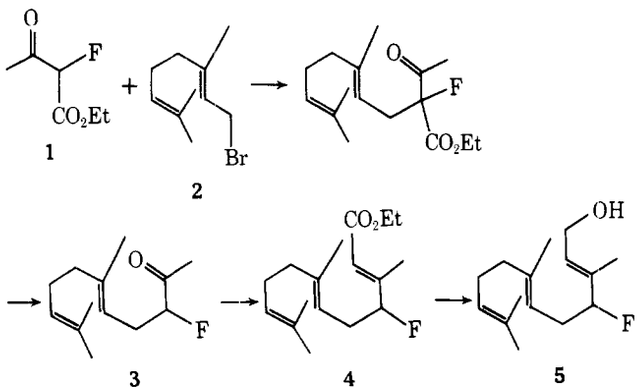

as a 9:1 mixture of 2-*E* and 2-*Z* isomers. The assignment of stereochemistry to the two isomers was based on the relative position of the C-2 proton in their NMR spectra, that of the major (2-*E*) isomer appearing at 5.85 ppm, while that of the minor (2-*Z*) isomer appeared at 5.68 ppm. This downfield shift of the vinyl proton when cis to a fluorinated carbon has been demonstrated in closely related systems.[2,5] The assignment of 2-*E* stereochemistry to the major isomer is consistent with its longer GLC retention time.[13] Ethyl 4-fluorofarnesoate (**4**) was cleanly reduced by lithium aluminum hydride to the previously described 4-fluorofarnesol (**5**).[12]

Experimental Section

All reactions were carried out under strictly anhydrous conditions under a nitrogen atmosphere. Infrared spectra were run as thin films on a Perkin-Elmer 337 spectrophotometer. ^{1}H NMR spectra were taken on a Varian A-60A in $CDCl_3$. Chemical shifts are reported in parts per million downfield from an internal tetramethylsilane standard. Analytical GLC was performed on a Varian 2100 Model equipped with flame ionization detectors and 6 ft × 2 mm i.d. glass columns packed with 3% OV-225 on 100–200 mesh Varaport 30 (18 mL/min N_2 carrier gas). Mass spectra were obtained on an AEI MS-9 adapted to a chemical ionization mode (isobutane gas). Microanalyses were done by the Berkeley Microanalytical Laboratory.

6,10-Dimethyl-3-fluoro-5(*E*),9-undecadien-2-one (3).[6] Ethyl 2-fluoroacetoacetate[8] (1.092 g, 7.37 mmol) was added to 0.40 g (7.40 mmol) of sodium methoxide in 15 mL of anhydrous methanol at 0 °C. After 10 min, 1.54 g (7.1 mmol) of geranyl bromide[10] was added and the mixture stirred for 1 h at ambient temperature, at which time no starting bromide remained (TLC). A solution of 0.40 g of NaOH in 15 mL of H_2O was added and the mixture was refluxed for 3 h at 60 °C. After addition of 50 mL more of water, the mixture was exhaustively extracted with CH_2Cl_2, the extracts dried over $MgSO_4$, and the solvent removed. The crude orange oil thus obtained was bulb-to-bulb distilled (75 °C, 0.20 mm), yielding 0.9532 g (63%) of colorless oil (better than 96% pure by GLC): IR 1730 cm^{-1}; NMR 1.62 and 1.68 (singlets, 9 H, vinyl methyls), 2.00–2.17 (m, 4 H, allyl CH_2), 2.20 (d, J = 4.5 Hz, 3 H, $COCH_3$ coupled to fluorine), 2.53 (doublet of triplets, J = 26 and 6 Hz, 2 H, CH_2CF), 4.67 (doublet of triplets, J = 50 and 6 Hz, 1 H, CHF), and 5.00–5.30 ppm (m, 2 H, vinyl H); CIMS *m/e* 213 (MH^+), 193 ($MH^+ - HF$). Anal. Calcd for $C_{13}H_{21}FO$: C, 73.54; H, 9.97. Found: C, 73.53; H, 9.93.

