give a 65% yield of pure material.[21-23]

Reaction of $(C_6H_5S)_2$. Trifluoroacetic acid (8.0 g, 70 mmol), $(C_6H_5S)_2$ (1.0 g, 4 mmol), and Mg (0.025 g, 1 mmol) were heated in a sealed reactor for 12 h at 150 °C. The TFA was removed in vacuo to leave an oil and a white solid. This mixture was then sublimed/molecular stilled at 60 °C (10 Pa). The sublimate as well as the residue contained phenylene sulfide polymers with n = 1–5 (mass spectroscopy).[24-28]

Hydrolysis Experiments. Distilled water (5 mL) and an equal volume of the ester were heated at reflux for 2 h. The products were identified by IR and confirmed by boiling or melting points. Except for the butyl ester, complete hydrolysis took place. The butyl ester did not hydrolyze. Equal volumes (2 mL) of the benzyl ester and water were heated at 190 °C in a sealed tube for 2 h. The major additional material isolated was polybenzyl polymer.

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Registry No. Trifluoroacetic acid, 76-05-1; ethyl trifluoroacetate, 383-63-1; *n*-butyl trifluoroacetate, 367-64-6; benzyl trifluoroacetate, 351-70-2; phenyl trifluoroacetate, 500-73-2; methyl trifluoroacetate, 431-47-0; 2-naphthol, 135-19-3; 2-naphthyl trifluoroacetate, 398-49-2; bis(1-phenylethyl)ether, 93-96-9; polystyrene, 9003-53-6; 2-naphthyl ethyl ether, 93-18-5; benzyl ether, 103-50-4; poly(phenylene-methylene), 31830-66-7; benzyl phenyl ether, 946-80-5; benzyl ethyl ether, 539-30-0; ethyl *n*-butyl ether, 628-81-9; diphenyl ether, 101-84-8; *S*-phenyl thiotrifluoroacetate, 2378-04-3; diphenyl disulfide, 882-33-7; phenylene sulfide polymer, 9016-75-5.

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Derivatives of the Thebaine Anion. 1. Structure of Metopon. A Direct Demonstration

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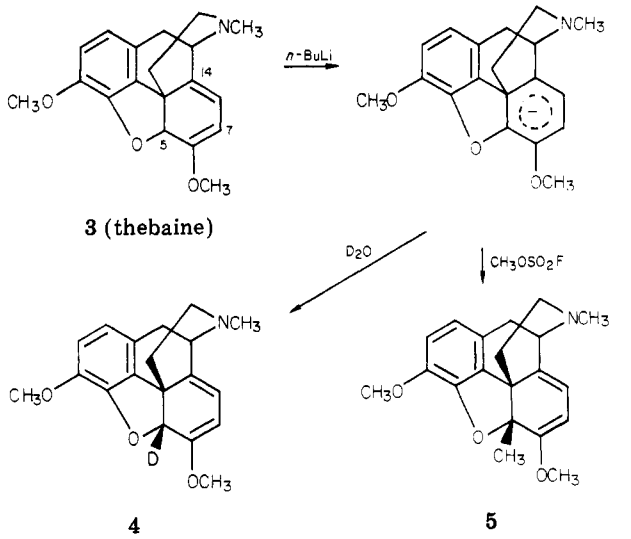
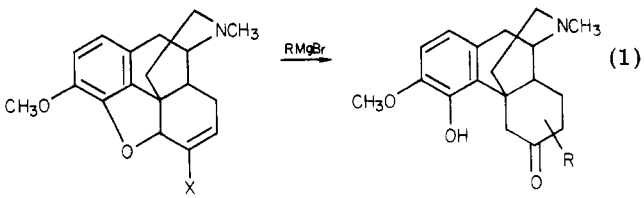
Small and his co-workers some years ago showed that the action of Grignard reagents on any of several $\Delta^{6,7}$ derivatives of the opium alkaloids led to abnormal products in which alkylation at two different positions had taken place and the oxide bridge had been opened.[1] Dihydrocodeinone behaves in a similar fashion although the reaction is very sluggish and must be forced.[2] Deoxycodeine

Scheme I



C (1, X = H) likewise yields alkyl derivatives in which the oxide bridge is open[1] (eq 1).



