t-2,*t*-3-epoxy-1,2,3,4-tetrahydronaphthalen-4-one (**7**, 144 mg, 57%).

7: colorless oil; IR (KBr) 1750 (ester C=O), 1700 (ketone C=O), and 1675 cm^{-1} (an unconjugated ketone); ^1H NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.67 (s, 3 H), 2.22 (s, 3 H), 2.40 (s, 3 H), and 7.20–7.94 (m, 4 H). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.78; H, 5.43.

A solution of **7** (100 mg) in methanol was treated with 0.1 N KOH methanol solution for 10 min at room temperature. The mixture was poured into water and extracted with ether. The organic layer was washed with dilute HCl solution and brine and dried over Na_2SO_4. *r*-1-Hydroxy-1-acetyl-*c*-2,*c*-3-dimethyl-*t*-2,*t*-3-epoxy-1,2,3,4-tetrahydronaphthalen-4-one (**8**) was obtained by preparative TLC in 62% yield.

8: colorless oil; IR (CCl_4) 3400 (OH), 1695 (C=O), and 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.44 (s, 3 H), 2.20 (s, 3 H), 6.00 (mobile, 1 H), and 7.35–7.90 (m, 4 H). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.32; H, 5.91.

Photochemical Reaction of 1 in Extremely Dilute Benzene Solution. A degassed benzene solution of **1** (200 mg/600 mL of benzene) was irradiated for 4 h. Separation of the products by column chromatography gave (*Z*)-1-(2-acetyl)ethylidenephthalide (**4a**, 42 mg, 21%) and (*E*)-1-(2-acetyl)ethylidenephthalide (**4b**, 35 mg, 18%).

4a: mp 104–105 °C; IR (KBr) 1781 and 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (C=CCH_3), 2.40 ($COCH_3$), and 7.60–8.00 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 192.1 (ketone), 170.4 (ester), 161.3 (s), 142.8 (s), 138.2 (s), 135.0 (d), 133.4 (s), 131.2 (d), 126.3 (d), 125.4 (d), 123.2 (s), 32.5 (q), and 12.7 (q). Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.38; H, 5.03.

4b: mp 115–120 °C; IR (KBr) 1781 and 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (C=CH_3), 2.62 ($COCH_3$), and 7.60–8.00 (m, 4 H). Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.05; H, 4.78.

Under the above conditions, irradiation was stopped after 1 h. Separation of the products by column chromatography gave 2-acetyl-2-methyl-1,3-indandione (**5**, 14 mg, 7%) together with **4a** (32 mg, 16%) and **4b** (29 mg, 14%).

5: mp 96–99 °C; IR (KBr) 1748 and 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (s, 3 H), 2.12 (s, 3 H), and 7.4–7.9 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 202.8 (ketone), 196.5 (ketone), 142.3 (s), 137.0 (d), 128.6 (d), 63.0 (s), 26.3 (q), and 21.1 (q). Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.53; H, 5.12.

Independent Synthesis of 4a and 4b. A solution of phthaloyl chloride (1 g) in 10 mL of ether was added to a mixture of ethyl methyl ketone and 50% sodium hydride (0.5 g) in 20 mL of ether. The mixture was stirred for 2 days at room temperature, poured into ice water, and extracted with ether, and the organic layer was dried over Na_2SO_4. Separation of the products over silica gel by using 5% ether/hexane as the eluant gave **4a** (170 mg, 17%) and **4b** (142 mg, 14%).

Registry No. **1**, 53948-58-6; **2a**, 73198-12-6; **2b**, 73245-74-6; **3a**, 73245-75-7; **3b**, 73245-76-8; **4a**, 73198-13-7; **4b**, 73198-14-8; **5**, 73198-15-9; **6**, 85-44-9; **7**, 73198-16-0; **8**, 73198-17-1.

Studies in the (+)-Morphinan Series. 7.[1] Unusual Crystallographic and Tautomeric Properties of (+)-4-Hydroxy-7-oxo-3-methoxy-17-methyl-5,6-dehydromorphinan: An Interlacing Double Helix

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(+)-4-Hydroxy-7-oxo-3-methoxy-17-methyl-5,6-dehydromorphinan (**3a**) was found, by IR and NMR (^1H and ^{13}C) spectroscopy and X-ray crystallography, to be a byproduct in the cyclization of dihydrosinomenine to dihydrocodeinone. In solution, it was in equilibrium with its tautomeric Michael addition product, (+)-4,5-epoxy-7-oxo-3-methoxy-17-methylmorphinan (**4a**). The 5,6-dehydromorphinan **3a** was observed to have infinite, hydrogen-bonded, interlacing double helices of molecules in the solid state by X-ray crystallography. The tautomeric mixture (**3a** + **4a**) was converted to (+)-4-hydroxy-7-oxo-3-methoxy-17-methylmorphinan (**6a**), the structure of which was proven by the synthesis of its enantiomer (**6b**) from thebaine.