Ethyl 4-Fluorofarnesoate (4). Reaction of **3** with diethyl 1-carboethoxyethylphosphonate by the procedure of Machleidt[6] gave crude **4** as a 9:1 (by GLC) 2-*E* to 2-*Z* isomeric mixture (retention times at 150 °C: 20.25 and 12.75 min, respectively). Fractional distillation provided pure **4** in 69% isolated yield, the 2-*E*:2-*Z* isomer ratio increasing from about 1:1 in the first fraction to better than 99:1 in the final ones: 2-*E* isomer (bp 108–110 °C, 0.05 mm) IR 1725, 1660 cm^{-1}; NMR 1.27 (t, J = 7 Hz, 3 H, ethyl CH_3), 1.60 and 1.68 (singlets, 9 H, vinyl methyls), 1.97–2.20 (m, 4 H, allyl CH_2), 2.12 (d, J = 2 Hz, 3 H, 3-Me), 2.47 (doublet of triplets, J = 23 and 6 Hz, 2 H, CH_2CF), 4.15 (q, J = 7 Hz, 2 H, CH_2O), 4.82 (doublet of triplets, $J \simeq 50$ and 6 Hz, 1 H, CHF), 4.90–5.33 (m, 2 H, vinyl H), and 5.85 ppm (m, 1 H, vinyl H); CIMS *m/e* 283 (MH^+), 263 ($MH^+ - HF$). Anal. Calcd for $C_{17}H_{27}FO_2$: C, 72.30; H, 9.64. Found: C, 72.07; H, 9.50. The 2-*Z* isomer had similar spectral properties, except for appearance of the C-2 vinyl proton in the NMR at 5.68 rather than 5.85 ppm.

4-Fluorofarnesol (5). Ester **4** was reduced with $LiAlH_4$ in 98% yield as previously described[12] to give **5**: IR 3325 cm^{-1} (OH); NMR 1.60 and 1.67 (singlets, 12 H, vinyl methyls), 1.98–2.17 (m, 4 H, allyl CH_2), 2.37 (doublet of triplets, J = 26 and 6 Hz, 2 H, CH_2CF), 2.93 (m, 1 H, OH), 4.02–4.33 (m, 2 H, CH_2O), 4.73 (doublet of triplets, $J \simeq 48$ and 6 Hz, 1 H, CHF), 4.92–5.30 (m, 2 H, vinyl H), and 5.45–5.82 ppm (m, 1 H, vinyl H); CIMS *m/e* 241 (MH^+), 223 ($MH^+ - H_2O$), and 221 ($MH^+ - HF$). Anal. Calcd for $C_{15}H_{25}FO$: C, 74.95; H, 10.48. Found: C, 74.74; H, 10.43.

Registry No.—**1**, 1522-41-4; **2**, 6138-90-5; **3**, 61812-56-4; **4** (2*Z* isomer), 61812-57-5; **4** (2*E* isomer), 2599-71-5; **5**, 5979-63-5; diethyl 1-carboethoxyethylphosphonate, 3699-66-9.

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Aporphines. 23. Normorphothebaine Derivatives: Synthesis of an Aporphine Nitrogen Mustard

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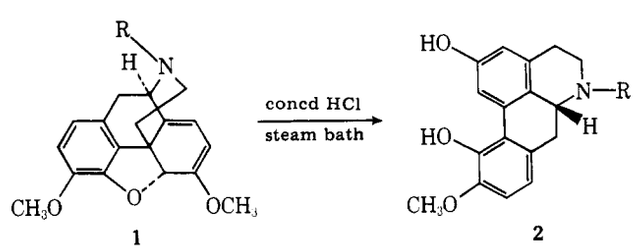
The known CNS activity[1-5] of a number of aporphine alkaloids led to the choice of this tetracyclic ring system for the synthesis of potential CNS penetrating antitumor agents bearing an alkylating function. The selection of normorphothebaine (**2b**) as the carrier base was governed chiefly by its ease of synthesis, its adaptability to large-scale preparations, and the availability of the natural alkaloid, thebaine. In the present communication we wish to report the synthesis of normorphothebaine (**2b**) and its derivatives, **3–5** and **7–10**.

