The residue after removal of the chloroform was chromatographed over silica gel (hexane eluant) to give 0.854 g (95%) of 9,10-dimethylphenanthrene: mp 140 °C (from methanol) (lit.[9] mp 140.5 °C); ^{1}H NMR δ 2.66 (s, 6 H), 7.50 (m, 4 H), 8.00 (m, 2 H), 8.53 (m, 2 H); ^{13}C NMR δ 15.86, 122.75, 124.54, 125.38, 126.51, 129.24, 129.43, 132.21; mass spectrum, *m/e* (relative intensity) 206 (100), 191 (82), 178 (12), 165 (32).

Dehydration of 6. A solution of **6** (100 mg) in 50 mL of absolute ethanol was saturated with hydrogen chloride and dehydrated as with **3**. The workup gave 65 mg of viscous oil which was resolved by gas–liquid chromatography (10% SE-30 on Chromosorb W at 200 °C) into two fractions. The first (25%) was 1,4,5,8,9,10-hexamethylphenanthrene (vide infra), and the second (75%) was its tautomer **8**: ^{1}H NMR δ 0.88 (d, *J* = 8 Hz, 3 H), 2.23 (s, 6 H), 2.33 (s, 3 H), 2.40 (s, 3 H), 3.43 (dq, *J* = 8, 2 Hz, 1 H), 4.93 (d, *J* = 2 Hz, 1 H), 5.20 (d, *J* = 2 Hz, 1 H), 6.86 (s, 2 H), 7.00 (s, 2 H); mass spectrum, *m/e* (relative intensity) 262 (trace), 220 (35), 205 (100), 145 (10); with chemical ionization, *m/e* 263 [(M + 1)$^+$].

Anal. Calcd for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 91.56; H, 8.49.

***N,N*-Bis(dimethylamino)-1,4,5,8,9,10-hexamethyl-1,4,5,8-tetrahydrophenanthrene-1,4:5,8-diimine (9).** The procedure and scale was the same as for the preparation of **2** except that *N*-(dimethylamino)-2,5-dimethylpyrrole[8] (1.38 g, 10 mmol) was used in place of furan. The crude product was triturated with hexane (20 mL) to give 0.45 g (24%) of a single isomer of **9**: mp 147–149 °C; ^{1}H NMR δ 1.80 (s, 6 H), 1.83 (s, 6 H), 2.16 (s, 6 H), 2.28 (br s, 12 H), 6.43 (br s, 4 H); ^{13}C NMR δ 14.93, 18.72, 19.43, 45.69, 74.71, 76.15, 126.44, 145.75, 146.00, 146.52, 146.75; mass spectrum, *m/e* (relative intensity) 321 (54), 276 (92), 262 (100), 116 (32); with chemical ionization, *m/e* 379 [(M + 1)$^+$].

The oily residue obtained from concentrating the hexane solution was chromatographed on alumina. Hexane eluted unreacted pyrrole. Further elution with chloroform gave 0.432 g (22%) of additional **9** as a mixture of anti and syn isomers.

***N,N*-Bis(dimethylamino)-1,2,3,4,5,6,7,8,9,10-decamethyl-1,4,5,8-tetrahydrophenanthrene-1,4:5,8-diimine (10).** The procedure and scale was the same as for **9** except that *N*-(dimethylamino)-2,3,4,5-tetramethylpyrrole[7] was used as the diene. A workup as with **9** gave 0.35 g (16%) of a single isomer of **10**: mp 174–175 °C; ^{1}H NMR δ 1.56 (s, 6 H), 1.60 (s, 6 H), 1.76 (s, 6 H), 1.80 (s, 6 H), 2.16 (s, 6 H), 2.43 (s, 12 H); ^{13}C NMR δ 10.50, 11.38, 14.77, 17.63, 18.69, 45.83, 76.12, 76.30, 125.68, 141.50, 145.16, 145.95, 148.31; mass spectrum, *m/e* (relative intensity) 318 (100), 304 (9), 288 (13); with chemical ionization, *m/e* 435 [(M + 1)$^+$]. Further workup of the hexane extract as with **9** gave an additional 0.614 g (28%) of **10** as a mixture of anti and syn isomers.

1,4,5,8,9,10-Hexamethylphenanthrene (7). Diadduct **9** (50 mg) was sealed under vacuum (0.1 torr) in a small glass tube and heated at 150 °C for 1 h. The product was chromatographed on alumina with hexane to give 31 mg (90%) of **7** which was recrystallized from methanol: mp 85–86 °C; ^{1}H NMR δ 2.449 (s, 6 H), 2.631 (s, 6 H), 2.817 (s, 6 H), 7.171 (AB q, *J* = 7.8 Hz, 4 H); ^{13}C NMR δ 20.79, 22.02, 25.47, 126.08, 129.69, 130.11, 130.59, 131.58, 132.93, 134.64; mass spectrum, *m/e* (relative intensity) 262 (100), 247 (13), 232 (23), 217 (10); IR (KBr) 2850, 2900, 1450, 1360, 800, 790 cm^{-1}; UV (heptane) λ_{max} 324 nm (log ε 4.43), 266 (4.90), 241 (4.64).

