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Reaction of 3-methoxy-17-methylmorphinan-6-one (**1**) and formaldehyde with the presence of calcium hydroxide in aqueous dioxane gave 7,7-*bis*(hydroxymethyl)-3-methoxy-17-methyl-5-methylenemorphinan-6$\beta$-ol (**2a**). Catalytic reduction of **2a** yielded the 5$\alpha$-methyl compound, **2b**. Tosylation of **2a,b** followed by lithium triethylborohydride reduction gave either 7$\alpha$-methyl-6$\beta$,7$\beta$-oxetanes **4a,b** or 7,7-dimethyl-6$\beta$-ols **5a,b**, depending on reaction conditions. The C-6 ketones **6a,b** were prepared by oxidation of **5a,b**. One compound in this series, **6a**, had antinociceptive activity.

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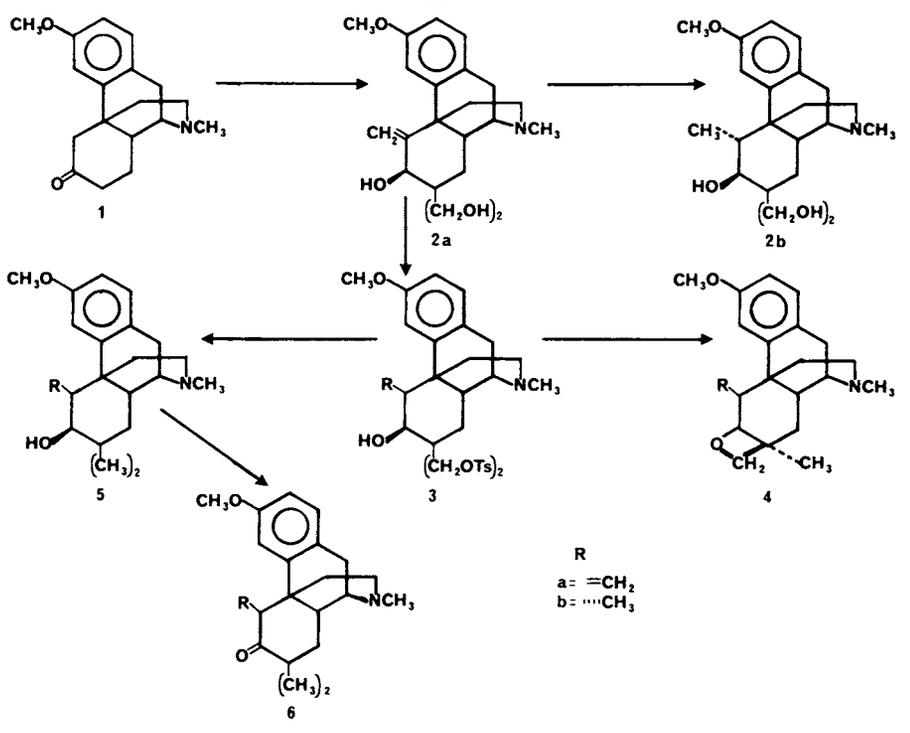
Previous publications from our laboratory have reported a number of modifications in the C-ring of the morphinan nucleus. We have shown that the introduction of short alkyl groups into the 7 and/or 8 position of *N*-(cycloalkylmethyl)morphinans results in a change in the agonist-narcotic antagonist profile in these compounds (2) when compared with the corresponding unsubstituted parents. Continuing our efforts to explore the chemistry of this ring system, we now report the reaction of 3-methoxy-17-methylmorphinan-6-one (3) with formaldehyde in the presence of calcium hydroxide. This report is based on our previous observations (4) and earlier work by Mannich and Schulte (5).

Reaction of **1** and formaldehyde with the presence of calcium hydroxide in aqueous dioxane (4) yielded, as the only product, 7,7-*bis*(hydroxymethyl)-3-methoxy-17-methyl-5-methylenemorphinan-6$\beta$-ol (**2a**) in 80% crystalline yield. The structure of this new product was confirmed by $^1$H-nmr and mass spectral data. The nmr spectrum of **2a** showed the methylene group as two broad one proton singlets at $\delta$ 5.42 and 5.13. In the mass spectrum the base peak was the $M^+$, 359. This 5-methylene product originates from a third aldol condensation at the 5-position followed by loss of water. The assignment of the $\beta$-configuration to the C-6 alcohol is based on our previous work in the dihydrocodeinone system (4). The 5-methylene group of **2a** could be catalytically reduced to the 5$\alpha$-methyl derivative **2b**.