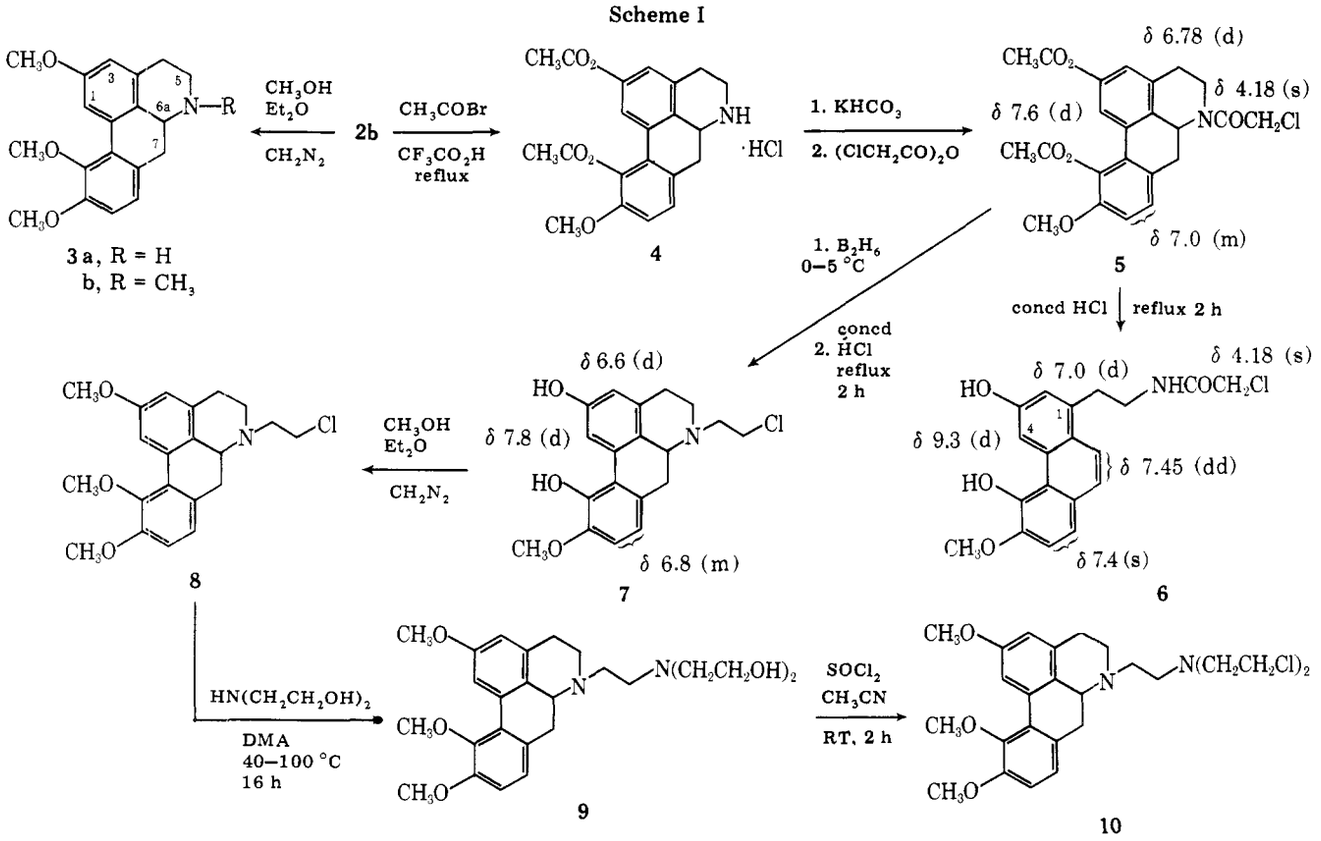
The rearrangement of morphine alkaloids to apomorphine derivatives has been hampered by the requirement of excessively strong acids (80–85% H_3PO_4 or CH_3SO_3H)[5,6] at high



1 **2**

a, R = CH_3
b, R = H

Scheme I



temperatures (145–150 °C), and occurs in only 10–25% yields. On the other hand, the rearrangement of thebaine (**1a**) proceeds in the presence of concentrated HCl at 95–100 °C in a sealed tube to morphothebaine (**2a**) in over 80% yield.[7a-d,8] Although several N-substituted northebaine derivatives have been described,[9] application of this method for the synthesis of derivatives of **2** has not been investigated.

Encouraged by the high yield of **2a** from **1a**, we embarked on the synthesis of the bis(chloroethyl) mustard derivative of normorphothebaine (**10**) shown in Scheme I. N-Demethylation of thebaine (**1a**) to northebaine (**1b**) using diethyl azodicarboxylate was achieved in 60% yield.[10] Rearrangement of northebaine (**1b**) to normorphothebaine (**2b**) was carried out in a sealed pressure bottle in concentrated HCl on a steam bath for 2.5 h. However, when the reaction was carried out in an open vessel, no precipitation of **2a** or **2b** occurred.[8] An attempt to methylate **2b** with diazomethane gave a mixture of **3a** and **3b** in a ratio of 3:1 in an overall yield of 65%. Acetylation of **2b** with CH_3COBr in refluxing CF_3CO_2H[11] gave **4** (45%) which further afforded the *N*-chloroacetyl derivative **5** (99%) by reaction with chloroacetic anhydride. Treatment of **5** with concentrated HCl led to scission of the nitrogen ring to give the phenanthrene analogue **6** (62%) whose structure was confirmed spectroscopically (NMR, UV, and MS). The NMR of **5** reveals that the proton at position 1 appears as a doublet at 7.6 ppm, whereas the proton at position 4 of **6** exhibits a doublet far downfield at 9.3 ppm, which is characteristic of phenanthrenes previously obtained by ring scission of other aporphines.[12-15] The mass spectrum of **5** shows the fragment *m/e* 366 as a result of cleavage of the chloroacetyl group from the molecular ion ($M^+ - COCH_2Cl$), as well as a fragment due to a retro-Diels–Alder, characteristic of the aporphine ring system.[16] On the other hand, **6** shows fragmentation due to the expulsion of $CH_2NHCOCH_2Cl$ (*m/e* 253) arising from cleavage of the carbon–carbon bond β to both the aromatic system and the heteroatom. Ring scission of aporphines to give phenanthrenes has been shown to occur in the presence of alkylating agents under basic conditions.[14,15] The formation of the phenanthrene **6** from **5** under acidic conditions is unique for an aporphine which, in this case, is apparently due to delocalization of the nitrogen electrons by the attached chloroacetyl group.