The essential step in our preparation of unnatural enantiomers of biologically important opioids is the cyclization of dihydrosinomenine to dihydrocodeinone[2-5] by a modification of the method of Goto et al.[6] In this cyclization a byproduct which could easily be detected by TLC analysis was consistently observed. The structure of this interesting byproduct is discussed in this paper.

Results and Discussion

Cyclization of dihydrosinomenine (**1a**)[6,7] with PPA at 65–70 °C afforded, in addition to dihydrocodeinone (**2a**) as the major reaction product, a 10% yield of ketonic material, mp 104–106 °C, separated by preparative chromatography. Recrystallization of this ketone, which proved to be a mixture of **3a** and **4a**, from ethyl acetate gave colorless needles, mp 156–157 °C (**3a**). The higher and

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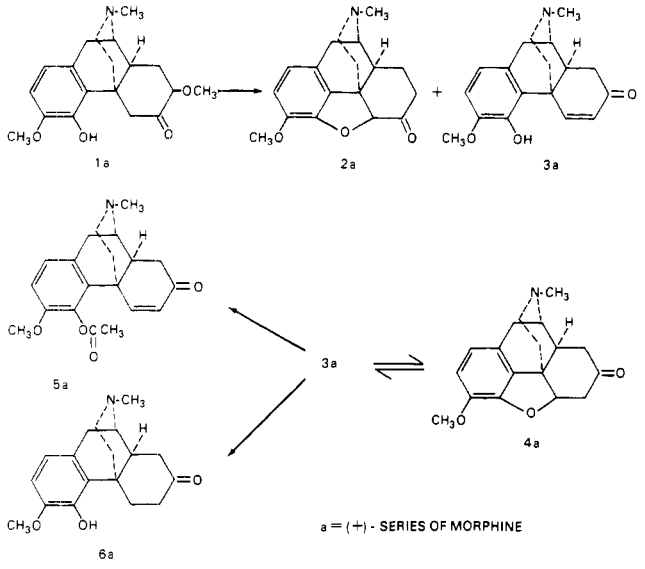
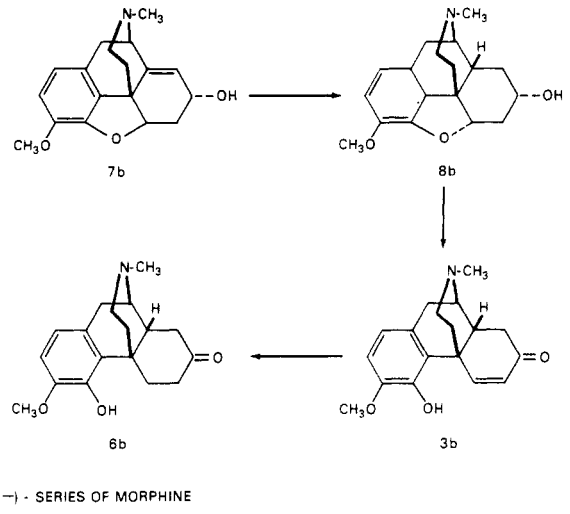
Scheme I



Scheme II



lower melting material had identical UV and IR spectra after standing in solution. These data and the mass spectra of the lower melting material suggested that the structure of the unsaturated ketone was 4-hydroxy-7-oxo-3-methoxy-17-methyl-5,6-dehydromorphinan (**3a**) (Scheme I).

The ^1H and ^{13}C NMR spectra of **3a** were more complex than anticipated and found to be consistent with the existence of a 1:1 equilibrium mixture of **3a** and its tautomeric Michael addition product **4a**. The 220-MHz ^1H NMR spectra of the equilibrium mixture showed the cis olefinic protons in the C ring of the morphinan **3a** as a pair of AB doublets at δ 5.87 and 7.71 (J = 10 Hz). In contrast, a methine doublet of doublets (δ 4.94, J_{vic} = 4 and 7 Hz) was observed for the C-5 proton in **4a**. Homonuclear proton–proton decoupling indicated the coupling of the C-5 and C-6 axial protons in **4a**. The C-6 axial proton, which was α to the saturated carbonyl in **4a**, appeared as a doublet of doublets at δ 2.67 ($J_{vic,5,6}$ = 7 Hz, $J_{gem,6ax,6eq}$ = 15 Hz).