(1)

From the methyldihydrothebainone (2, R = CH_3) formed in larger amount, a methyldihydromorphinone was prepared by reclosure of the oxide bridge and demethylation[1b]; the substance so produced (metopon, **9**) was at one time thought to be of great promise as an analgesic. The position of the methyl group in this substance was not ascertained by Small. Stork and Bauer[3] were able to show that the isomer formed in lesser amount carried the new methyl group at C_7 by demonstrating the identity of "isomethyldihydrocodeinone" with 7-methyldihydrocodeinone prepared unambiguously from dihydrocodeinone. By exclusion, the structure of metopon is thus 5-methyldihydromorphinone.

Although thebaine (**3**) has been the subject of chemical studies since 1835 and at least 300 papers on the chemistry of it and its derivatives have been published, to our knowledge the easy formation of an anion from it has not hitherto been reported. During the course of work on another problem, one of us (R.M.B.) observed[4] the formation of a deep burgundy-red color on treatment of a solution of thebaine in tetrahydrofuran with *n*-butyllithium at −78 °C (Scheme I). Quenching the solution with deuterium oxide yielded a monodeuteriothebaine (**4**) whose NMR spectrum no longer showed the characteristic singlet at δ 5.34 of the proton on C_5. Treatment of the anion with methyl fluorosulfonate gave a methylthebaine (**5**) whose NMR no longer showed the C_5 proton singlet but did show a new methyl singlet at δ 1.76 as well as the C_7–C_8 vinyl protons as an AB quartet as in thebaine itself. Of the possible ring C methylation products (methyl at C_5, C_7, or C_{14}), these data are consistent only with 5-methylthebaine. Methylation at C_7 would yield substances with only one vinyl proton (C_8), and a methyl group at C_{14} should show

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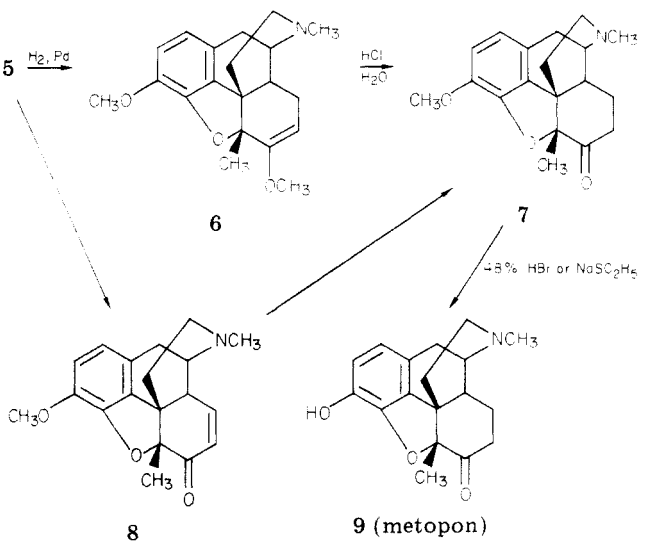
Scheme II



resonance at δ 1.30 or lower. Alkylation with benzyl chloride and acylation of this anion were also successful and will be reported separately.

The formation of a pentadienate anion by removal of the C_5 proton is readily understandable. The preference for C_5 for both deuteration and methylation is presumably a reflection of the fact that these reactions at C_7 or C_{14} would, at least initially, place unsaturation between C_5 and C_6, a position at which planarity is difficult if not impossible.

With an easy and unambiguous route to 5-methylthebaine at hand, it was a simple matter to proceed to 5-methyldihydrocodeinone (5-methylcodone) and to metopon by either of two routes. Hydrogenation of **5** yields 5-methyldihydrothebaine (**6**) cleanly (Scheme II). This reaction on thebaine itself is less clean and gives dihydrothebaine, dihydrothebainone, and dihydrothebainol, depending on the conditions;[1b,5] with **5** there is presumably more hindrance to cleavage of the oxide ring on hydrogenation. Acid hydrolysis of **6** yields 5-methyldihydrocodeinone **7**[1b] and cleavage of **7** with 48% HBr or with sodium thioethoxide[6] gives metopon (**9**).

An alternative route to **7** proceeds through 5-methylcodeinone (**8**), prepared from **5** by the method of Dauben, Baskin, and von Riel.[7] Reduction of **8** by L-Selectride[8] proceeds exclusively by the 1,4-route to give **7** in 91% yield.

In all of these substances, the methyl group at C_5 has the same configuration (axial or pseudoaxial) as the hydrogen atom at C_5 in the parent substances since the highly rigid fused-ring system allows the oxide bridge between C_4 and C_5 to close *only* with the equatorial bond at C_5.