Reduction of **5** with B_2H_6 in tetrahydrofuran followed by hydrolysis with concentrated HCl afforded **7** (74%).

Treatment of **7** with diazomethane gave the trimethyl ether **8** (62%), which was further converted with diethanolamine in dimethylacetamide to give **9** (99%). The latter was readily converted to the chloro mustard **10** (53%) by reaction with $SOCl_2$.

Optical activity was retained for the entire sequence of reactions from **2b–10.**

Experimental Section

General Methods. Evaporations were carried out in a Büchi rotary evaporator in vacuo at a bath temperature below 50 °C. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Samples for analysis were dried at 10^{-2} mm over silica gel at 55 °C. Thin layer chromatography (TLC) was performed on 7 × 3 cm precoated silica gel 13179, poly(ethylene terephthalate) foils (Eastman Kodak, Rochester, N.Y.) in solvent S_1 (EtOAc–MeOH, 2:1), S_2 (EtOAc–hexane, 1:1), S_3 (EtOAc–MeOH, 3:1), S_4 (EtOAc–MeOH, 2:1), S_5 (EtOAc–hexane, 6:4), S_6 (EtOAc–hexane, 6.5:3.5), and S_7 (EtOAc–MeOH, 9:1). Preparative TLC was carried out on silica gel plates (Analtech, 20 × 20 cm, 2000 μ). Column chromatography was performed on silica gel (Baker, 5-3405, 60–200 mesh). Detection was done in UV light (Mineralight) or with iodine vapors. The IR spectra were measured in $CHCl_3$ or KBr in a Perkin-Elmer Model 700 spectrophotometer. NMR spectra were obtained using a Varian T-60 spectrometer in $CDCl_3$ or CD_3SOCD_3; $(CH_3)_4Si$ was used as an internal standard. The UV spectra were carried out in EtOH using a Beckman DB-G grating spectrophotometer. Mass spectra were determined on a 12-90-G Nuclide mass spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter (Model 141).

Tetrahydrofuran (THF), dimethylacetamide (DMA), and acetonitrile (CH_3CN) were distilled and dried over Linde Molecular Sieves. Thebaine was a product of S.B. Penick & Co., Lyndhurst, N.J.

Normorphothebaine (2,11-Dihydroxy-10-methoxynoraporphine Hydrochloride, 2b). A solution of northebaine[10] (5 g, 0.017

mol) in concentrated HCl (25 mL) was heated on the steam bath in a sealed pressure bottle for 2.5 h. The mixture was cooled and the dark precipitate was filtered and washed with 10 mL of cold concentrated HCl and 20 mL of cold EtOH. The crude product was heated on the steam bath with 50 mL of EtOH for 30 min, filtered, washed with 25 mL of cold EtOH, and dried to give 3.2 g of **2b** as a green, crystalline solid. Yields (60–70%) of **2b** were obtained. The product was washed with a small volume of cold MeOH, and the "wet" solid stirred with aqueous $KHCO_3$ for 2 h. The mixture was filtered, the solid dissolved in 20 mL of MeOH and filtered under N_2 pressure, and the dark filtrate acidified with ethereal HCl. A light tan hydrochloride separated which was homogeneous on TLC (S_1): mp 269–270 °C; NMR (CD_3SOCD_3) δ 7.8 (d, 1 H, C_1 H), 6.8 (m, 2 H, C_8 H and C_9 H), 6.5 (d, 1 H, C_3 H), 3.85 (s, 3 H, CH_3O), 3.2 (m, 7 H); UV max (EtOH) 300 nm (log ϵ 4.02), 278 (4.22), 270 (4.21), 220 (4.65); IR (KBr) 3250, 2920, 2800, 1600 cm^{-1}; $[\alpha]^{23}D$ −119.8° (*c* 0.27, EtOH).