Anal. Calcd for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 91.65; H, 8.46.

Decamethylphenanthrene (11). The procedure, with 100 mg of **10**, was the same as for **7**, except that the tube was heated at 170–180 °C for 2 h. The resulting **11** (64 mg, 97%) was recrystallized from methanol–chloroform: mp 165–167 °C; ^{1}H NMR δ 2.33 (br s, 18 H), 2.46 (s, 6 H), 2.53 (s, 6 H); in C_6D_6 δ 2.227 (s, 12 H), 2.356 (s, 6 H), 2.368 (s, 6 H), 2.491 (s, 6 H); ^{13}C NMR δ 16.57, 20.88, 21.08, 21.96, 128.15, 128.98, 130.06, 131.73, 133.73, 134.38; mass spectrum, *m/e* (relative intensity) 318 (100), 303 (7), 288 (17), 273 (14); UV (heptane) λ_{max} 325 nm (log ε 4.14), 277 (4.73).

Anal. Calcd for $C_{24}H_{30}$: C, 90.50; H, 9.50. Found: C, 90.69; H, 9.50.

Isomerization of 7 to 8. A solution of **7** (100 mg) in ethanol (50 mL) saturated with hydrogen chloride was treated as described for the dehydration of **6**. GLC analysis of the crude reaction product showed it to contain 24% of recovered **7** and 76% of **8**.

Isomerization of 11 to 12. To a solution of **11** (30 mg) in 5 mL of chloroform was added 10 drops of trifluoroacetic acid. The resulting blue solution was stirred at room temperature for 10 min, and then 5 mL of water was added. The organic layer was dried ($MgSO_4$) and concentrated to give a quantitative yield of **12** which was recrystallized from ethanol: mp 208–209 °C; ^{1}H NMR δ 0.93 (d, *J* = 7 Hz, 3 H), 2.06 (s, 6 H), 2.30 (br s, 12 H), 2.40 (s, 6 H), 3.56 (q, *J* = 7 Hz, 1 H), 4.80 (d, *J* = 2 Hz, 1 H), 5.26 (d, *J* = 2 Hz, 1 H); mass spectrum, *m/e* (relative intensity) 318 (94), 303 (100), 288 (8), 273 (26), 258 (11).

Acknowledgment. We are indebted to the National Science Foundation (Grant No. CHE 80-17746) and the National Institutes of Health (Grant No. GM 15997) for financial support of this research.

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Electrochemical Oxidation of Morphinandienones[1]

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The (±)-morphinandienones, *O*-methylflavinantine, *O*-benzyllaudanine, and *O*-methylflavinine, were synthesized by electrochemical oxidation of laudanosine, *O*-benzylpallidine, and norlaudanosine. With use of acetonitrile containing fluoroboric acid as solvent, the yields exceeded 70%. Upon further, separate oxidation in acidic acetonitrile, *O*-methylflavinantine produced *trans*-10-hydroxy-*O*-methylflavinantine stereospecifically in 38% yield, together with an oxohomomorphinan containing an acetal function in 41% isolated yield. The structure of the latter was determined by X-ray crystallography. Similarly, anodic oxidation of *O*-benzylpallidine produced *trans*-10-hydroxy-*O*-benzylpallidine (41%) and the corresponding oxohomomorphinan (37%). *trans*-10-Hydroxy-*O*-methylflavinine was isolated in 13% yield from the oxidation of *O*-methylflavinine.

The facile formation of morphinandienones through anodic coupling of benzyltetrahydroisoquinolines is now well established.[2] With use of acetonitrile containing fluoroboric acid as solvent-supporting electrolyte system,

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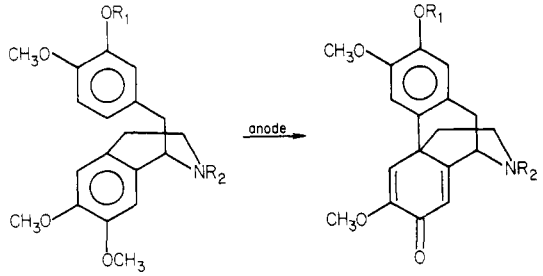
a number of dienones have been produced in high yields,[3] and the mechanism has been elucidated.[4]

Although it has been proposed that morphinandienones themselves could be oxidized, little is known of such reactions. Since oxidation is a common metabolic route and because the products of anodic oxidations could have interesting pharmacological properties, we have studied the oxidation of several flavinantine derivatives.

Results and Discussion

The three (±)-benzyltetrahydroisoquinolines, laudanosine (**1a**), *O*-benzyllaudanine (**1b**), and norlaudanosine (**1c**), were synthesized in high yield according to already published methods.[2a,5] These three compounds were oxidized at a platinum electrode in acetonitrile containing aqueous fluoroboric acid. Yields of 70–75% of the morphinandienones, *O*-methylflavinantine (**2a**), *O*-benzylpallidine (**2b**), and *O*-methylflavanine (**2c**) were obtained.