Besides demonstrating the structure of metopon in a direct way, these new syntheses provide much more efficient routes to this substance than the method developed by Small. Yields are in the neighborhood of 51% overall.

The abnormal Grignard reactions observed by Small[1] appear to be yet further examples of the tendency of the oxide bridge in the opium alkaloids to open under the influence of Lewis acids, a tendency first recognized by Stork, whose brilliant clarification of a number of diverse rearrangements of these substances made use of this tendency as a common initiating step.[9]

Experimental Section

IR spectra were recorded on a Beckman Acculab 8 infrared spectrometer or on a Perkin-Elmer 467 grating infrared spectrometer. NMR spectra were recorded on either a Varian EM 390 NMR spectrometer or a Bruker WH 400 NMR spectrometer in $CDCl_3$. Mass spectra were determined on a Du Pont 21490B mass spectrometer. The elemental analyses were carried out by Galbraith Laboratories. All melting points are corrected.

Thebaine Anion. 5-Methylthebaine (5). A solution of 5.00 g of thebaine in 400 mL of tetrahydrofuran, freshly distilled from either LAH or sodium benzophenone ketyl, was treated with stirring under N_2 at −78 °C with 18 mL of 1.33 M *n*-butyllithium in hexane. A deep wine-red color was produced immediately. After 20 min at −78 °C, 1.6 mL of methyl fluorosulfonate was added. Only a slight change in color was observed. After being stirred a further 20 min at −78 °C the solution was allowed to come to room temperature over 2 h, during which the color changed to orange-yellow. Water (5 mL) was added, and most of the solvent was removed at diminished pressure. The yellow-brown residue was taken into chloroform, washed twice with water, filtered through anhydrous Na_2SO_4, and concentrated. The residue crystallized spontaneously as a chloroform solvate. Recrystallization from ethyl acetate gave 3.31 g of product, mp 157–158 °C. The mother liquor after concentration and chromatography on silica gel (elution with 2% methanol in chloroform) gave an additional 1.30 g of product of comparable quality (total yield of **5** 4.61 g, 88%). A sample was crystallized several times from ethyl acetate for analysis: mp 158–159 °C; mass spectrum, *m/e* 325, 310, 269, 188; IR ($CHCl_3$) 2917, 2857, 1617, 1450, 1115, 910, 870 cm^{-1}; NMR δ 1.76 s (3 H, C_5 Me), 2.45 (s, 3 H, NMe), 3.53 (s, 3 H, C_6 OMe), 3.80 (s, 3 H, C_3 OMe), 4.90 (d, 1 H, J = 6 Hz, C_8 H), 5.50 (d, 1 H, J = 6 Hz, C_7 H), 6.57 (br s, 2 H, aromatic H); $[\alpha]^{23}_D$ −259° (*c* 1.16, alcohol). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.73; H, 7.21; N, 4.25.

5-Deuteriothebaine (4). To a solution of thebaine anion produced as described above from 1.00 g of thebaine at −78 °C was added 30 mL of D_2O. The color faded to yellow, and after the mixture warmed to room temperature, the organic layer was separated and dried over $MgSO_4$. Concentration of the solution and crystallization of the residue from ethyl acetate gave 472 mg (47%) of **4**, mp 193–194.5 °C. Its NMR was indistinguishable from that of thebaine except for the absence of the singlet at δ 5.34 (C_5 proton).

5-Methyldihydrothebaine (6). A mixture of 650 mg of **5**, 95 mg. of 10% $PdCl_2$ on charcoal, and 25 mL of alcohol was stirred under hydrogen at 1 atm for 1 h during which 58 mL (55 mL, theory) of hydrogen was absorbed. The catalyst was removed by filtration, and the filtrate was concentrated to yield 656 mg of residue which crystallized spontaneously; mp 153–162 °C. Recrystallization from alcohol gave a total of 460 mg (70%) of **6** (mp 169–171 °C) in several crops. A small sample was crystallized several more times for analysis: mp 170.5–172 °C; mass spectrum, *m/e* 327, 312, 270, 190; IR (Nujol) 1660, 1500, 1270, 1205, 1050, 875, 855, 811, 800 cm^{-1} inter alia; NMR δ 1.67 (s, 3 H), 2.40 (s, 3 H), 3.52 (s, 3 H), 3.78 (s, 3 H), 5.20 (dd, 1 H), 6.56 (complex d, 2 H); $[\alpha]^{23}_D$ −152° (*c* 1.33, alcohol). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.53; H, 7.93; N, 4.22.