Anal. Calcd for $C_{17}H_{18}ClNO_3$: C, 63.86; H, 5.67; Cl, 11.09; N, 4.38. Found: C, 63.65; H, 5.72; Cl, 11.30; N, 4.29.

2,10,11-Trimethoxynoraporphine (3a) and 2,10,11-Trimethoxyaporphine (3b). A solution of **2b** (442 mg, 1.38 mmol) in MeOH (60 mL) was treated with diazomethane[17] (3 g, 0.076 mol) in Et_2O (300 mL). The solution was stirred for 16 h at room temperature and evaporated to dryness. The residue was dissolved in $CHCl_3$ and washed with 20% aqueous Na_2CO_3 and aqueous brine. The dried (Na_2SO_4) $CHCl_3$ solution was evaporated to dryness, and the resultant oil purified by preparative TLC (S_3). The slower moving band (R_f 0.18–0.41) was recovered to give **3a** (154 mg, 36%). The upper band (R_f 0.42–0.68) gave **3b** (130 mg, 29% yield).

NMR of **3a** ($CDCl_3$) δ 7.95 (d, 1 H, C_1 H), 6.82–6.95 (m, 2 H, C_8 H and C_9 H), 6.65 (d, 1 H, C_3 H), 3.95 (s, 3 H, CH_3O), 3.90 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 2.6–3.3 (m, 7 H), 1.85 (s, 1 H, NH, D_2O exchanges); UV max (EtOH) 272 nm (log ϵ 4.09), 268 (4.10), 305 (3.73).

NMR of **3b** ($CDCl_3$) δ 7.95 (d, 1 H, C_1 H), 6.95 (s, 1 H, C_9 H), 6.82 (s, 1 H, C_8 H), 6.65 (d, 1 H, C_3 H), 3.92 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 3.75 (s, 3 H, CH_3O), 2.6–3.4 (m, 7 H), 2.55 (s, 3 H, NCH_3).

The desired product, **3a**, in MeOH–Et_2O (1:1) was acidified with ethereal HCl, yielding the hydrochloride salt of **3a** as a colorless solid, mp 260–263 °C.

Anal. Calcd for $C_{19}H_{22}ClNO_3$: C, 65.61; H, 6.37; Cl, 10.19; N, 4.03. Found: C, 65.47; H, 6.37; Cl, 10.03; N, 3.96.

2,11-Diacetoxy-10-methoxynoraporphine Hydrochloride (4). A solution of **2b** (8 g, 0.025 mol) in CF_3CO_2H (80 mL) was reacted with CH_3COBr (62.5 g, 0.51 mol) under cooling conditions, and then refluxed for 2.5 h under N_2. The solution was evaporated under reduced pressure, and ether was repetitively distilled from the residue to remove traces of CH_3COBr. The residue in $CHCl_3$ was shaken with aqueous $KHCO_3$, dried (Na_2SO_4), and evaporated. The residue was extracted with Et_2O, washed again with aqueous $KHCO_3$, dried (Na_2SO_4), and evaporated to give the free base of **4** as an oil (5 g, 45%). An analytical sample was obtained by preparative plate TLC (S_4) of 500 mg of the oil. The product was dissolved in Et_2O, washed with 2% aqueous NaOH and H_2O, dried (Na_2SO_4), and converted to the hydrochloride salt (**4**, 200 mg, mp 265 °C dec) using ethereal HCl, $[\alpha]^{23}D$ −70.6° (*c* 0.59, 10% aqueous CH_3CO_2H).

Anal. Calcd for $C_{21}H_{22}ClNO_5$: C, 62.46; H, 5.49; Cl, 8.78; N, 3.47. Found: C, 62.33; H, 5.65; Cl, 8.90; H, 3.47.

Spectra of the free base of **4**: NMR ($CDCl_3$) δ 7.6 (d, 1 H, C_1 H), 6.9–7.1 (m, 2 H, C_8 H and C_9 H), 6.9 (d, 1 H, C_3 H), 3.82 (s, 3 H, CH_3O), 2.6–3.2 (m, 7 H), 2.4 (2 s, 6 H, CH_3CO_2–), 2.2 (s, 1 H, NH, D_2O exchanges); UV max (EtOH) 265 nm (log ϵ 4.19), 310 (3.68); MS *m/e* 367 (M^+), 366 ($M^+ - 1$), 324 ($M^+ - CH_3CO$).