Compound **2** was treated with 2.5 molar equivalents of *p*-toluenesulfonyl chloride in pyridine solution to give the *bis* tosylates **3** in about 90% yield. Displacement of the tosyl groups in **3a** with lithium triethylborohydride (6)

SCHEME 1

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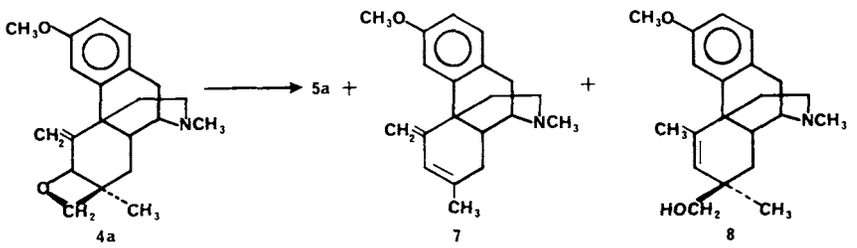
SCHEME 2




occurred very slowly to give a moderate yield of the 7,7-dimethyl compound **5a**. When this reaction was conducted at reflux, a good yield of the 7α-methyl-6β,7β-oxetane **4a** was obtained. The nmr spectrum of this oxetane showed the signal for H6 as a singlet at δ 4.65. The 7β-methylene proton signals were observed as a doublet of doublets centered at δ 4.28 with coupling constants of 26 Hz and 6 Hz. The 7α-methyl group signal appeared as a singlet at δ 1.13. Treatment of the *bis*-tosylate **3b** with lithium triethylborohydride under similar conditions gave a mixture of oxetane **4b** and dimethyl compound **5b**.

Attempted opening of the oxetane bond in **4a** using a 3:1 ratio of lithium aluminum hydride-aluminum chloride (7) yielded a mixture of three products which were separated by chromatography. The fastest migrating component was identified as 6,7-didehydro-3-methoxy-7,17-dimethyl-5-methylenemorphinan (**7**). The signal for the 7-methyl group in the nmr spectrum of this compound appeared as a singlet at δ 1.63 and the H-6 signal occurred as a singlet at δ 5.93.

The second product was the expected 7,7-dimethyl-6β-hydroxy compound **5a**, identical with that prepared from the reaction of **3a** and lithium triethylborohydride.

The most polar component was identified as 5,6-didehydro-7β-hydroxymethyl-3-methoxy-5,7α,17-trimethylmorphinan (**8**). The 5- and 7α-methyl group signals were observed as singlets at δ 2.15 and 0.78, respectively, in the nmr spectrum. The H-6 signal appeared as a broad singlet at δ 5.30. The mass spectrum, characteristically, exhibited a molecular ion at m/e 327 with the base peak at m/e 297, a loss of 31 for -$CH_2OH$.

In contrast to our previous work (4) where cleavage of the oxetane ring was a facile reaction yielding only one product, this particular substrate **4a**, reacts to give several products.

Oxidation of the secondary alcohols **5a,b** with dimethylsulfoxide-trifluoroacetic anhydride (8) proceeded smoothly to give the desired C-6 ketones in about 85% yield.

Preliminary testing for antinociceptive properties revealed that none of the reported compounds had exceptional activity. Compound **6a** was approximately equal in potency to dihydrocodeinone. Our search for new analgesic agents through exploration of the chemistry involving the morphinane C ring continues.

## EXPERIMENTAL

Melting points were taken in open capillary tubes on a Thomas-Hoover apparatus and are not corrected. $^1$H-nmr spectra were determined in deuteriochloroform unless otherwise indicated, on a Varian T60A Spectrometer. Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane. Only certain characteristic nmr data are presented. The presence of solvent of crystallization was confirmed by nmr in an appropriate solvent. Mass spectra were determined using a Hewlett-Packard 5985A GC/MS system and are reported as m/e (relative intensity). Only selected, significant peaks are reported. Elemental analyses were determined by Analytical Services, Chemistry Department, Miles Laboratories, Elkhart, Indiana.

