(7) While one could picture iminotriphenylphosphorane itself effecting the transformation described here, its experimental use proves to be less than ideal. Since simple exposure to the atmosphere results in hydrolysis to ammonia and triphenylphosphine oxide, rigorously anhydrous conditions are required for its synthesis, storage, and use. Reactions of this reagent with other than the most highly reactive of ketones are thus often complicated by decomposition of the reagent. In contrast, the trimethylsilyl-protected compound employed here is stable to atmospheric moisture and requires no undue care in its manipulations.

Studies in the (+)-Morphinan Series. 4.[1] A Markedly Improved Synthesis of (+)-Morphine

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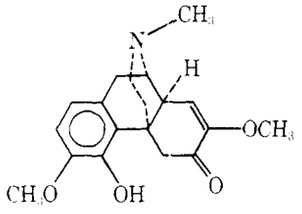
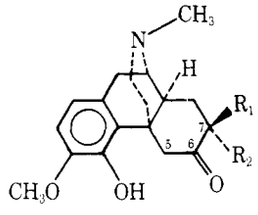
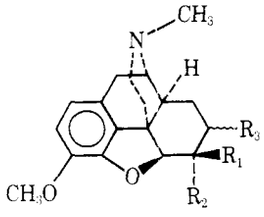
The absolute configuration of the morphinan skeleton of (−)-sinomenine (**1**)[3] is enantiomeric to natural (−)-morphine, and conversion of **1** into (+)-morphine (**10**) was reported by



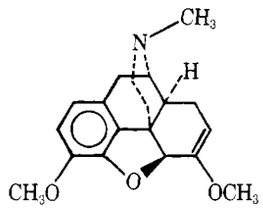
1



2a, R_1 = OCH_3; R_2 = H
b, R_1 = H; R_2 = OCH_3



3, R_1, R_2 = O; R_3 = H
4, R_1 = R_2 = OCH_3; R_3 = H
6, R_1 = R_2 = OCH_3; R_3 = Br



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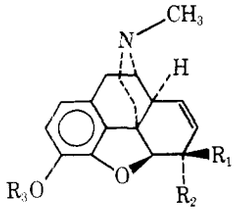

7, R_1 = R_2 = OCH_3; R_3 = CH_3
8, R_1, R_2 = O; R_3 = CH_3
9, R_1 = OH; R_2 = H; R_3 = CH_3
10, R_1 = OH; R_2 = R_3 = H
11, R_1 = OAc; R_2 = H; R_3 = Ac

Goto's group.[4a-c] To define morphine's interaction with opiate receptors more clearly,[5] we wanted to prepare large quantities of unnatural enantiomer **10** and several of its congeners. We now summarize our results that followed, in principal, Goto's original scheme,[4a-c] but which implemented novel reactions and the findings of others, especially those of Rapoport et al.[6] Rapoport's results in the natural (−) series became available only after we had started our project. A tenfold increase in the overall yield of (+)-morphine (**10**), previously reported by Goto, from (−)-sinomenine (**1**) was accomplished as follows.

Catalytic reduction[7] of **1** afforded a mixture of two diastereomers (**2a** and **2b**) which was separated by preparative thin-layer chromatography. The equilibrium mixture was reestablished by brief boiling of either isomer in methanol. Deuterium exchange of **2a** and **2b** allowed definitive assignment of the chemical shift of the C-5 and C-7 protons. Assuming that the preferential conformation of ring C is the chair form, the absolute configuration of **2a** and **2b** at C-7 could be determined. Major isomer **2a** and minor isomer **2b** were assigned 7*R* (axial H) and 7*S* (equatorial H) configurations, respectively, for the following reasons. The chemical shift of the C-7 equatorial proton, due to the shielding effect of the carbonyl group in the 7*S* isomer, lies upfield of the C-7 axial proton in the 7*R* isomer, in accord with previous work on α-methoxydecalones.[8] The chemical shift of the C-7 proton of the 7*S* isomer was δ 3.36 (t, J = 3.5 Hz) and that of the C-7 proton in the 7*R* isomer was δ 3.90 (center of d of d, J = 7, 12 Hz), and the coupling constants were of the magnitude expected. The equatorially oriented C-7 methoxyl group in the 7*R* isomer was deshielded by the carbonyl group (δ 3.43), as compared with the methoxy group in the 7*S* isomer (δ 3.30), again in accord with α-methoxydecalones.[8] Molecular models (Dreiding) indicate that the major product might well be the 7*R* isomer because of the less sterically hindered methoxyl group. The C-5 equatorial proton in both 7*R* and 7*S* isomers was considerably deshielded, presumably due to its proximity to the aromatic ring (see Experimental Section). A similar effect was noted in dihydrothebainone.[6]