6-Chloroacetyl-2,11-diacetoxy-10-methoxynoraporphine (5). Chloroacetic anhydride (1.74 g, 0.010 mol) in CH_3CN (25 mL) was added dropwise to a solution of **4** (2.5 g, 0.0068 mol) in CH_3CN (60 mL) and Na_2CO_3 (1.4 g 0.013 mol). The mixture was stirred at room temperature for 16 h, filtered, and evaporated to dryness and the residue was dissolved in $CHCl_3$. The organic solution was shaken with 10% aqueous Na_2CO_3, dried (Na_2SO_4), and evaporated to give **5** as a near-colorless solid (3 g, 100%). A 2-g sample was chromatographed on a silica gel column (S_5, 250 mL, and S_6, 200 mL) giving 1.3 g of pure **5**: mp 110–115 °C; NMR ($CDCl_3$), see Scheme I; UV max (EtOH) 265 nm (log ϵ 4.09), 310 (3.38); MS *m/e* 443 (M^+), 401 ($M^+ - CH_3CO$), 366 ($M^+ - COCH_2Cl$); $[\alpha]^{23}D$ −239.5° (*c* 0.58, EtOH).

Anal. Calcd for $C_{23}H_{22}ClNO_6$: C, 62.24; H, 5.12; Cl, 7.98; N, 3.15. Found: C, 62.11; H, 4.95; Cl, 8.12; N, 3.06.

1-(2-Chloroacetamido)ethyl-3,5-dihydroxy-6-methoxyphenanthrene (6). A suspension of **5** (200 mg, 0.45 mmol) in concentrated HCl (5 mL) was refluxed with stirring under N_2. During the heating complete solution occurred, followed by separation of an oil which slowly crystallized. After 2 h the mixture was cooled and filtered, and the product washed with 2 mL of cold concentrated HCl and cold CH_3CN and dried to give **6** (100 mg, 62%): mp 240–241 °C; NMR ($CDCl_3$), see Scheme I; UV max (EtOH) 225 nm (log ϵ 4.09), 242 (4.43), 258 (4.68), 290 (3.92), 310 (4.09), 319 (4.14); MS *m/e* 359 (M^+), 253 ($M^+ - CH_2NHCOCH_2Cl$).

Anal. Calcd for $C_{19}H_{18}ClNO_4$: C, 63.43; H, 5.04; Cl, 9.85; N, 3.89. Found: C, 63.58; H, 5.15; Cl, 9.70; N, 3.87.

6-(2-Chloroethyl)-2,11-dihydroxy-10-methoxynoraporphine Hydrochloride (7). A solution of **5** (1.33 g, 0.003 mol) in THF (30 mL) was treated with 1 M diborane in THF (15 mL, 0.015 mol) at −5 to 0 °C and stirred at 5 °C for 17 h. Excess reagent was destroyed by dropwise addition of H_2O and the mixture evaporated to dryness. The residue was dissolved in $CHCl_3$, and the organic solution washed with H_2O and aqueous brine, dried (Na_2SO_4), and evaporated to give a colorless solid residue (1.32 g). An IR of the solid exhibited no carbonyl absorption at 1640 cm^{-1}, confirming reduction of the amide carbonyl. The product was suspended in concentrated HCl (25 mL) and the mixture refluxed with stirring under N_2 (considerable foaming) for 20 min. The suspension was cooled and filtered, and the solid washed with cold concentrated HCl, cold H_2O, CH_3CN, and Et_2O to give 0.85 g (74%). Recrystallization from a mixture of MeOH/Et_2O (1:2) gave **7** (0.45 g): mp 210–211 °C dec; NMR (CD_3SOCD_3), see Scheme I; UV max (EtOH) 270 nm (log ϵ 4.13), 278 (4.16), 305 (3.94); MS *m/e* 345 (M^+), 344 ($M^+ - H$), 296 ($M^+ - CH_2Cl$), 254 ($M^+ - CH_2NCH_2CH_2Cl$); $[\alpha]^{23}D$ −66.6° (*c* 0.48, EtOH).

Anal. Calcd for $C_{19}H_{21}Cl_2NO_3$: C, 59.70; H, 5.54; Cl, 18.55; N, 3.66. Found: C, 59.84; H, 5.63; Cl, 18.30; N, 3.57.

