can be isolated. The UV–VIS spectra of the products (**15**) and (**16**) are shown in Figure 3.

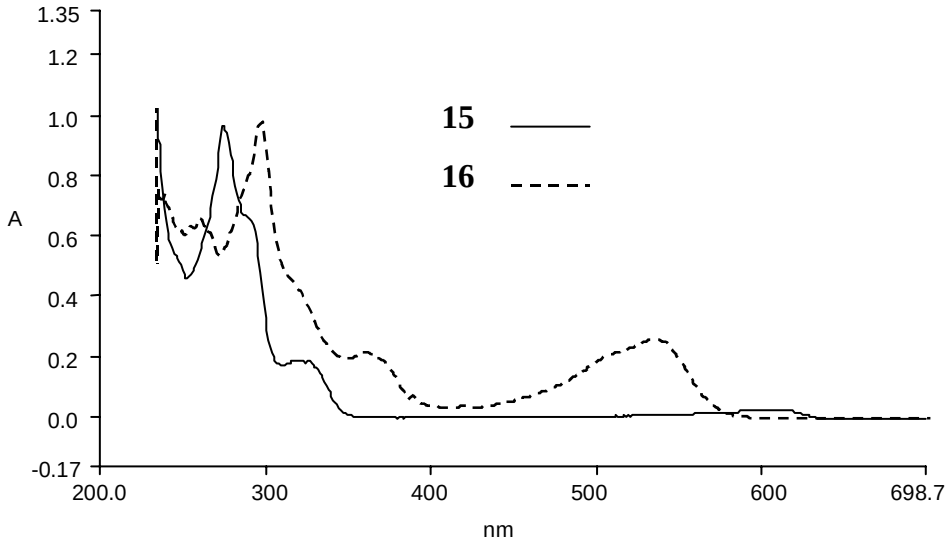

Figure 3

EXPERIMENTAL

General: Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin layer chromatography was performed on precoated Merck 5554 Kieselgel 60 F254 foils using a 9:1 chloroform-methanol developing system. The spots were visualized with Dragendorff's reagent. Optical rotations were carried out by using a Perkin Elmer 311 polarimeter. IR spectra were recorded on Perkin-Elmer 283 B spectrometer. ^{1}H and ^{13}C NMR experiments were run either at 200/50 MHz, or 500/125 MHz Bruker spectrometer for solution as indicated. The chemical shifts are referenced to internal TMS (^{1}H) or to residual solvent signals (^{13}C). MS spectra were obtained with a VG–TRIO–2 spectrometer. X-Ray data were collected with an Enraf Nonius MACH3 diffractometer.

Rearrangement of thebaine (1) with methanesulfonic acid in the presence of *S*-nucleophiles – General procedure: To a mixture of the appropriate thiol (8 mmol) and thebaine (**1**) (1 g, 3.2 mmol) 99% methanesulfonic acid (6 mL) is added under external ice-cooling. The reaction mixture is heated at 100°C for 30 min, then cooled to rt, and poured onto ice-water (100 mL). The pH of the mixture is adjusted to 8 – 9 with concentrated ammonium hydroxide and extracted with chloroform (3x15 mL). The

combined chloroform solution is dried over $MgSO_4$,, concentrated, and the products are purified by means of column chromatography (Kieselgel, eluent; 8:2 chloroform–methanol).

2-Phenylthioapocodeine (7): From **1** and thiophenol. Yield: 0.6 g (48.0%); mp 90 – 95°C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.4 (s, 3H, NMe), 3.7 (s, 3H, 10-OMe), 2.5 – 3.1 (m, 7H, CH), 6.4 (s, 1H, 11-OH), 6.6 (s, 2H, 8-H and 9-H), 7.0 (d, 1H, $J_{1,3}$ = 4.2, 3-H), 7.1 – 7.4 (m, 5H, S-Ph), 8.3 (d, 1H, $J_{1,3}$ = 4.2, 1-H). MS (70 eV), m/z (%) 389 (50) [M^+]. Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.01; H, 5.95; N, 3.60; S, 8.23. Found: C, 74.1, H, 5.9, N, 3.60; S, 8.3.

2-Phenylthioapomorphine (8): From **1** and thiophenol with the following addition: after 30 min reaction time methanesulfonic acid (6 mL) and methionine (1 g, 0.67 mmol) are added to the hot reaction mixture, and it is heated at 100 °C for additional 2 h. Work-up is carried out as described in the general procedure. Yield: 0.2 g (16.6%); HCl salt mp 225 – 235°C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.6 – 3.2 (m, 7H, CH), 5.2 (s, 2H, 10-OH, 11-OH), 6.6 (s, 2H, 8-H and 9-H) , 7.0 (d, 1H, $J_{1,3}$ = 4.1, 3-H) , 8.3 (d, 1H, $J_{1,3}$ = 4.1, 1-H), 7.2 – 7.4 (m, 5H, S-Ph). MS (70 eV), m/z (%) 375 (75) [M^+]. Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73; S, 8.54. Found: C, 73.6; H, 5.6; N, 3.6; S, 8.6.