The ^{13}C NMR spectra, obtained on the same solution as the ^1H NMR, supported the conclusion that **3a** and **4a** were present in roughly equal amounts. The fully ^1H-decoupled spectrum consists of 36 lines, not counting the Me_4Si internal reference signal at δ 0.00 and the $CDCl_3$ solvent line at δ 77.0 (triad,[8] J_{CD} = 32.1 Hz) but allowing for a coincidence of two CH_2 lines at δ 39.2 to give the tallest line in the spectrum. All the lines fell into one of the four sets CH_3, CH_2, CH, and C, depending on their q, t, d, and s patterns in the partially decoupled single-frequency off-resonance (SFOR) spectrum. The q lines were readily assigned since the OMe groups appeared at a lower field than the NMe groups by 13.4 ppm. The saturated ketone carbonyl was found at δ 206.9, in good agreement with 208.4 for 3-methylcyclohexanone,[9] while the conjugated ketone carbonyl (C-7) of **4a** at δ 199.2 was comfortably close to the 197.1 ppm found for 2-cyclohexenone.[10] The other main spectral differences between **3a** and **4a** were the presence of sp^2-hybridized C-6 and C-5 olefin bands at 125.9 and 158.8, respectively, in **3a**, comparable to 129.3 and 150.7 ppm, respectively, found for C-3 and C-4 of 2-cyclohexenone but in marked contrast to 45.1 (t, CH_2) and 90.0 (d, CH) attributable, respectively, to C-6 and C-5 of **4a**. These critical differences in C-5, -6, and -7 indicated that the two components present in the sample possess the relationship expressed by formulas **3a** and **4a**. The δ values of all other carbons of **3a** and **4a** were the same within a narrow range of ±2.6 ppm and consistent with ring–chain tautomeric structures.

Confirmation of this equilibrium mixture was obtained from ^1H NMR in D_2O containing NaOD, where the spectrum of **3a** alone, in the form of its sodium salt, was observed, showing that the equilibrium was completely driven to the phenolate form. Also, a $CDCl_3$ solution prepared from freshly recrystallized **3a** could be seen, in ^1H NMR, to change from a spectrum of mostly **3a** to the equilibrium mixture (ca. 1:1) of **3a** and **4a** within ca. 2 h.

Acetylation of the equilibrium mixture afforded amorphous **5a**, which could be hydrolyzed back to **3a** with aqueous base. The equilibrium was shifted to the salt of **3a** by the base. Catalytic hydrogenation of the tautomeric pair (**3a** + **4a**) gave a crystalline saturated ketone **6a** in 90% yield. The saturated ketone **6a** appeared to be identical with (+)-epidihydrothebainone prepared by Goto et al.[6] and Okabe[7] in lengthy and low-yield sequences from sinomenine. The structure of **6a** was proven by an unequivocal synthesis of its enantiomer, **6b**, from thebaine. The IR and NMR spectra and TLC of **6b** were identical with those of **6a**. The allylic alcohol **7b**, obtained from thebaine in low yield by hydroboration,[11] afforded the alcohol **8b** after its catalytic reduction (see Scheme II). Oppenauer oxidation of **8b** gave the enantiomeric ketone **3b** in 78% yield. This compound (**3b**) showed spectral properties in solution identical with those of the equilibrium mixture of **3a** + **4a**, except for its opposite optical rotation. Similar opening of the oxide bridge in the salutaridine series was recently noted[12] after our work had been completed.[13] In the salutaridine series the equilibrium was not established, due, perhaps, to the presence of the second double bond in the C ring which could stabilize the α,β-unsaturated ketone form. The saturated ketone **6b** was obtained by catalytic reduction of **3b**, and **6b** was shown to be the enantiomer of **6a**.