Since the next step, the acid-catalyzed S_N2' cyclization of **2a** and **2b** to **3**, with loss of methanol, proceeds under conditions which equilibrate the two epimers, the mixture was treated directly with polyphosphoric acid at 65–70 °C. Ketone **3** is rather stable under these reaction conditions, in contrast to Goto's[9] more drastic conditions; and yields of desired ketone **3** were consistently 70–75%.

Introduction of a double bond in the 7,8 position of **3** is not easy, and attempts to introduce it by direct oxidation were unsuccessful. This could, however, be accomplished by phenylselenation and oxidative elimination, but only after the *N*-methyl group was replaced by a *N*-carbethoxy group.[10] Meanwhile, Rapoport's modification for converting (−)-dihydrocodeinone (enantiomer of **3**) into (−)-codeinone (enantiomer of **8**) became known[6] and was successfully implemented in our plan, which now took the following course: ketalization of **3** to dimethyl ketal **4** (98%); elimination of methanol with *p*-toluenesulfonic acid in chloroform to give enol methyl ether **5** (83%); addition of methyl hypobromite, leading to bromodimethyl ketal **6** (75%); elimination of HBr with potassium *tert*-butoxide in Me_2SO at room temperature instead of 60 °C[6] to give **7** (87%); and deketalization of **7** with 5% HCl instead of AcOH[6] to give (+)-codeinone (**8**; 96%).

Compounds **3** and **5–8** showed the properties previously reported by Goto et al., and **3–8** had properties identical with the corresponding compounds in the (−) series prepared as described by Rapoport,[6] except for the optical rotation. Reduction of unsaturated ketone **8** with sodium borohydride in methanol[11] afforded (+)-codeine (**9**), which was converted into (+)-morphine (**10**) by O-demethylation[12] with boron tribromide in chloroform. Unknown (+)-heroin (**11**) was obtained from **10** by treatment with acetic anhydride. Crystallization from ethyl acetate gave prisms identical with authentic (−)-heroin (enantiomer of **11**), except for the sign of optical rotation. (−)-Heroin showed specific optical rotation 10° higher than previously reported.[13]

(+)-Codeine (**9**), (+)-morphine (**10**), and (+)-heroin (**11**) showed no analgesic activity on subcutaneous injection in mice in routine screening for centrally active analgesics. Unnatural

(+)-morphine (**10**) showed interesting central effects when injected intracerebrally in rats, suggesting the existence of multiple morphine receptors in the brain.[14]

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 this Laboratory. The identity and chemical purity of **3–11** were confirmed by direct comparison with authentic samples of the enantiomeric (−) series. IR, NMR (using tetramethylsilane at δ 0.0 as an internal reference), and mass spectra were obtained on Perkin-Elmer 257, Varian Model HR-220, and Hitachi RMU-6E (70 eV) instruments, respectively. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Silica gel GF plates for analytical and preparative TLC were purchased from Analtech, Inc., Newark, Del.