Reaction of thebaine (1) with thiosalicylic acid

The reaction of **1** (4 g) in the presence of thiosalicylic acid was carried out as described in the general procedure. After pouring onto ice-water the mixture is alkalized and the resulting precipitate is filtered off and dried. Recrystallization of the crude product (5.3 g) from a chloroform – methanol mixture furnished the yellow, crystalline cyclic ketone (**12**). The mother liquor is concentrated, dissolved in ethyl acetate, and the solution is acidified with 10% HCl in ethanol. The red hydrochloride salt precipitated is a mixture of the cyclic acetal (**15**) and 2,10-dimethoxy-11-hydroxyaporphine (**6**). This salt-mixture is dissolved in water, alkalized, and extracted with chloroform. The combined chloroform solution is concentrated, and the two products separated by means of column chromatography. The ethyl acetate mother liquor of the hydrochloride salts is alkalized with concentrated ammonium hydroxide, dried, and concentrated. Following column chromatography the methyl ester (**11**) is obtained.

Physical data of the isolated compounds:

(8a*R*)-13-Hydroxy-12-methoxy-8-methyl-5,6,7,8,8a,9-hexahydronaphtho[3,2,1-*ij*]thiochromeno-[3',2'-*f*]isoquinolin-5-one (12) (cyclic ketone): Yield: 2.08 g (38.9%), mp 140 – 145°C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.35 (m, 1H, 7-H_{ax}), 2.56 (s, 3H, NMe), 2.59 (d, 1H, $J_{9ax,9eq}$=11.9, 9-H_{ax}), 3.07-3.18 (m, 3H, 8a-H,9-H_{eq}, 9-H_{ax}), 3.50 (d, 1H, $J_{6ax,6eq}$ =17.8, 6-H_{ax}), 3.65-3.82 (m, 1H, 6-H_{eq}), 3.91 (s, 3H, OMe), 6.76 (d, 1-H, $J_{10,11}$=8.1, 11-H), 6.78 (d, 1H, $J_{10,11}$=8.1, 10-H), 7.4 (dt, 1H, 2-H), 7.44 (d, 1H, $J_{1,2}$=8.3, 1-H), 7.52 (dt, 1H, 3-H), 8.40 (d, 1H, $J_{3,4}$=8.3, 4-H), 8.43 (s, 1H, 14-H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 30.5 (6-C), 34.1 (9-C), 44.0 (NMe), 52.9 (7-C), 56.3 (OMe), 63.3 (8a-C), 110.5 (11-C), 118.5 (8-C),

118.8 (13a-C), 125.0 (14-C), 125.0 (1-C), 125.6 (13b-C), 125.8 (2-C), 129.5 (4-C), 131.8 (3-C), 135.2 (9a-C), 130.6, 131.8, 133.9, 136.2 (4a-C, 5a-C, 14a-C, 15a-C), 143.9 (13-C), 146.0 (12-C), 182.1 (5-C). IR (KBr): $\nu_{C=O}$ 1624 cm^{-1}. MS (70 eV), m/z (%) 415 (100) [M^+]. Anal. Calcd for $C_{25}H_{21}O_3NS$: C, 72.20; H, 5.05; N, 3.37; S, 7.70. Found: C, 72.1; H, 5.0; N, 3.4; S, 7.7. $[\alpha]_D^{20}$ –108.7 ^{o} (c = 0.675, $CHCl_3$).

(4a*R*,13b*S*)-1,13b-Dimethoxy-5-methyl-4,4a,5,6,7,13b-hexahydrobenzo[8',9']thiochromeno-[2",3",4"-*f'g'*]isochromeno[6,5,4-*def*]quinoline (15) (cyclic acetal).

The first-eluted product of the chromatographic separation is crystallized from dry ether to give pure **15**. Yield: 0.44 g (8.2%), mp 150°C (decomp). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.6 (s, 3H, NMe), 2.7 – 3.6 (m, 7H, CH), 3.1 (s, 3H, 13b-OMe), 4.0 (s, 3H, 1-OMe), 6.9 (s, 2H, 2-H, 3-H), 7.3 (s, 1H, 8-H), 7.4 – 7.5 (m, 2H, 11-H, 12-H), 7.6 (d, 1H, $J_{10,11}$=8.1, 10-H), 8.4 (d, 1H, $J_{12,13}$=8.1, 13-H). MS (70 eV), m/z (%) 429 (5) [M^+]. Anal. Calcd for $C_{26}H_{23}NO_3S$: C, 72.64; H, 5.36; N, 3.26; S, 7.45. Found: C, 72.6; H, 5.4; N, 3.2; S, 7.4. $[\alpha]_D^{20}$ +243.9 ^{o} (c = 0.235, $CHCl_3$).