The crystals with mp 156–157 °C (**3a**) were suitable for X-ray crystal analysis, and the results of this study substantiated the assignment of the structure **3a**. The col-

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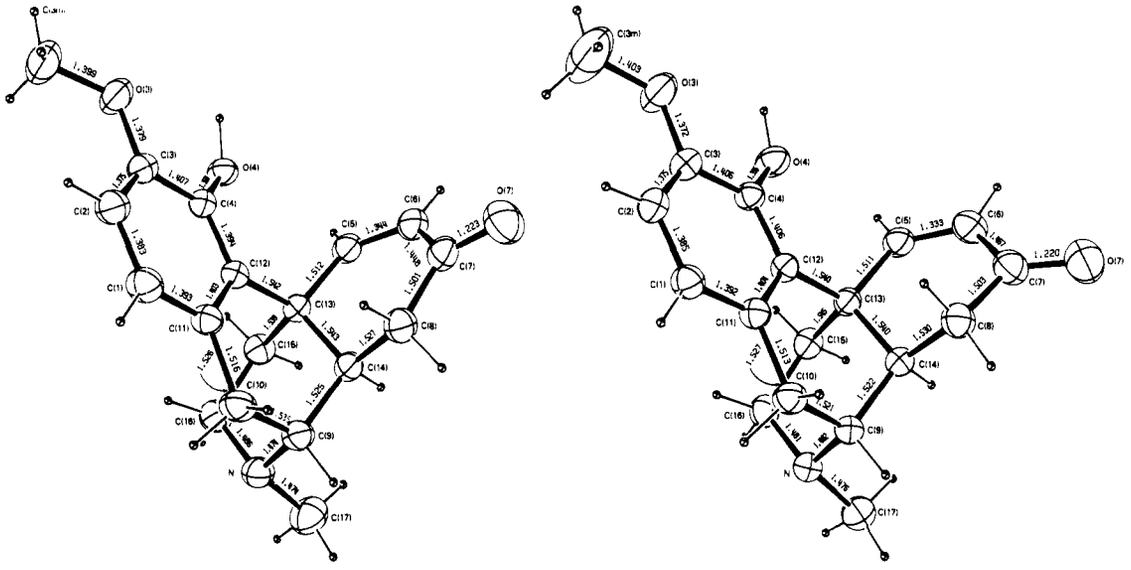

Figure 1. ORTEP[19] drawing of the two independent molecules (**3a**) showing bond lengths and crystal conformations. Estimated standard deviations of bond lengths are less than or equal to 0.003 Å. A configuration as in natural morphine was assumed in the X-ray studies and is represented in the diagram.

orless needles of **3a**, with a square cross section, are tetragonal, space group $I4_1$, with 16 molecules in the I cell. This is an extremely uncommon space group which appears to be represented by only two solved structures.[14,15]

The crystal conformations, X-ray nomenclature, and bond lengths for the two independent molecules are shown in Figure 1. The bond angles are listed in Table II and the torsion angles are shown in Table III of the supplementary material. The absolute configuration was not determined by the X-ray work and Figure 1 represents a configuration as in natural morphine. Since the crystals were from the unnatural (+) series, the real configuration would be the mirror image of that depicted in Figure 1. It seems relevant to discuss the molecular packing before the molecular structure since packing bears on the chemical results and is unusual. The basic packing unit is shown in Figure 2 and consists of a stack of molecules with approximate 4_2 symmetry connected by relatively strong O(4)–N hydrogen bonds. The two independent hydrogen bonds have lengths of 2.711 and 2.648 Å. Since the stacks are coextensive with the crystal domains, the tetragonal-needle crystal habit can be readily understood. Each stack is a double helix of molecules, and the available space is used economically although the individual helices are not connected, and contacts between molecules related by twofold axes appear to be of the van der Waals type. Had the space group been $P4_2$, all the stacks would have had molecules at the same level and there would have been rather large gaps in the crystal. By shifting each adjacent stack by $c/4$, rotating by 90°, and retaining only the 2-fold axis of the 4_2 operation, the space group becomes $I4_1$, and the packing is much more efficient.

Since the 4_2 symmetry is neither required by the space group nor retained exactly, an increase in packing efficiency is obtained by making use of the flexibility of the cyclohexenone ring, and thus the conformations of this ring are not identical in the two molecules. The conformation of the cyclohexenone ring could be described as half-chair[16] in the first molecule, whereas in the second molecule the

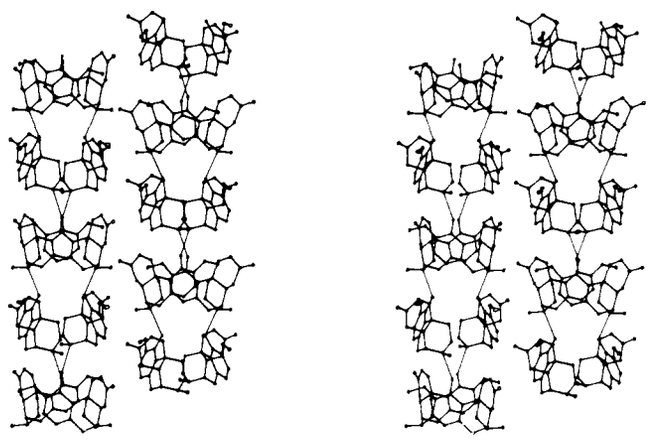

Figure 2. ORTEP[19] drawing of the two adjacent helices of **3a** showing hydrogen bonds.