5-Methyldihydrocodeinone (7). (a) From 5-Methyldihydrothebaine (6). A solution of 300 mg of **6** in 10 mL of 10% HCl was heated to boiling for 10 min, cooled, made basic with ammonia, and extracted four times with chloroform. The extracts were washed with water, filtered through anhydrous sodium sulfate, and concentrated to give 291 mg (101%) of colorless glass which crystallized spontaneously: mp 143–145.5 °C (lit.[1b] mp 144–144.5 °C); $[\alpha]^{23}_D$ −151° (*c* 0.960, alcohol) (lit.[1b] $[\alpha]^{23}_D$ −146.9°); IR 1722, 1427, 1100, 980, 960, 903 cm^{-1} inter alia; NMR δ 1.58

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(7) Dauben, W. G.; Baskin, C. P.; van Riel, H. C. A. *J. Org. Chem.* **1979**, *44*, 1567.

(8) Lithium tri-*sec*-butylborohydride

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(s, 3 H), 2.40 (s, 3 H), 3.85 (s, 3 H), 6.60 (complex d, 2 H).

(b) From 5-Methylcodeinone (8). A solution of 622 mg of 8 in 5 mL of dry tetrahydrofuran was treated at 0 °C under N_2 with 2.4 mL of a 1 M solution of lithium tri-*sec*-butylborohydride in tetrahydrofuran. The mixture was allowed to warm to room temperature over 30 min when a TLC probe indicated complete disappearance of 8 and formation of a single product. Saturated ammonium chloride was added, and the mixture was extracted several times with $CHCl_3$. The extracts were washed with water, filtered through anhydrous Na_2SO_4, and concentrated to give 7: 566 mg (90%); mp 144–145 °C.

5-Methyldihydromorphinone (Metopon). (a) A solution of 132 mg of 7 in 1 mL of 48% HBr was heated to reflux for 30 min. As much as possible of the HBr solution was removed at 100 °C under diminished pressure. The residue (203 mg; theory, 166 mg for the hydrobromide) was triturated with 0.2 mL of concentrated ammonia to give a gray powdery solid which was collected and washed with water (118 mg). Its TLC was indistinguishable from that of an authentic sample of metopon.[10] Crystallization from alcohol gives solvated material of indeterminate melting point, so the sample was sublimed at 129–132 °C (10^{-3} mmHg) to give colorless prismatic needles: 33 mg; mp 242–248 °C dec; mmp (with authentic metopon, mp 238–244 °C dec) 240–246 °C dec. Both its IR and NMR spectra were indistinguishable from those of authentic metopon: IR (Nujol) 3530, 3400 (br), 1730, 1610, 1250, 1030, 850, 800 cm^{-1} inter alia; NMR δ 1.59 (s, 3 H), 2.45 (s, 3 H), 6.59 and 6.70 (AB, 2 H) inter alia.

(b) A suspension of 500 mg of sodium hydride in 5 mL of dry dimethylformamide was treated under N_2 with 313 mg of 5-methyldihydrocodeinone (7) and 620 mg of ethanethiol. After being stirred at room temperature for 15 min, the mixture was heated to 100 °C (bath) for 24 h. TLC indicated complete disappearance of 7 and the production of a single more polar substance. Saturated ammonium chloride was added, and the mixture was extracted several times with chloroform; the extracts were washed with water, filtered through anhydrous Na_2SO_4, and concentrated. The residue was chromatographed on silica gel, eluting with $CHCl_3/CH_3OH$ (9:1) to yield a nearly colorless amorphous powder, 272 mg (96% crude). Recrystallization of a small sample from $CHCl_3$ gave material of melting point 190–192 °C.[11] Its IR spectrum was indistinguishable from that of the sample described above.

5-Methylcodeinone (8). A stirred solution of 5-methylthebaine (1.50 g) in 100 mL of 3 M formic acid was treated under N_2 with 110 mg of mercuric acetate. The mixture was stirred at room temperature for 12 h, 120 mL of a saturated K_2CO_3 solution was added carefully, and the mixture was extracted with $CHCl_3$ four times. The extracts were washed with water and then brine and concentrated to yield 1.42 g of brownish red residue which was passed through a silica gel column in $CHCl_3/CH_3OH$ (50:1). Removal of the solvent and crystallization of the residue from anhydrous ether gave 1.28 g (85%) of 8: mp 178–179.5 °C; IR ($CHCl_3$) 1690 cm^{-1} inter alia; NMR δ 1.61 (s, 3 H), 2.44 (s, 3 H), 3.81 (s, 3 H), 6.01 (dd, 1 H), 6.63 (m, 3 H); $[\alpha]^{23}_D$ −156° (*c* 1.05, alcohol). Anal. Calcd for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.18; H, 6,85; N, 4.40.