7(*R*)- and 7(*S*)-(+)-Dihydrosinomenine (2a and 2b). Sinomenine (**1**; 16.6 g, 50.40 mmol) was dissolved in MeOH (450 mL) and hydrogenated using 10% Pd/C as a catalyst until the absorption of hydrogen stopped at approximately 1 mol. After filtration of the catalyst, the solvent was evaporated to give an oil residue which solidified on the addition of ether (200 mL), and the product was collected by filtration. This product (16.5 g) melted at 190–195 °C (lit.[7] mp 198 °C) and was used for conversion to **3** without further purification. Preparative TLC of a portion (150 mg) of this mixture of position 7 epimers over silica gel GF (Et_2O–MeOH, 9:1) gave as the major component the lower R_f 7*R* epimer (100 mg, 67%), which showed, after crystallization from $CHCl_3$–Et_2O (1:10), mp 196.5–197.5 °C; $[\alpha]^{23}_D$ +121° (*c* 1.28, $CHCl_3$); IR ($CHCl_3$) 1733 cm^{-1}; NMR ($CDCl_3$) δ 6.60 (2 H, AB system, J = 8 Hz, aromatic H), 6.44 (1 H, brd s, OH), 4.30 (1 H, d, J = 13 Hz, C-5 equatorial H), 3.90 (1 H, dd, J = 7, 12 Hz, C-7 axial H), 3.80 (3 H, s, aromatic OCH_3), 3.43 (3 H, s, C-7 OCH_3), 2.41 (3 H, s, N–CH_3), 2.25 (1 H, d, J = 13 Hz, C-5 axial H).

Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.04; H, 7.54; N, 4.18.

The higher R_f 7*S* epimer (39 mg, 26%) was obtained as the minor isomer and showed, after crystallization from $CHCl_3$–Et_2O (1:10), mp 196.5–197.5 °C; $[\alpha]^{23}_D$ +87° (*c* 1.49, $CHCl_3$); IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 6.64 (2 H, dd, J = 8 Hz, aromatic H), 6.26 (1 H, brd s, OH), 4.07 (1 H, d, J = 13 Hz, C-5 equatorial H), 3.82 (3 H, s, aromatic OCH_3), 3.36 (1 H, t, J = 3.5 Hz, C-7 equatorial H), 3.30 (3 H, s, C-7 OCH_3), 2.73 (1 H, d, J = 13 Hz, C-5 axial H), 2.42 (3 H, s, N–CH_3).

Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.08; H, 7.54; N, 4.13.

(+)-Dihydrocodeinone (3). The mixture of **2a** and **2b** from above (3.00 g, 9.05 mmol) and polyphosphoric acid (Matheson, Coleman and Bell, 60 g) was heated at 65–70 °C for 1.25 h while stirring. The cooled reaction mixture was basified by the careful addition of ammonium hydroxide (28%) at 0 °C, saturated with NaCl, and extracted with $CHCl_3$. The extracts were dried over Na_2SO_4 and evaporated to afford a solid, which was recrystallized from Et_2O–$CHCl_3$ (3:1) to give **3** (1.98 g, 73%): mp 196 5–197.5 °C (lit.[9] mp 197–198 °C); $[\alpha]^{23}_D$ +205.3° (*c* 0.9, $CHCl_3$) [lit.[3] $[\alpha]_D$ +207.4° ($CHCl_3$)].

Conversion of (+)-Dihydrocodeinone (3) to (+)-Codeine (9). (+)-Codeine (**9**) was prepared from (+)-dihydrocodeinone (**3**) essentially as described by Rapoport[6] in the (−) series via the following intermediates. (+)-Dihydrocodeinone dimethyl ketal **4**: mp 121–122 °C; $[\alpha]^{23}_D$ +167.2° (*c* 1.1, EtOH) [lit.[15] (−) enantiomer of **4**: mp 122–123 °C, $[\alpha]_D$ −151° (*c* 0.9, EtOH)]. (+)-8,14-Dihydrothebaine (**5**): mp 162–165 °C; $[\alpha]^{23}_D$ +268.6° (*c* 1.1, C_6H_6) [lit.[4c] mp 162–163 °C, $[\alpha]_D$ +268.2° (*c* 1.544, C_6H_6)]. (+)-7-Bromodihydrocodeinone dimethyl ketal **6**: mp 116–117 °C; $[\alpha]^{23}_D$ +165.1° (*c* 1, $CHCl_3$) [lit.[4c] mp 117 °C, $[\alpha]_D$ +164.5° (c 1.536, $CHCl_3$)]. Treatment of **6** with potassium *tert*-butoxide at 25 °C (48 h) instead of 60 °C[6] gave (+)-codeinone dimethyl ketal **7**: mp 135–136.5 °C; $[\alpha]^{23}_D$ +238.3° (*c* 1.2, EtOH) [lit.[4c] mp 138 °C, $[\alpha]_D$ +236° (*c* 1.016, EtOH)]. Hydrolysis of **7** with 5% HCl (0.5 h, 75 °C) instead of AcOH–H_2O[6] gave (+)-codeinone (**8**): mp 185–186 °C; $[\alpha]^{23}_D$ +204.5° (*c* 1, EtOH) [lit.[4d] mp 186 °C, $[\alpha]_D$ +206.0° (EtOH)]. Reduction of **8** with $NaBH_4$ in MeOH gave (+)-codeine (**9**): mp 157.5–158.5 °C; $[\alpha]^{23}_D$ +136.2° (*c* 0.7, EtOH) [lit.[4a] mp 158 °C, $[\alpha]^{25}_D$ +137.4° (*c* 0.743, EtOH)].