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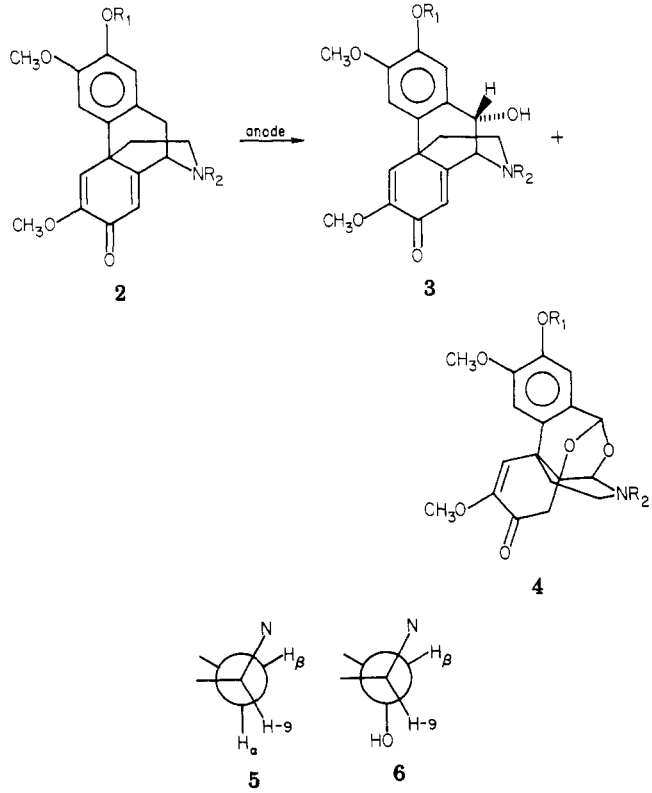
1a, $R_1 = CH_3$; $R_2 = CH_3$
b, $R_1 = CH_3Ph$; $R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = H$

A cyclic voltammogram of morphinandienone (**2a**) in acetonitrile at platinum shows that it is oxidized at a potential only slightly more positive than that of laudanosine (**1a**), giving an anodic peak at $E_p = 1.15$ V vs.Ag|Ag$^+$ at a scan rate of 200 mV/s. This peak is followed by a second oxidation peak at $E_p = 1.33$ V.

Preparative oxidation of **2a** was conducted at 1.2 V in CH_3CN/0.2 M HBF_4 to produce *trans*-10-hydroxy-*O*-methylflavinantine (**3a**) stereospecifically in 38% yield together with the cyclic acetal (**4a**) in 37% yield.

The structure of **3a** was elucidated from the spectral data and elemental analysis. IR spectroscopy showed the pattern characteristic for a cross-conjugated dienone with bands in the range 1680, 1660, and 1640 cm^{-1} and the presence of a hydroxy group. NMR showed this hydroxy group to be positioned at the C-10 carbon, and the stereochemistry was determined in the following fashion. In the NMR spectrum of precursor **2a**, a partly resolved ABX pattern is formed by H-9, H-10α, and H-10β[6] (partial structure **5**). This pattern is replaced in the spectrum of



2 3 4 5 6

3a by two barely resolved doublets at δ 3.62 and 4.90, with a very small coupling constant $J \leq 1$ Hz. Examination of a molecular model (partial structure **6**) shows that **3a** maintains a rather rigid conformation in which the dihedral angle between H-10β and H-9 is between 70 and 90°. This is compatible with the observed small coupling constant. An alternative structure in which the hydroxy group was substituted at the C-10β position would require a dihedral angle between H-9 and H-10α of ~30° and a large coupling constant incompatible with the observed spectrum.

The structure of **4a** was more difficult to determine. The molecular formula (elemental analysis and high-resolution mass spectrometry) indicated the incorporation of two more oxygens into the structure of **2a**. However, no hydroxy groups were present (IR) and the dienone structure in the infrared had disappeared. It was replaced with a single carbonyl stretching band at 1700 cm^{-1}. Large prismatic crystals of **4a** were obtained upon recrystallization from methanol and the structure was unequivocally determined by X-ray diffraction. In the ortho rombic space group $p2_12_12_1$, the measured cell constants were $a = 10.198$ (4) Å, $b = 12.821$ (5) Å, and $c = 14.411$ (3) Å and gave a calculated density of 1.316 g/cm^3 for four molecules in the unit cell. After Lorentz–polarization corrections, 1965 out of 2269 unique reflections with $2\theta = 0$–156° were observed for $[F_o \geq 2.5\sigma(F_o)]$. A combination of direct methods and difference Fourier synthesis was used to locate all nonhydrogen atoms. Thermal anisotropic refinement was applied to all nonhydrogen atoms. The positions of all hydrogen atoms were calculated by difference Fourier synthesis. The R factor for the structure was 0.049. An ORTEP drawing of **4a** is shown in Figure 1 where the hydrogen atoms are left out for clarity. Table I gives important bond length and bond angles. The numbering is adopted from the homomorphinan skeleton. Curiously, the X-ray structure of **4a** showed that it was chiral. Apparently, it crystallized in pure enantiomeric form.