conformation is roughly diplanar. The different conformations may be seen in Figure 1, particularly in the position of O(7), and are more quantitatively indicated in Table III of the supplementary material. If the exact 4_2 symmetry had been retained, the stacks of molecules would have to have been slightly further apart in the crystal. If the second molecule is generated from the first by a 4_2 operation, two close contacts of the carbonyl oxygen atom, O(7), with atoms in adjacent stacks are produced (O(7)–C(8) = 2.42 Å and O(7)–C(14) = 2.99 Å). In the actual crystal structure, the contacts are longer than 3.3 Å. The bond lengths and angles are similar to those in comparable compounds, conformational differences are explicable in terms of packing, and the agreement in bond lengths and angles of the two independent molecules is satisfactory. Only three differences in lengths appear to be significant, C(5)–C(6), C(6)–C(7), and C(9)–C(10), and even here the differences are very small. In the cyclohexenone ring the differences in bond lengths could result from slightly different degrees of overlap in the conjugated system since the shorter of the two C(5)–C(6) bonds corresponds to the smaller C(13)–C(5)–C(6)–C(7) torsion angle, and the longer of the C(6)–C(7) bonds is correlated with a greater deviation from planarity of the C(5)–C(6)–C(7)–O(7) group. The C(9)–C(10) difference may also be caused by packing but is not as easily rationalized. The differences between

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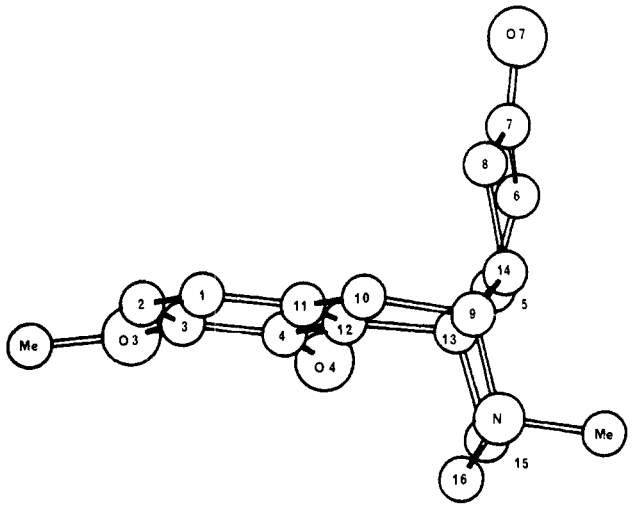

Figure 3. PLUTO[20] drawing of **3a** showing the organization of the atoms into two nearly perpendicular planes.

the appropriate angles are more significant, but the environments of the two molecules are not identical and angles are more susceptible to being changed by intermolecular forces.

The opening of the oxide bridge produces a molecule considerably changed in conformation from morphine itself. The basic structure consists of two nearly flat portions approximately at right angles to each other and is shown in Figure 3.

The isolation of an apparently pure isomer from the EtOAc solution where chemical evidence indicates an equilibrium is consistent with the crystal structure. The molecules of the tautomeric compound **4a** could not form hydrogen bonds with each other and are thus possibly less rapidly crystallized than **3a**, which can form infinite, hydrogen-bonded, interlacing double helices of molecules. A microscopic examination of the crystals used for X-ray work indicated a completely homogeneous sample.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of the Laboratory of Chemistry, NIAMDD. IR, UV, and mass spectra were obtained on Beckman 4230, Beckman DBG, and Hitachi RMU-6E (70 eV) spectrometers, respectively. ^{1}H NMR were obtained (with 1% v/v tetramethylsilane as internal reference) on Varian A-60 and Varian HR-220 spectrometers; ^{13}C NMR were obtained on a Varian XL-100 spectrometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Silica gel GF plates for analytical and preparative TLC were purchased from Analtech, Inc., Newark, DE.