6-(2-Chloroethyl)-2,10,11-trimethoxynoraporphine Hydrochloride (8). A solution of **7** (300 mg, 0.8 mmol) in MeOH (20 mL) was treated with CH_2N_2 (2 g, 23 mmol) in Et_2O (250 mL). After 1 h the mixture was filtered by N_2 pressure, and allowed to stand for 24 h at 5 °C. The solution was filtered, concentrated, diluted with more MeOH (15 mL), and treated once again with CH_2N_2 (1 g, 12 mmol) in Et_2O (125 mL). After standing for 5 days at 5 °C the solution was filtered, evaporated to dryness, and purified by preparative TLC (S_2) to give the free base of **8** as an oil: NMR ($CDCl_3$) δ 7.95 (d, 1 H, C_1 H), 6.85 (m, 2 H, C_8 H and C_9 H), 6.6 (d, 1 H, C_3 H), 3.90 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 3.60 (s, 3 H, CH_3O), 3.5–2.4 (m, 11 H); UV max (EtOH) 300 nm (log ϵ 3.82), 278 (4.17), 270 (4.19).

The oil was converted to the hydrochloride salt in the usual way, giving **8** (203 mg, 62%), mp 205–209 °C dec, $[\alpha]^{23}D$ −112.7° (*c* 0.49, EtOH).

Anal. Calcd for $C_{21}H_{25}Cl_2NO_3$: C, 61.47; H, 6.14; Cl, 17.28; N, 3.41. Found: C, 61.45; H, 6.20; Cl, 17.12; N, 3.46.

6-[2-Bis(2-hydroxyethyl)aminoethyl]-2,10,11-trimethoxynoraporphine (9). A solution of **8** (0.53 g, 0.0014 mol) and diethanolamine (2 g, 0.019 mol) in dimethylacetamide (30 mL) was heated at 90–95 °C in the presence of KI (0.6 g, 0.0036 mol) for 16 h. The mixture was evaporated under reduced pressure at 50–60 °C, and the residue dissolved in $CHCl_3$. The organic solution was washed with 5 × 20 mL of H_2O, dried (Na_2SO_4), and evaporated to dryness to give **9** (615 mg, 99%): NMR ($CDCl_3$) δ 7.80 (d, 1 H, C_1 H), 6.85 (m, 2 H, C_8 H and C_9 H), 6.60 (d, 1 H, C_3 H), 4.1 (s, 2 H, OH), 3.9 (s, 3 H, CH_3O), 3.8 (s, 3 H, CH_3O), 3.7 (s, 3 H, CH_3O), 3.5 (m, 3 H), 3.3–2.6 (m, 16 H).

Without further purification, **9** was used directly for the preparation of **10**.

6-[2-Bis(2-chloroethyl)aminoethyl]-2,10,11-trimethoxynoraporphine Dihydrochloride Monohydrate (10). A solution of **9** (1.4 g, 0.0032 mol) in CH_3CN (50 mL) was treated at room temperature with $SOCl_2$ (4.1 g, 0.024 mol) dropwise with stirring under N_2. After stirring for 3 h at room temperature the solution was evaporated to dryness, and $CHCl_3$ distilled from the residue several times to remove traces of $SOCl_2$. The residue was dissolved in $CHCl_3$ and acidified with ethereal HCl, giving a dark, gummy precipitate which was triturated with Et_2O until crystallization occurred. The crude product was recrystallized from CH_3CN to give **10** (0.94 g, 53%), mp 235 °C dec, as a monohydrate: NMR ($CDCl_3$ + CD_3SOCD_3) δ 7.70 (d, 1 H, C_1 H), 6.8 (m, 2 H, C_8 H and C_9 H), 6.5 (d, 1 H, C_3 H), 3.1–4.0 (m, 19 H), 3.8 (s, 3 H, CH_3O), 3.7 (s, 3 H, CH_3O), 3.65 (s, 3 H, CH_3O); UV max (EtOH) 298 nm (log ϵ 4.03), 278 (4.28), 270 (4.30); IR (KBr) 3350 (br), 2350 (br), 1600 cm^{-1} (s); $[\alpha]^{23}D$ −75.0° (*c* 0.26, EtOH).

Anal. Calcd for $C_{25}H_{36}Cl_4N_2O_4$: C, 52.64; H, 6.36; Cl, 24.86; N, 4.91; H_2O, 3.15. Found: C, 52.68; H, 6.36; Cl, 24.91, N, 4.91; H_2O, 3.38 (Karl Fischer).

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Registry No.—**1b**, 2579-67-1; **2b**, 61752-20-3; **3a**, 61752-21-4; **3a** HCl, 61752-22-5; **3b**, 61752-23-6; **4**, 61752-24-7; **4** free base, 61752-25-8; **5**, 61752-26-9; **6**, 61752-27-0; **7**, 61752-28-1; **8**, 61752-29-2; **8** free base, 61752-30-5; **9**, 61752-31-6; **10**, 61752-32-7; chloroacetic anhydride, 541-88-8; 6-(2-chloro-1-hydroxyethane)-2,11-diacetoxy-10-thoxynoraporphine, 62139-41-7.