Oxidation of *O*-benzylpallidine (**2b**) resulted similarly in the formation of benzylic alcohol **3b**, isolated in 41%

(1) Taken in part from the Ph.D. Thesis of Leif Christensen, University of Minnesota, 1980.
(2) (a) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.*, **95**, 2651 (1973); (b) L. L. Miller, F. R. Stermitz, J. Y. Becker, and V. Ramachandran, *ibid.*, **97**, 2922 (1975); (c) J. Y. Becker, L. L. Miller, and F. R. Stermitz, *J. Electroanal. Chem.*, **68**, 181 (1976).
(3) (a) E. Kotani, N. Takeuchi, and S. Tobinaga, *Chem. Commun.*, 550 (1973); (b) E. Kotani and S. Tobinaga, *Tetrahedron Lett.*, 4759 (1973); (c) T. Kametani, K. Shishido, and S. Takano, *J. Heterocycl. Chem.*, **12**, 305 (1975); (d) S. M. Kupchan and Chang-kyu Kim, *J. Am. Chem. Soc.*, **97**, 5623 (1975).
(4) J. B. Kerr, T. C. Jempty, and L. L. Miller, *J. Am. Chem. Soc.*, **101**, 7338 (1979).
(5) (a) J. R. Falck, L. L. Miller, and F. R. Stermitz, *Tetrahedron*, **30**, 931 (1974); (b) I. Baxter, L. T. Allan, and G. A. Swan, *J. Chem. Soc.*, 3645 (1965).
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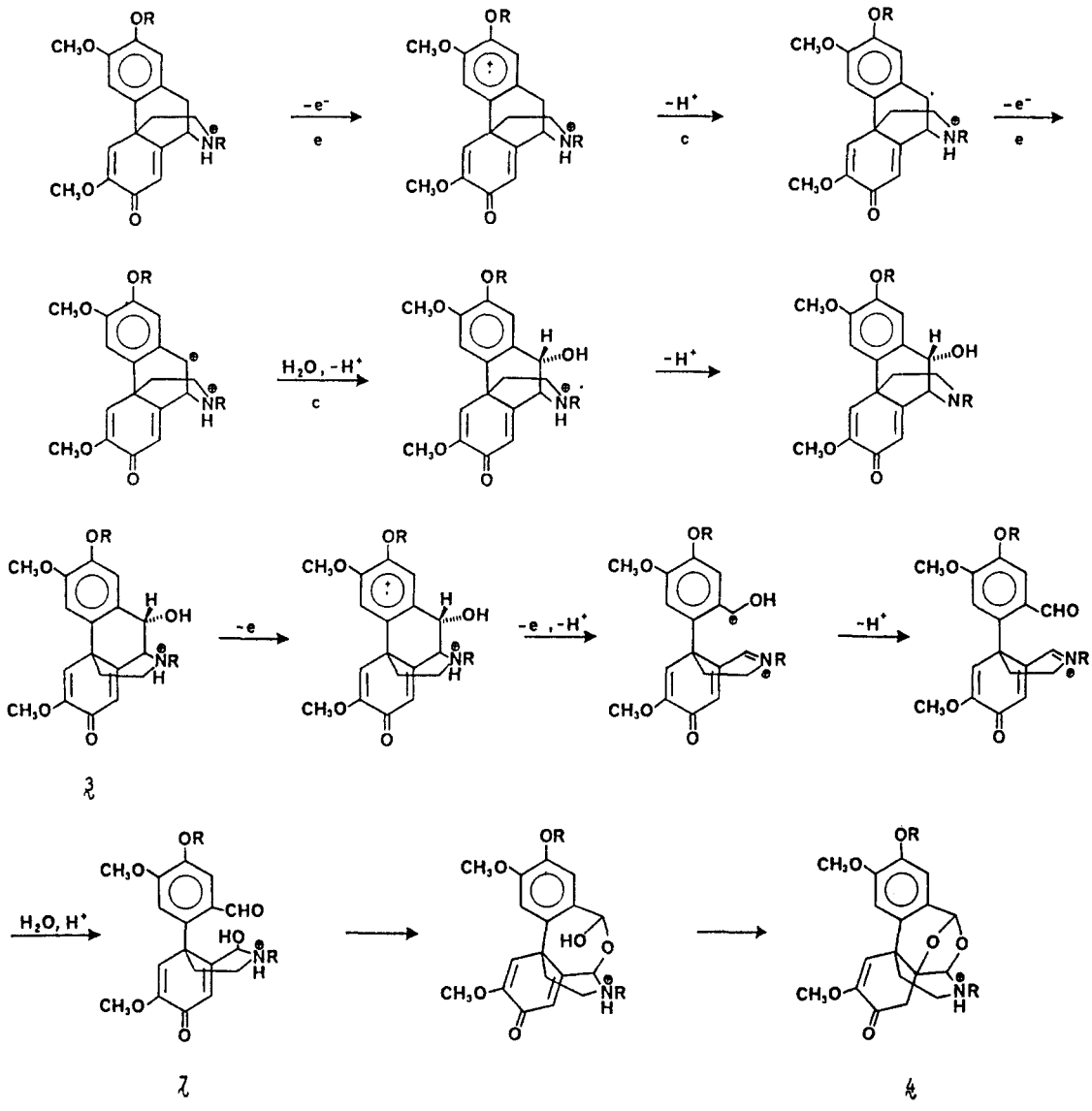

yield, and acetal **4b**, isolated in 38% yield. The structures were confirmed from their spectral data in analogy with those of **3a** and **4b**. Oxidation of *O*-methylflavinine (**2c**) on the other hand was less successful. During workup, upon neutralization of the acidic anolyte, the solution turned black and heavy material loss was suffered during extraction. Chromatography of the residue produced **3c** in 13% yield.