(+)-Morphine (10). To a stirred solution of BBr_3 (6.00 g, 24 mmol) in $CHCl_3$ (70 mL) was added **9** (1.167 g, 3.9 mmol) in $CHCl_3$ (10 mL) at 23–26 °C over a 2-min period, and stirring was continued for 15 min. The reaction mixture was poured into a stirred mixture of ice (32 g) and NH_4OH (28% NH_3, 8 mL) and stirred for 30 min at 0 °C. The crystalline material which formed was filtered, washed with cold $CHCl_3$ and then water, and dried to give **10** (800 mg). The aqueous phase from the filtrate was saturated with NaCl and extracted with $CHCl_3$–EtOH (3:1). The combined extracts were evaporated, and the residue was purified by silica gel thin-layer chromatography using $CHCl_3$–MeOH (8:2) as a solvent to yield **10** (241 mg). Total yield was 88%. Recrystallization from MeOH gave **10**·H_2O as colorless prisms: mp 253–255 °C; $[\alpha]^{23}_D$ +132.1° (*c* 0.49, MeOH) [lit.[4a] mp 247–248 °C, $[\alpha]^{23}_D$ +132.1° (*c* 0.383, MeOH)].

Anal. Calcd for $C_{17}H_{19}NO_3$·H_2O: C, 67.30; H, 6.98; N, 4.62. Found: C, 67.47; H, 7.25; N, 4.63.

(+)-Heroin (**11**). A mixture of **10** (285 mg, 1 mmol) and acetic anhydride (2 mL) was heated at 90–100 °C for 4 h. Ether was added to the cooled solution, and the mixture was basified with 10% KOH while cooling. The ether phase was separated, the aqueous phase was extracted with ether, and the combined extracts were dried over Na_2SO_4. The solvent was evaporated to give a solid, which was recrystallized from AcOEt to afford **11** (295 mg, 80%): mp 169–170.5 °C; $[\alpha]^{23}_D$ +176° (*c* 0.63, MeOH) [lit.[13] (−) enantiomer of **11**: mp 173 °C, $[\alpha]^{25}_D$ −166.4° (*c* 1.49, MeOH)].

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.97; H, 6.37; N, 3.44.

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Registry No.—**1**, 115-53-7; **2a**, 65120-75-4; **2b**, 65120-76-5; **3**, 64520-24-7; **4**, 65165-95-9; **5**, 65165-96-0; **6**, 65165-97-1; **7**, 65165-98-2; **8**, 65494-91-9; **9**, 64520-25-8; **10**, 65165-99-3; **11**, 65166-00-9.

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Cleavage of Tetrahydrofuran by Lithium Bis(2,6-di-*tert*-butylphenoxy)aluminum Hydride

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The reaction of lithium aluminum hydride ($LiAlH_4$) with 2 or 3 molar equiv of 2,6-di-*tert*-butylphenol (I) at room temperature gives lithium bis(2,6-di-*tert*-butylphenoxy)-aluminum hydride (II; eq 1). This is confirmed in Table I for

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