X-Ray analysis of cyclic acetal (**15**): Orange prism crystals (0.72 x 0.39 x 0.3 mm) of $C_{26}H_{23}NO_3S$, M=429.51, orthorhombic, a = 11.9928(10) Å, b = 12.1491(10) Å, c = 14.8745(10) Å, V = 2167.2(3) $Å^3$, Z = 4, space group: $P2_12_12_1$, ρ_{calc}= 1.316 g cm^{-3}. Data were collected at 293(1) K, Enraf Nonius MACH3 diffractometer, Mo Kα radiation λ = 0.71073 Å, ω-2θ motion, θ_{max} = 28°, 3259 measured, 1814 reflections were unique with I > 2σ(I), decay: 2%. The structure was solved using the SIR-92 software[6] and refined on F^2 using SHELX-97[7] program, publication material was prepared with the WINGX-97 suite[8] , R(F) = 0.0503 and *w*R(F^2) = 0.1214 for 3015 reflections, 280 parameters.
Residual electron density: 0.161/ – 0.197 e/$Å^3$.

2,10-Dimethoxy-11-hydroxyaporphine (6) The second-eluted product of the chromatographic separation is crystallized from a mixture of acetone and water to give pure **6**. Yield: 0.24 g (4.5%). The physical data of the product are in good agreement with those reportedin the literature.[3]

Benzo[*g*]hexahydroquinolino[4',4a',5'-*a,b*]thioxanthylium chloride (16) (thioxanthylium salt).

A solution of the cyclic acetal (**15**) is treated with 10% HCl in ethanol. Red solid, mp 200°C (decomp) (ethanol-ethyl acetate) ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.0-4.0 (m, 7H, C-H), 3.3 (s, 3H, NMe), 3.5 (s, 3H, 5-OMe), 4.2 (s, 3H, 7-OMe), 6.9 (s, 1H, 6-OH), 7.3 (s, 2H, 8-H, 9-H), 7.4 (d, 1H, $J_{2,3}$=8.1, 2-H), 7.5 (d, 1H, $J_{2,3}$=8.1, 3-H), 7.9 – 8.3 (m, 3H, 4-H, 11-H, 14-H).

2-(11-Hydroxy-10-methoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline-2-sulfonyl)-benzoic acid methyl ester (11) (methyl ester). Yield: 0.80 g, HCl salt mp 131 – 136°C (ethanol). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.65 (s, 3H, NMe), 2.65 – 2.82 (m, 3H, 5-H_{ax}, 7-H_{ax}, 4-H_{ax}), 3.07 – 3.30 (m, 4H, 5-H_{eq}, 7-H_{eq}, 6a-H, 4-H_{eq}), 3.90 (s, 3H, 10-OMe), 3.96 (s, 3H, ester-OMe), 6.75 (d, 1H, $J_{8,9}$=8.1, 9-H), 6.78 (d, 1H, $J_{8,9}$=8.1, 8-H), 6.95 (d, 1H, $J_{5',6'}$=8.3, 6'-H), 7.10 (dt, 1H, 4'-H), 7.22 (dt, 1H, 5'-H), 7.29

(s, 1H, 3-H), 7.97 (d, 1H, $J_{3',4'}$=8.3, 3'-H), 8.49 (s, 1H, 1-H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 28.7 (4-C), 34.1 (7-C), 43.8 (N-Me), 52.1 (ester-OMe), 52.9 (5-C), 56.3 (10-OMe), 62.4 (6a-C), 106.0 (10-C), 109.5 (9-C), 118.6 (8-C), 119.4 (11a-C), 123.9 (4'-C), 126.1 (11b-C), 127.2 (6'-C), 129.3 (7a-C), 129.7 (3a-C), 130.9 (3'-C), 132.3 (5'-C), 133.1 (1'-C), 133.4 (1-C), 134.1 (2-C), 134.4 (3-C), 143.2 (11-C), 143.9 (2'-C), 146.0 (10-C), 166.0 (oxo-C). MS (70 eV), m/z (%) 447 (60) [M^+]. Anal. Calcd for $C_{26}H_{25}NO_4S$: C, 69.72; H, 5.57; N, 3.13; S, 7.15. Found: C, 69.7; H, 5.6; N, 3.1; S, 7.1. $[\alpha]_D^{20}$ –72.1° (c = 0.595, $CHCl_3$).

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