The formation of benzylic alchols (**3**) upon oxidation of the parent dienones is not totally unexpected. An analogous example of a benzylic oxidation in an alkaloid is found in the stereoselective hydroxylation of (+)-cataline.[7] Similarly, Rapoport has shown the formation of *trans*-10-hydroxycodeine by oxidation with chromic acid.[8]

A mechanistic rationale for the oxidation of morphinandienones is outlined below. It is not surprising that these compounds are electroactive at 1.2 V, since this is within the expected range for the oxidation of an activated dimethoxy aromatic compound to the cation radical. For example, a cyclic voltammogram of 3,4-dimethylveratrole in CH_3CN shows a reversible couple at $E_p = 0.90$ V.[9] It is therefore most likely that the protonated dienone in CH_3CN/HBF_4 is oxidized via the aromatic cation radical, benzyl radical, and benzyl cation (ece mechanism). The latter is trapped by the strongest nucleophile present (H_2O) to form, stereospecifically by attack from the least hindered side, the 10-hydroxymorphinandienone. This is quite similar to the accepted pathway for anodic benzylic substitution of simple alkyl aromatics.[10]

For the same reasons argued above, **3** is also expected to be electroactive in the applied potential range. Upon oxidation, **3** undergoes cleavage, presumably in unprotonated form, to produce the stabilized iminium aldehyde, which is trapped by water to give **7**. In turn, **7** forms a hemiacetal, which now through Michael addition produces **4**. It is, of course, quite possible that some of the later steps actually take place during the workup.

Oxidative benzylic cleavages, like the one invoked in the above mechanism, are also not uncommon and have been studied.[11] For example, 2,2-diphenylethanol undergoes anodic oxidative cleavage in acetonitrile to form benzophenone and *N*-benzylacetamide. Another example is the cleavage of 1-benzyltetrahydroisoquinolines sometimes

(7) J. Hartenstein and G. Satzinger, *Angew. Chem., Int. Ed. Engl.*, **16**, 730 (1977).
(8) (a) H. Rapoport and G. W. Stevenson, *J. Am. Chem. Soc.*, **76**, 1796 (1954); (b) H. Rapoport and Masamune *ibid.*, **77**, 4330 (1955).
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(10) For reviews on anodic substitution, see: (a) L. Eberson and K. Nyberg, *Tetrahedron*, **32**, 2185 (1976); (b) L. Eberson and K. Nyberg, *Acc. Chem. Res.*, 106 (1973).
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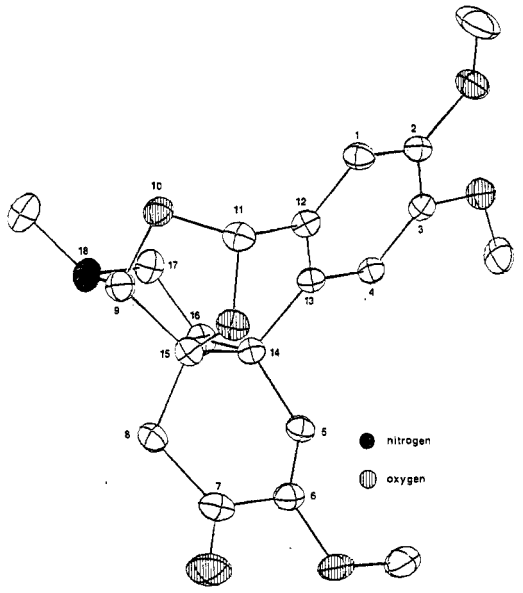

Figure 1. An ORTEP drawing of **4a** with hydrogen atoms omitted.

Table I. Selected Bond Lengths and Bond Angles for (4a)