Acknowledgment. We are indebted to Dr. Arthur Jacobson and Dr. Everette L. May for a sample of authentic metopon and to Mr. Daniel Mantell for aiding in the preparation of 5-methylthebaine. The generous financial support of the National Institute on Drug Abuse under Grant No. 5 R01 DAO 2469 is also gratefully acknowledged.

Registry No. 3, 115-37-7; 3 anion, 80583-33-1; 4, 80583-34-2; 5, 80583-35-3; 6, 80583-36-4; 7, 63868-37-1; 8, 80630-18-8; 9, 143-52-2.

(10) A sample of metopon was graciously supplied us by Dr. Arthur Jacobson through the intermediacy of Dr. Everette May.

(11) The melting point of metopon appears to depend very much on the history of the sample. When crystallized from alcohol, it melts partially at 155–160 °C, resolidifies, and then melts at 190–192 °C. When crystallized from chloroform it melts at 190–191 °C. Only after sublimation is the higher melting point (242–248 °C dec) observed.

Ring-Forming Reactions: Adjustable Regiocontrol on a Polyfunctional Substrate

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In the course of a study directed at sesquiterpene total synthesis, we had occasion to investigate the intramolecular reactivity of 4-(2,2-dimethyl-4-oxobutyl)-4-acetylcyclopent-2-en-1-one (**1**).[1] The results of this investigation, which uncovered an intriguing regiochemical trichotomy, are reported herein.

Note that in structure **1** (Scheme I) we have designated several potential nucleophilic (check marks) and electrophilic (asterisks) sites. Our ultimate goal, based upon this study, was to effect the conversion of the monocyclic compound **1** to the novel antitumor sesquiterpene quadrone (**3**)[2] via the key tricyclic enedione **2**.[3] The construction of **2** from **1** necessitated a specific double pairing of electrophile–nucleophile conjugates to form the carbon–carbon bonds A and B as shown. This was clearly a demanding requirement in the face of other possibilities (vide infra).

Three conformations of **1**, each highlighting a single electrophile–nucleophile pairing, are represented in Scheme II as **1a–c**. The products which would result from each of these specific pairings are depicted as **4–6**, respectively. Remarkably, by simple adjustment of the reaction conditions we could guide the reaction selectively along each one of these pathways, to the near or complete exclusion of the other two. Details of the entry to this manifold are presented below.

When a solution of the cyclopentenone **1** in tetrahydrofuran (THF) at −35 °C was treated with 1 equiv of $TiCl_4$ followed by 2 equiv of *N*-methylanilinium trifluoroacetate (TAMA)[4] and allowed to warm slowly to ambient temperature, there was obtained a 50% yield of crystalline 7-formyl-6,8,8-trimethylspiro[4.4]nona-1,6-dien-3-one (**4**, mp 108–111 °C) as the sole isolable product.[5,6] It was noted with little satisfaction that in **4** ($C_{13}H_{16}O_2$) we had managed to generate an isomer of the targeted tricyclic **2**.

We felt that the likelihood of triggering the desired Michael addition (closure A in **1**) would be enhanced by acid catalysis. It was hoped that preferential protonation at the cyclopentenone carbonyl with the resultant increase in the electrophilicity of the enone β-carbon would favor closure A over the process which led to the formation of **4**. In the event, treatment of **1** with a catalytic amount

(1) The functionalized cyclopentenone **1** is available in nearly quantitative yield by oxidative cleavate of the trisubstituted olefin linkage in 6,9,9-trimethylspiro[4.5]deca-1,6-dien-3-one (Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Strickland, S. M. S.; Saunders, J. O. *J. Org. Chem.* **1981**, *46*, 2400–2402).

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(3) This general strategy for the construction of the key tricyclic unit **2** has been reduced to practice. Details of this and the elaboration to quadrone (**3**) will be presented elsewhere.

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(5) All yields reported herein are based on chromatographically homogeneous, crystalline material.

(6) The structures reported herein are fully supported by IR, mass, 400-MHz ^1H NMR, and ^{13}C NMR spectra and by combustion analysis data. See the Experimental Section for details.

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