(+)-4-Hydroxy-7-oxo-3-methoxy-17-methyl-5,6-dehydromorphinan (3a) and (+)-4,5-Epoxy-7-oxo-3-methoxy-17-methylmorphinan (4a). Dihydrosinomenine (5.0 g, 15 mmol) (**1a**) was reacted with polyphosphoric acid (ca. 100 g) at 65–70 °C for 1.25 h. After the usual workup, 3.37 g of a crude product was obtained. The reaction was repeated 11 times on the same scale, and the combined products (37.4 g) were purified by column chromatography (silica gel, 1:9 MeOH–Et_2O). The byproduct **3a** + **4a** (mp 104–106 °C; $[\alpha]^{20}_D$ +66.2° (*c* 1.10, $CHCl_3$)) was obtained from the initial eluate and recrystallized from EtOAc: 4.8 g (9.7%); mp 156–157 °C; mass spectrum, *m/e* 299 (M^+); $[\alpha]^{20}_D$ +34.1° (*c* 0.46, $CHCl_3$); UV (MeOH) λ_{max} 230, 282 nm (ϵ 15 000, 2200); IR ($CHCl_3$) 3530 (m, OH), 1715 (m, CO), 1680 (s, CO) cm^{-1}; ^{1}H NMR (220 MHz, $CDCl_3$) δ 7.71 (d, 1 H, J = 10 Hz, C_5H in **3a**), 6.60–6.74 (m, 4 H, aromatic H), 5.87 (d, 1 H, J = 10 Hz, C_6H in **3a**), 4.94 (d of d, 1 H, J_{vic} = 4 and 7 Hz, C_5H in **4a**), 3.81 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 2.67 (d of d, 1 H, $J_{vic,5,6}$ = 7 Hz, $J_{gem,6ax,6eq}$ = 25 Hz, C_{6ax}H in **4a**), 2.37 (s, 3 H, NCH_3), 2.35 (s, 3 H, NCH_3); ^{13}C NMR (15.2 Hz, $CDCl_3$) δ 206.9 (C-7 in **4a**), 199.2 (C-7 in **3a**), 158.8 (C-5 in **3a**), 125.9 (C-6 in **3a**), 90.0 (C-5 in **4a**), 56.3 and 55.9 (OCH_3 in **3a** and **4a**), 45.1 (C-6 in **4a**), 42.9 and 42.5 (NCH_3 in **3a** and **4a**); ^{1}H NMR of **3a** (NaOD, D_2O) δ 8.31 (s, 1 H, C_5H), 6.75 (d, 1 H, J = 9 Hz, C_2H), 6.24 (d, 1 H, J = 9 Hz, C_1H), 3.68 (s, 3 H, OCH_3), 2.22 (s, 3 H, NCH_3). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.40; H, 7.28; N, 4.96.

(+)-4-Acetyl-7-oxo-3-methoxy-17-methyl-5,6-dehydromorphinan (5a) and Its Hydrolysis. The tautomeric mixture (**3a** + **4a**) (0.3 g, 1 mmol) was dissolved in 3.0 mL of pyridine–acetic anhydride (1:1) and the solution was heated on a steam bath for 1.0 h. After removal of solvent in vacuo, the residue was treated with NH_4OH (2–3 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), the extracts were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The residue (ca. 0.4 g) was purified by using preparative TLC (silica gel, 1:9 MeOH–Et_2O). The acetyl derivative **5a** was obtained (0.27 g, 79%) as a pale yellow oil which resisted crystallization from a variety of solvents but which was homogeneous on TLC: IR ($CHCl_3$) 1760 (CH_3CO_2R), 1672 (C=CCO) cm^{-1}; NMR ($CDCl_3$) δ 7.36 (d, 1 H, J = 10 Hz, C_5H), 7.07 (d, 1 H, J = 9 Hz, C_2H), 6.86 (d, 1 H, J = 9 Hz, C_1H), 5.93 (d, 1 H, J = 10 Hz, C_6H).

The acetylated compound **5a** (103 mg) was suspended in 3 mL of 1 N NaOH, and the mixture was heated on a steam bath for 1 h. The solution was made acidic with 10% HCl and then made basic again with NH_4OH. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and dried over Na_2SO_4 and the solvent was evaporated. The residue (97 mg) was purified by preparative TLC (silica gel, 1:9 MeOH–$CHCl_3$) to give 69 mg (77%) of product (**3a** + **4a**); mp 103–105 °C (Et_2O–hexane). NMR showed that the product was a ca. 1:1 mixture of **3a** + **4a**. A mixture melting point with authentic sample gave no depression.