bond	bond length, Å	bonded atoms	bond angles, deg
C1-C2	1.386 (3)	C1-C2-C3	118.78 (18)
C2-C3	1.392 (3)	C2-C3-C4	121.01 (17)
C3-C4	1.374 (3)	C3-C4-C13	120.32 (17)
C4-C13	1.414 (3)	C13-C12OCl	120.81 (18)
C13-C14	1.531 (3)	C12-C1-C2	120.52 (18)
C5-C14	1.503 (3)	C5-C6-C7	121.80 (20)
C5-C6	1.318 (3)	C6-C7-C8	115.80 (19)
C6-C7	1.479 (3)	C7-C8-C15	114.85 (18)
C7-C8	1.497 (3)	C8-C15-C14	111.95 (17)
C8-C15	1.520 (3)	C15-C14-C5	112.18 (17)
C14-C15	1.572 (3)	C14-C5-C6	125.92 (20)
C9-C15	1.520 (3)	C14-C15-C9	114.13 (20)
C9-O10	1.460 (3)	C15-C9-O10	103.60 (17)
O10-C11	1.418 (3)	O10-C11-O19	106.30 (17)
C11-C12	1.495 (3)	C11-O19-C15	101.27 (15)
C12-C13	1.376 (3)	O19-C15-O19	100.93 (17)
C14-C16	1.551 (3)	C11-C12-C13	117.28 (18)
C16-C17	1.508 (3)	C12-C13-C14	121.13 (17)
C17-N18	1.472 (3)	C13-C14-C15	109.73 (15)
C9-N18	1.429 (3)	C15-C14-C16	108.40 (15)
C11-O19	1.423 (3)	C14-C16-C17	111.40 (17)
C15-O19	1.442 (2)	C16-C17-N18	108.80 (19)
		C17-N18-C9	113.44 (17)
		N18-C9-C15	116.33 (18)
		C9-C15-C14	114.13 (16)

observed during oxidative cyclization.[2,12]

Experimental Section

General Procedures. Melting points are uncorrected open capillary tube measurements, obtained with a Mel Temp melting point apparatus. Nuclear magnetic resonance spectra were obtained with a Varian CFT-20 spectrometer. Peak positions are measured relative to Me_4Si. Mass spectra were obtained from an AEI MS-30 spectrometer, and infrared spectra were recorded on a Perkin-Elmer 727B or 297 spectrophotometer. For the X-ray structure determination, data were collected on a fully automated Enraf-Nonius CAD4 diffractometer, using a variable rate ω–2θ scan technique and graphite monochromatized Cu K_α radiation (λ = 1.54184 Å). All calculations were carried out on a PDP 11/34 computer, using the Enraf-Nonius SDP programs. Thin-layer chromatographic analysis was performed on Polygram SIL G/UV silica gel plastic sheets, 40 × 80 mm, with UV indicator, distributed by Brinkman. Elemental analysis was obtained from M-H-W Laboratories, Phoenix, AZ.

Preparation of (±)-Morphinandienones. Laudanosine (**1a**), *O*-benzyllaudanine (**1b**), and norlaudanosine (**1c**) were prepared according to the literature and had properties consistent with these reports.[2a] *O*-Methylflavinantine (**2a**), *O*-benzylpallidine (**2b**), and *O*-methylflavinine (**2c**) were produced anodically under various conditions. The best procedure was similar to that of Kametani.[3c] It is described below for the oxidation of morphinandienones. The scale was about 1 g and the anode potential was 1.1 V.

Electrochemical Oxidations. Controlled potential electrochemical oxidations were performed in a two-compartment H-type cell with a medium-porosity frit as a divider. The anode compartment (volume 120 mL) was equipped with a 55/50 glass joint and a matching top, which had 14/20 ground joints for insertion of the working electrode, reference electrode, and a N_2 inlet. A 60 × 80 mm platinum sheet was used as working electrode (unless otherwise specifically mentioned). The $Ag|Ag^+$ reference electrode consisted of a Ag wire immersed in a separate compartment, filled with a 0.1 M solution of $AgNO_3$ in acetonitrile, positioned as close to the working electrode as possible. A stainless steel spatula was used as auxiliary electrode. The potentiostat was a Wenking Model 70 HVI/90. It was used in conjunction with a digital voltmeter and Integrator-Totalizer Model 212-XL-1, manufactured by Acromag Inc., Wixom, MI.

All oxidations were conducted under ice cooling in CH_3CN/0.2 M HBF_4. The acetonitrile was Omni Solv reagent grade and used without further purification. Fluoroboric acid was a 50% aqueous solution supplied by J. T. Baker Chemical Co.

Generally, the electrolyses always consumed more than the theoretical amount of electricity (2 F/mol), and the current never dropped to the background level (usually less than 1 mA) measured prior to the addition of substrate. Optimum conditions were found to be oxidation of 1.0–1.5 mmol of substrate with an initial current of approximately 150 mA (current density 3 mA/cm^2) dropping to about 20 mA in less than 1 h.

After completion of the reaction, the anolyte was immediately neutralized with solid $NaHCO_3$ and concentrated in vacuo and the residue was partitioned between water and chloroform. A brown foam, insoluble in both layers, was always present at the interphase and was discarded. Evaporation of the chloroform fraction produced the crude product, generally a dark oil or semisolid. TLC analysis of the crude product always indicated some brown R_f 0 material in addition to the major products in the crude mixture. The TLC plates were developed in 95% EtOAc, 5% Et_2NH and visualized either with UV light or spraying with "alkaloid reagent" [0.15% hexachloroplatinic (IV) acid in 3% aqueous potassium iodide].[13] Several other solvent mixtures were tried for development, and it was found that the above system gave the best general separation of the tetrahydroisoquinolines, and their oxidation products, without "streaking".