Processing in the usual fashion implies that the organic phases were washed with dilute ammonium hydroxide, dried (magnesium sulfate) and evaporated at 40°. The residue was further dried at 50° under high vacuum. Column chromatography was performed over silica gel G (E. Merck) using chloroform-methanol mixtures (8:1 to 15:1) containing 1.0 to 0.5% v/v concentrated ammonium hydroxide.

7,7-*bis*(Hydroxymethyl)-3-methoxy-17-methyl-5-methylenemorphinan-6β-ol (**2a**).

A mixture of **1** (10.2 g, 35 mmoles), calcium hydroxide (5.0 g, 67 mmoles) and 37% aqueous formaldehyde (50 ml) in dioxane (100 ml) -water (100 ml) was stirred overnight at room temperature. The suspension was filtered and the filtrate concentrated. The residue was diluted with water, extracted with chloroform and processed in the usual manner to yield a foam which crystallized from ethyl acetate to give 10.4 g (81%) of **2a**, mp 222-224°. Recrystallization (methanol-ethyl acetate) gave analytically pure **2a**, mp 223-226°; ms: 359 ($M^+$, 100); nmr (DMSO-$d_6$): δ 7.17-6.77 (m, 3H), H1, H2, H4; 5.42 and 5.13 (two broad s, each 1H), 5=$CH_2$; 3.67 (s, 3H), -$OCH_3$; 2.30 (s, 3H), -$NCH_3$; exchangeable -OH at 4.73, 4.22 and 3.93.

*Anal.* Calcd. for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.38; H, 8.17; N, 3.85.

7,7-*bis*(Hydroxymethyl)-3-methoxy-5α,17-dimethylmorphinan-6β-ol (**2b**).

A mixture of **2a** (10.4 g, 28.9 mmoles), platinum oxide (1.0 g), concentrated hydrochloric acid (2 ml), water (20 ml) and 95% ethanol (200 ml) was hydrogenated at an initial pressure of 50 psi for four hours. The suspension was filtered and the filtrate evaporated. The residue was diluted with water, made basic with concentrated ammonium hydroxide and extracted with chloroform. The organic extracts were processed to give 7.7 g (74%) crystalline **2b**. Recrystallization (ethanol) gave analytically pure **2b**, mp 225-226°; ms: 361 ($M^+$, 100); 346 (34); 59 (40); nmr (DMSO-$d_6$): δ 3.73 (s, 3H); 2.27 (s, 3H); 1.35 (d, 3H), 5α-$CH_3$, $J_{5CH_3\text{-}5H}$ = 7Hz.

*Anal.* Calcd. for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.87. Found: C, 69.46; H, 8.68; N, 3.87.

7,7-*bis*(Tosyloxymethyl)-3-methoxy-17-methyl-5-methylene- and 5α-Methylmorphinan-6β-ol (**3a** and **3b**).

A mixture of *p*-toluenesulfonyl chloride (2.2 equivalents) and **2a** or **2b** in pyridine (1 g/15 ml) was protected from moisture and stirred at room temperature overnight. The reaction was quenched by the addition of ice and evaporated to a small volume. The residue was partitioned between chloroform and water. Evaporation of the organic extracts gave **3a** of sufficient purity for further reactions. For **3b** the residue after extraction and evaporation was chromatographed (400 g, 12:1:1%) to yield **3b** as a homogeneous foam in 90% yield.

3-Methoxy-5α,7α,17-trimethyloxetane[b-6β,7β]morphinan (**4b**) and 3-Methoxy-5α,7,7,17-tetramethylmorphinan-6β-ol (**5b**).