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Electronic Structure of the Bicyclo[5.4.1]dodecapentaenylium Cation

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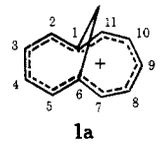
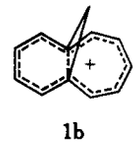
The structure of the bicyclo[5.4.1]dodecapentaenylium cation (**1**) has been the subject of some discussion in the recent literature. Vogel and co-workers[1b] have formulated the ion in terms of a perturbed [11]annulenium system (**1a**), whereas Masamune and co-workers[2] have suggested a benzohomotropenylium structure (**1b**). In a timely x-ray crystallographic



1a



1b

study, Destro, Pilati, and Simonetta[3] have concluded that **1** is quite similar to the neutral bridged [10]annulenes, on the basis of the 1–6 distance, which was found to be 2.299 Å.

In this communication we report a reinvestigation of the ion using the perturbational molecular orbital (PMO) theory,[4] as previously employed[5] in our general study of homoaromaticity.[6] In particular, we focus on the experimental bond lengths found for **1a** by Simonetta and co-workers.[3] In the treatment we adopt the peripheral (annulene) π-electron framework as reference system. In the presence of perturbations $\delta\beta_{kl}$ (to the resonance integrals of bonds k–l), the i–j bond order is changed by an amount δp_{ij}, where[5]

$$\delta p_{ij} = \sum_{kl} \pi_{ij,kl}\, \delta\beta_{kl} \tag{1}$$

and $\pi_{ij,kl}$ is the mutual bond polarizability.

We consider specifically two perturbations to the electronic structure of the peripheral π-electron system which might be responsible for the variations in bond length observed in the bridged annulenes.[7] In the first case we allow for the dislocations in overlap which must occur in these systems, due to the pπ orbital misalignment. Following Heilbronner and co-workers[8] we introduce this factor as a perturbation to the resonance integrals (β_{kl}), which in this treatment take the value $\beta \cos\theta_{kl}$ (where θ_{kl} is the torsional angle about the bond k–l), thus $\delta\beta_{kl} = (\cos\theta_{kl} - 1)\beta$. In the second model account is taken of the possibility of a 1–6 homoaromatic interaction[5] ($\delta\beta_{kl} = \delta\beta_{16}$, where $\delta\beta_{16}$ is in units of β). Thus from eq 1 we obtain

$$\delta p_{ij} = \sum_{kl} \pi_{ij,kl}\, (\cos\theta_{kl} - 1) \tag{2}$$

(torsional model)

and

$$\delta p_{ij} = \pi_{ij,16}\delta\beta_{16} \tag{3}$$

(homoaromatic interaction model)

The results of these two perturbation schemes take slightly different forms, as the torsional angles (θ_{kl}) are directly available from crystallographic studies,[3,9] whereas the value of the homoaromatic interaction resonance integral ($\delta\beta_{16}$) is unknown (within the present context). Thus the δp_{ij} are obtained explicitly in the first case but only within a multiple of $\delta\beta_{16}$ in the second scheme. We adopt the well-known proportionality between bond lengths and bond orders[10] in the analysis (note, however, that we are considering perturbations to these quantities, rather than absolute values). Within the framework of this approximation, an increase in bond order is expected to lead to a decrease in bond length. We define

$$\delta r_{ij} = \bar{r} - r_{ij} \tag{4}$$

where $\bar{r}$ is the mean peripheral bond length. In such circumstance short bonds have positive δr_{ij}, and if the correlation between bond orders and bond lengths is valid there should be a direct proportionality between the δp_{ij} and δr_{ij}.

As a test of the scheme, we first analyze the x-ray crystallographic structure[9] of 1,6-methano[10]annulene (**2**)[11] in terms of the two perturbations discussed above. The results are presented in Table I, and it is immediately apparent that there is a strong correlation between the perturbed bond orders of the homoaromatic interaction model and the experimentally

Table I. Perturbed Bond Orders and Bond Lengths of 1,6-Methano[10]annulene (2)

Bond i–j	Torsional model[a,e] δp_{ij}	Homoaromatic interaction model[b,e] δp_{ij} (units of $\delta\beta_{16}$)	δr_{ij}[c,d]
1–2	−0.00601	−0.0631	−0.015
2–3	0.00384	0.0852	0.017
3–4	0.00433	−0.0442	−0.009

[a] Equation 2. [b] Equation 3. [c] Equation 4. $\bar{r}$(**2**) = 1.400 Å. [d] Reference 9. [e] Correlation coefficient for zero intercept regression analysis: 0.327 (torsional), 0.993 (homoaromatic), 0.995 (bivariate analysis).