The crude oxidation product was subjected to column chromatography on deactivated neutral alumina (activity IV, 6.6% water added, or activity between III and IV, 5.5% water added, Brockmann activity scale). Fractions were eluted with mixtures of hexane/chloroform containing 1% diethylamine. The separation was monitored by TLC.

Anodic Products from *O*-Methylflavinantine (2a). 2a (0.5 g, 1.46 mmol) was oxidized in CH_3CN/0.2 M HBF_4 at 1.2 V vs. $Ag|Ag^+$, using a 20-cm^2 Pt sheet anode. The initial current of 80 mA dropped to 10 mA after the passage of 2.8 F/mol in the course of 90 min. The electrolysis was discontinued and the slightly yellow anolyte worked up to produce 0.5 g of bluish foam containing three major products (TLC). Chromatography on Al_2O_3 (IV) produced 200 mg (36%) of **4a** as a white solid recrystallized from acetonitrile as white needles and from methanol as large, colorless prisms: mp 186–8 °C; NMR (benzene-d_6) δ 1.7–2.2 (m, 4 H, CH_2CH_2), 1.65 (s, 3 H, NCH_3), 2.80 (d, J = 15 Hz, 1 H, H-8), 3.06 (d, J = 15 Hz, 1 H, H-8), 3.15 (s, 3 H, OMe), 3.36 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 4.54 (s, 1 H, H-9), 5.50 (s, 1 H, H-11), 5.93 (s, 1 H, aromatic), 6.35 (s, 1 H, aromatic), 6.82 (s, 1 H, H-5); IR (KBr) 1700 cm^{-1}; mass spectrum, m/e (relative intensity) 373 (M^+, 2), 355 (4), 314 (3), 301 (4), 287 (100, $C_{16}H_{15}O_5$); high-reso-

(12) L. Christensen, Ph.D. Thesis, University of Minnesota, 1980.

(13) Reagent No. 147, "Thin-Layer Chromatography", 2nd ed., E. Stahl, Ed., Springer Verlag, New York, 1969.

lution mass spectrum 373.1527, calculated for $C_{20}H_{23}NO_6$ 373.1525. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.13; H, 6.33; N, 3.56. The NMR spectrum of **4a** taken in $CDCl_3$ was in agreement with the above interpreted spectrum except for the presence of an extra proton exchangeable with D_2O: NMR ($CDCl_3$) δ 1.57 (s, 1 H, exchangeable with D_2O), 2.0–2.6 (m, 4 H, CH_2CH_2), 2.66 (d, J = 15 Hz, 1 H, H-8), 3.16 (d, J = 15 Hz, 1 H, H-8), 3.59 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 4.59 (s, 1 H, H-9), 5.71 (s, 1 H, H-11), 5.87 (s, 1 H, aromatic), 6.65 (s, 1 H, aromatic), 6.90 (s, 1 H, H-5).

Further elution produced 20 mg of starting material (**2a**) together with a minor unidentified product, followed by 200 mg (38%) of **3a** as a yellow syrup crystallized from acetonitrile as tan plates: mp 193–95 °C; NMR ($CDCl_3$) δ 1.8–2.6 (m, 5 H, one exchangeable with D_2O), 2.50 (s, 3 H, NCH_3), 3.62 (unresolved d, $J < 1$ Hz, 1 H, H-9), 3.71 (s, 3 H, OMe), 3.87 (s, 6 H, 2 × OMe), 4.90 (unresolved d, $J < 1$ Hz, 1 H, H-10) 6.28 (s, 1 H, H-4), 6.37 (s, 1 H, H-8), 6.76 (s, 1 H, H-1 or H-5), 6.90 (s, 1 H, H-5 or H-1); IR (KBr) 3550 (OH), 1682, 1660, 1638 cm^{-1}; mass spectrum, m/e (relative intensity) 357 (M^+, 83), 342 (40), 326 (37), 192 (100). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.27; H, 6.47; N, 3.92. Found: C, 67.25; H, 6.37; N, 3.92.

Anodic Products from *O*-Benzylpallidine (2b). Oxidation of 0.4 g (0.92 mmol) of **2b** at 1.18 V produced, after passage of 2.1 F/mol, 0.38 g of brown oil. Chromatography on Al_2O_3 (III–IV) gave 140 mg (32%) of **4b** as a colorless oil, which crystallized on standing: NMR ($CDCl_3$) δ 1.54 (s, 1 H, exchangeable with D_2O), 2.43 (s, 3 H, NCH_3), 2.0–2.5 (m, 4 H), 2.66 (d, J = 16 Hz, 1 H), 3.16 (d, J = 16 Hz, 1 H), 3.59 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 4.56 (s, 1 H), 5.12 (s, 2 H), 5.66 (s, 1 H), 5.82 (s, 1 H), 6.68 (s, 1 H), 6.90 (s, 1 H), 7.3–7.4 (m, 5 H); IR (KBr) 1700 cm^{-1}; mass spectrum, m/e (relative intensity) 449 (M^+, 7), 434 (3) 363 (100), 358 (10), 340 (8), 272 (12), 108 (23), 91 (60), 79 (20), 58 (19); high-resolution mass spectrum 449.1839, calculated for $C_{26}H_{27}NO_6$ 449.1836.