Lithium triethylborohydride (48 ml of a 1*M* solution in tetrahydrofuran, 48 mmoles), was added to a 0° solution of **3b** (10.3 g, 16.1 mmoles) in tetrahydrofuran (200 ml) under argon. The mixture was stirred at room temperature for 24 hours, an additional portion of hydride (40 ml) added, and the reaction heated at reflux for 24 hours. The solution was cooled and the excess of hydride quenched by the dropwise addition of water (12 ml) followed by 3*N* sodium hydroxide (30 ml) and 30% hydrogen peroxide (30 ml). The mixture was refluxed for 1 hour, cooled and evaporated. The residual aqueous layer was extracted with ethyl acetate. The extracts were processed in the usual manner to give a residue which was chromatographed (400 g, 10:1:1%). Fractions containing the faster migrating product were combined to yield 2.2 g (42%) of **4b** as a glass; ms: 327 ($M^+$, 100); 312 (43); 175 (52); 59 (50); nmr: δ 4.65 (d, 1H), H6, $J_{5,6}$ = 6 Hz; 4.00 (m, 2H) 7β-$CH_2$; 3.77 (s, 3H); 2.43 (s, 3H); 1.50 (d, 3H), 5α-$CH_3$, J = 7 Hz; 1.08 (s, 3H), 7α-$CH_3$. Fractions containing the slower moving component were combined to yield 0.99 g (19%) of **5b**. Crystallization (ethyl acetate) gave pure **5b**, mp 148-149.5°; ms: 329 ($M^+$, 100); 314 (52); 175 (52); 59 (82); nmr: δ 3.47 (s, 3H); 2.42 (s, 3H); 1.47 (d, 3H), 5α-$CH_3$, 1.00 (s, 3H), 7β-$CH_3$, 0.88 (s, 3H), 7α-$CH_3$.

*Anal.* Calcd. for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.87; H, 9.50; N, 4.18.

3-Methoxy-7,7,17-trimethyl-5-methylenemorphinan-6β-ol (**5a**).

Lithium triethylborohydride (20 ml, 20 mmoles) was added to a solution of **3a** (3.34 g, 5 mmoles) in tetrahydrofuran (50 ml) under argon. After 5 hours an additional portion of hydride (20 ml) was added and the mixture stirred at room temperature for 72 hours. The excess hydride was quenched by the dropwise addition of water (12 ml) followed by 3*N* sodium hydroxide (30 ml) and 30% hydrogen peroxide (30 ml). The solution was refluxed for 1 hour, cooled and evaporated. The aqueous residue was extracted with ethyl acetate and the organic extracts combined and evaporated to a residue which was purified by chromatography (200 g, 8:1:1%). Appropriate fractions were combined to give 0.54 g (34%) of crystalline **5a**. Two crystallizations (chloroform-hexane) gave analytically pure **5a**, mp 147-149°; ms: 327 ($M^+$, 100); 312 (16); 59 (38); nmr: δ 5.40 and 5.20 (broad s, 1H each), 5=$CH_2$; 3.70 (s, 3H); 2.38 (s, 3H); 0.92 (s, 3H); 0.80 (s, 3H).

*Anal.* Calcd. for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.77; H, 8.75; N, 4.34.

3-Methoxy-7α,17-dimethyl-5-methyleneoxetane[b-6β,7β]morphinane (**4a**).

Lithium triethylborohydride (193 ml, 193 mmoles) was added to a 0° solution of **3a** (32.3 g, 48.4 mmoles) in tetrahydrofuran (600 ml) under argon. After addition, the mixture was heated at reflux overnight. The solution was cooled and an additional portion of hydride (95 ml) added. The reaction was stirred for 2 hours at room temperature. The excess of hydride was quenched by the dropwise addition of water (40 ml) followed by 3*N* sodium hydroxide (80 ml) and 30% hydrogen peroxide (80 ml). After heating at reflux for 1 hour, the solution was processed as above and chromatographed (750 g, 8:1:1%) to yield 10.6 g (67%) of **4a**. Two crystallizations (ethyl acetate) gave pure **4a**, mp 119-121°; ms: 325 ($M^+$, 100); 294 (28); nmr: δ 5.53 (broad d, 2H), 5=$CH_2$, J = 6 Hz; 4.65 (broad s, 1H), H6; 4.28 (d of d, 2H), 7β-$CH_2$, J = 26 Hz and J = 6 Hz; 3.75 (s, 3H); 2.45 (s, 3H); 1.13 (s, 3H), 7α-$CH_3$.