(+)-4-Hydroxy-7-oxo-3-methoxy-17-methylmorphinan (6a). The tautomeric mixture (**3a** + **4a**) (300 mg, 1 mmol) in MeOH (10 mL) was hydrogenated (10% Pd/C, 0.2 g) at 25 °C (760 mm). After removal of catalyst, the solvent was evaporated in vacuo and the residual material purified via preparative TLC (silica gel; 1:9 MeOH–$CHCl_3$). Recrystallization from Et_2O gave 0.27 g (90%) of **6a**: mp 133.5–134.5 °C (lit.[7] mp 130 °C); $[\alpha]^{20}_D$ +37.3° (*c* 2.2, $CHCl_3$); mass spectrum, *m/e* 301 (M^+); IR ($CHCl_3$) 3560 (OH), 1700 (CO) cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.70; H, 7.86; N, 4.80.

(−)-4,5-Epoxy-7α-hydroxy-3-methoxy-17-methylmorphinan (8b). (−)-8,14-Dehydro-4,5-epoxy-7α-hydroxy-3-methoxy-17-methylmorphinan (**7b**, 789 mg, 2.6 mmol), obtained from thebaine,[11] was dissolved in MeOH (50 mL) and hydrogenated over 10% Pd/C (350 mg, 760 mm, 25 °C, 10 h). After removal of the catalyst by filtration, the solvent was removed in vacuo. The residual material (ca. 750 mg) was purified by column chromatography (silica gel, 2:5 MeOH–Et_2O) to give **8b** which was recrystallized from Et_2O (605 mg, 77%): mp 157–158 °C; $[\alpha]^{20}_D$ −95.4° (*c* 0.37, $CHCl_3$); IR ($CHCl_3$) 3600 (OH) cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.51; H, 7.58; N, 4.83.

(−)-4-Hydroxy-7-oxo-3-methoxy-17-methyl-5,6-dehydromorphinan (3b). A mixture of **8b** (550 mg, 1.7 mmol), benzophenone (680 mg, 37 mmol), and *t*-BuOK (4.0 g, 36 mmol) in benzene (20 mL) was heated to reflux for 1 h under nitrogen. The cooled mixture was made acidic with 10% HCl. The aqueous layer was separated, and the benzene layer was extracted with 10% HCl (2 × 30 mL). The combined acidic extracts were made basic with NH_4OH and the solution was extracted with CH_2Cl_2 (5 × 50 mL). The organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue (ca. 600 mg) was recrystallized twice from EtOAc to afford pure **3b**: 431 mg (78%); mp 156–157 °C; $[\alpha]^{20}_D$ −34.0° (*c* 0.532, $CHCl_3$). IR and NMR spectra and TLC were identical with those of the (+) enantiomer (**3a**). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 71.78; H, 6.97; N, 4.59.

(−)-4-Hydroxy-7-oxo-3-methoxy-17-methylmorphinan (6b). The alcohol **3b** (300 mg, 1 mmol) was dissolved in MeOH (10 mL) and hydrogenated over 10% Pd/C (200 mg, 760 mm, 25 °C). After removal of the catalyst, the filtrate was concentrated to dryness. The residue was purified by using preparative TLC (silica gel, 1:9 MeOH–$CHCl_3$). The product (ca. 250 mg) was recrystallized from Et_2O to afford pure **6b**: 220 mg (73%); mp 131–132 °C; $[\alpha]^{20}_D$ −35.8° (*c* 0.19, $CHCl_3$). IR and NMR spectra and TLC were

Table I. Crystal and Experimental Data for 3a

molecular formula: $C_{18}H_{21}NO_3$	crystal size: 0.3 × 0.2 × 0.2 mm
molecular weight: 299.37	reflections: 3138 (715 unobserved 1σ)
habit: prismatic tetragonal needles	maximum $(\sin\theta)/\lambda$: 0.62 A^{-1}
radiation: Cu Kα (graphite monochromator)	diffractometer: Nonius CAD-4
wavelength: 1.5418 Å	LS weighting after Peterson and Levy[a]
space group: $I4_1$ (No. 80)	function minimize: $\Sigma w\Delta^2$
cell dimensions (from LS reft. of $\pm\theta$ data)	anisotropic temperature factor: $\exp[-2\pi^2 \times (\Sigma_i\Sigma_j U_{ij}U_{jj}a^*_i a^*_j h_i h_j)]$
$a = b = 21.228$ (2) Å	final R factor (observed reflections only): 3.1%
$c = 13.614$ (2) Å	
$V = 6134.85$ Å^3	
$Z = 16$ (asymmetric unit is two molecules)	
$D_m = 1.29$ (1) g cm^{-3}	
$D_x = 1.296$ g cm^{-3}	

[a] S. W. Peterson and H. A. Levy, *Acta Crystallogr.*, **10**, 70 (1957).

identical with those of the (+) enantiomer (**6a**).