Further elution gave 30 mg of starting material **2b** (TLC, NMR), followed by 170 mg (41%) of **3b** as a yellow oil: NMR ($CDCl_3$) δ 1.7–2.5 (m, 5 H, one exchangeable with D_2O), 2.47 (s, 3 H, NCH_3), 3.54 (d, $J < 1$ Hz, 1 H, H-9), 3.77 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 4.81 (d, $J < 1$ Hz, 1 H, H-10), 5.09 (s, 2 H), 6.30 (s, 1 H), 6.34 (s, 1 H), 6.80 (s, 1 H), 6.98 (s, 1 H), 7.3–7.6 (m, 5 H); IR (film) 3430 (OH), 1665, 1640, 1620 cm^{-1}; mass spectrum, m/e (relative intensity) 433 (M^+, 33), 418 (9), 402 (12), 390 (5), 342 (36), 192 (33), 91 (100), 57 (53), 42 (23); high-resolution mass spectrum 433.1902, calculated for $C_{26}H_{27}NO_5$ 433.1887.

Electrochemical Oxidation of *O*-Methylflavinine (2c). The compound (0.5 g, 1.5 mmol) was oxidized at 1.18 V. After passage of 2.6 F/mol the current had dropped from 150 to 40 mA and the electrolysis was discontinued. During the reaction the anolyte remained almost colorless. However, upon neutralization it turned completely black and extractive workup produced only 0.3 g of black semisolid. TLC indicated two major products besides starting material, but chromatography on Al_2O_3 (III–IV) only resulted in a few milligrams of an unidentified oil, followed by 70 mg (13%) of **3c** as a dark viscous oil, which crystallized upon standing: NMR ($CDCl_3$) δ 1.7–2.7 (m, 6 H, 2 exchangeable with D_2O), 3.77 (s, 3 H, OMe) 3.87 (s, 6 H, 2 × OMe), 4.75 (s, 1 H, H-10) 6.30 (s, 1 H), 6.32 (s, 1 H), 6.76 (s, 1 H), 6.92 (s, 1 H); IR (KBr) 3450 (OH, NH), 1665, 1645, 1620 cm^{-1}; mass spectrum, m/e (relative intensity) 343 (M^+, 44), 328 (24), 326 (18), 325 (25), 312 (36), 310 (22), 301 (18), 282 (26), 178 (46), 152 (14), 84 (21), 59 (27), 43 (100); high-resolution mass spectrum 343.1426, calculated for $C_{19}H_{21}NO_5$ 343.1420.

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Registry No. 1a, 1699-51-0; **1b**, 41183-02-2; **1c**, 26642-09-1; **2a**, 22169-18-2; **2b**, 27841-87-8; **2c**, 53403-81-9; **3a**, 79255-32-6; **3b**, 79255-33-7; **3c**, 79255-34-8; **4a**, 79313-46-5; **4b**, 79313-47-6.

Preparation of 3-Hydroxycyclohexaneacetonitriles

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Preparation of *cis*-4-*tert*-butyl-*cis*-3-hydroxycyclohexaneacetonitrile (**2**) and the parent *cis*-3-hydroxycyclohexaneacetonitrile (**1**) is described. In intermediates leading to **2** severe crowding at axially substituted C(3) leads to unusual reactions, including rapid intramolecular oxonium ion formation at 0–5 °C, abnormally easy hydride reduction of a nitrile, and formation of an open-chain hemiacetal that is relatively stable to aqueous acid.

In connection with another investigation we required *cis*-3-hydroxycyclohexaneacetonitrile (**1**, Chart I) and the related *cis*-4-*tert*-butyl derivative **2**, in which the *tert*-butyl group holds the other two substituents effectively locked in axial positions on the ring. We describe here routes to these two nitriles along with related transformations. As might be expected, reactions leading to **2** are dominated by interactions between the two axial substituents, and several examples of unusual chemical behavior resulting from these interactions are noted below. These effects, of course, are absent in **1** and its precursors.

Our first approach to **2** was through the readily available aromatic acid **3**,[1] which absorbed 3 equiv of hydrogen over rhodium-on-alumina to furnish stereoselectively a cyclohexanecarboxylic acid. This was tentatively assumed to be the cis,cis isomer **4a**, since hydrogenation of the phenol corresponding to **3** gives largely the cis,cis product.[1] Furthermore, NMR evidence indicated the methoxy group in the hydrogenated acid to be axial, as the carbinyl proton at C(3) appears at δ 3.5. Our general observation with various compounds in this work has been that this carbinyl proton resonates at ~3.5 ppm when equatorial and at ~3.1 ppm when axial. Such stereochemical effects on chemical shifts are well-known in cyclohexanes.[2] Hydride reduction of **4a** gave the alcohol **5a**, which could be converted to its tosylate **5b** under controlled conditions. If the tosylation reaction was prolonged, the yield of **5b** was reduced with accumulation of a second product, assumed

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