*Anal.* Calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.78; H, 8.52; N, 4.26.

Attempted Cleavage of **4a** with Lithium Aluminum Hydride-Aluminum Chloride.

Lithium aluminum hydride (3.0 g, 79.5 mmoles) was added to a cold (5°) mixture of aluminum chloride (3.5 g, 26.5 mmoles) in ether (250 ml). The mixture was stirred for 30 minutes in the ice bath and then **4a** (8.6 g, 26.5 mmoles), as a suspension in ether (500 ml), was added in a thin stream. The reaction mixture was then heated at reflux overnight. Excess hydride was destroyed by the cautious addition of water and the suspension made basic (*p*H 9-10) by the addition of 3*N* sodium hydroxide. The mixture was filtered and the filtrate extracted with ethyl acetate. The extracts were evaporated to a residue which was resolved by chromatography (400 g, 12:1:1%). First eluted was 3.0 g (38%) of 6,7-didehydro-3-methoxy-7,17-dimethyl-5-methylmorphinan (**7**); nmr δ 5.93 (broad, 1H), H6; 5.11 (broad d, 2H), 5=$CH_2$; 3.73 (s, 3H); 2.45 (s, 3H); 1.63 (s, 3H), 7-$CH_3$. Crystallization (ethyl acetate-methanol) as the hygroscopic *d*-tartrate salt gave **7**, mp sinters 98°, melts 140-158°; ms: 295 ($M^+$, 100), 294 (37), 280 (18), 59 (30).

*Anal.* Calcd. for $C_{20}H_{25}NO \cdot C_4H_6O_6 \cdot 0.75\ H_2O$: C, 62.80; H, 7.14; N, 3.05. Found: C, 62.95; H, 7.06; N, 2.87.

Next eluted was 3.37 g (39%) of **5a**, identical in all respects to that prepared by lithium triethylborohydride reduction of the ditosylate **3a**. The most polar product eluted was 1.18 g (14%) of **8** nmr: δ 5.30 (broad s, 1H), H6; 3.82 (s, 3H); 2.42 (s, 3H); 2.15 (s, 3H), 5-$CH_3$; 0.78 (s, 3H), 7α-$CH_3$. Crystallization (ethyl acetate-methanol) as the hygroscopic hydrochloride salt gave **8**-HCl; mp 153-157°; ms: 327 ($M^+$, 58), 296 (100), 59 (22).

*Anal.* Calcd. for $C_{21}H_{29}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 67.63; H, 8.38; N, 3.76. Found: C, 67.24; H, 8.26; N, 3.68.

3-Methoxy-7,7,17-trimethyl-5-methylene and 5-Methylmorphinan-6-one (**6a** and **6b**).

Trifluoroacetic anhydride (1.5 equivalents) in methylene chloride (1 mmole/1 ml) was added, dropwise, to a cold (−65°) solution of dimethyl sulfoxide (2 equivalents) in methylene chloride (1 mmole/0.5 ml) under argon, then **5a** or **5b** in methylene chloride (1 g/10 ml) was added to the solution and the mixture stirred at −65° for 90 minutes. Triethylamine (0.4 ml/1 mmole) was added and the reaction allowed to warm to room temperature. The solution was evaporated and the residue chromatographed to give an 85% yield of **6a**. Two crystallizations (hexane) gave analytically pure **6a**; mp 110-112°; nmr: δ 5.42 and 5.29 (two broad s, each 1H), 5=$CH_2$; 3.73 (s, 3H); 2.47 (s, 3H), 1.18 (s, 3H); 7-$CH_3$; 0.98 (s, 3H) 7-$CH_3$.

*Anal.* Calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.27; H, 8.27; N, 4.24.

In a similar manner **6b** was isolated in 82% yield. Trituration with Skelly A gave analytically pure **6b**; mp 104-105°; nmr: δ 3.77 (s, 3H); 2.47 (s, 3H); 1.53 (d, 3H), 5-$CH_3$, J = 7 Hz; 1.28 (s, 3H), 7-$CH_3$; 0.88 (s, 3H), 7-$CH_3$.

*Anal.* Calcd. for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.02; H, 9.13; N, 4.08.

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