X-ray Crystallography. X-ray experimental data are given in Table I. Given that the X-ray symmetry is $4/m$ and that the absence patterns (hkl only for $h + k + l = 2n$ and $00l$ only for $l = 4n$) were definite, the space group was unambiguous. Since there are eight equivalent positions in the cell, the asymmetric unit would consist of two molecules if the suggested chemical formula of either isomer was correct. It was not possible to decide whether or not the two molecules were identical with only the foregoing information.

There were 176 nonhydrogen atoms in the primitive cell and thus the crystallographic phase problem was not, in principle, particularly formidable except for the possibility of pseudosymmetry (later substantiated) and the fact that the tetragonal body-centered space group allowed only one origin-determining reflection and thus necessitated the use of more undefined phases than a space group of lower symmetry.

During the data collection, three standard reflections were measured after each interval of 2-h X-ray exposure, and no significant evidence of radiation damage was detected.

The MULTAN78[17] set of programs was used in this work but initial attempts, using up to 10 variable phases, were unsuccessful. Invariably, despite considerable variation of input parameters, all phase solutions were essentially identical and led to E maps with one peak of height at least four times that of any other. Such "solutions" had very good R(Karle) values but very unsatisfactory PSIZERO values.

An analysis of the complete set of E values did not indicate much deviation from expected statistics although the distribution of the $hk0$ E values was hypercentric. However, if one considered only the larger E values, as in the set used with MULTAN78, the number of E values with l even was considerably greater than that for l odd and the 17 largest E values all had l even. A renormalization, involving an increase of the scale factor by 10% for reflections with l odd and a corresponding decrease for those with l even, was carried out to produce similar distributions for E values greater than 2.0 in the two groups. The modified set, consisting of 440 E values, was used with eight variable phases. Fully 50% of the solutions corresponded to the previous large peak result but six solutions out of 103 had reasonable values of both R(Karle) and PSIZERO. The large peak result had R(Karle) = 25% and PSIZERO = 3.7, while the promising results had R(Karle) = 32% and PSIZERO = 1.1. The three MULTAN78 tests, ABSFOM, PSIZERO, and R(Karle), were weighted in the ratio 0.5:1.5:1.0, and the best three solutions were tested in order of overall figure of merit. The first solution showed two molecules differing only in a single substituent, with corresponding atoms related by a 4_2 axis and a structure essentially that predicted chemically for an opened oxide bridge. There were a few extra peaks, but all final heavy atoms were visible in one molecule and all but one in the other. The two next best results were similar, but, since they possessed more extra peaks, interpretation was less definite.

All further X-ray work used the programs of the XRAY72 system.[18] Refinement of the model derived from the first solution, despite the pseudosymmetry, was fairly routine, extra peaks were readily eliminated, another atom was found to make the two independent molecultes identical chemically, and there was a gradual small deviation from the initially nearly exact 4_2 positional symmetry. It was fortunate that the pseudosymmetry did not tend to generate a space group of higher symmetry and thus cause computational problems. (The final list of heavier atom parameters, in Table IV, also shows the distances of the atoms of the second molecule from a set generated from the first by the 4_2 operation.) All hydrogen atoms were found and refined without difficulty. The final refinements used anisotropic thermal parameters for the heavier atoms and isotropic parameters for the hydrogen atoms. As usual, in a large structure with a polar axis, the strategy of fixing the origin by holding one parameter constant was unsatisfactory because of finite computer word length, especially since considerable partitioning of the normal equations matrix was required. The method of using alternate cycles, holding one molecule completely fixed and refining the other, produced convergence. The final two cycles of refinement were done with the hydrogen atom parameters held constant and led to essentially complete convergence although there were no significant changes in the R factor or bond lengths. The final R factor was 3.1% and final atomic parameters are given in Tables IV and V (Supplementary Material). A table of observed and calculated structure factors was provided for the use of the referees and may be obtained from J.V.S.

Registry No. **1a**, 65494-41-9; **3a**, 73079-27-3; **3b**, 73135-95-2; **4a**, 73079-28-4; **5a**, 73079-29-5; **6a**, 73079-30-8; **6b**, 73135-96-3; **7b**, 22952-70-1; **8b**, 73079-32-0.

Supplementary Material Available: Tables of the bond angles and torsion angles and parameters of heavier atoms and of the hydrogen atoms of **3a** (4 pages). Ordering information is given on any current masthead page.

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