Preparation of 7β-Methyldihydrothebaine-φ[1]

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Received April 28, 1980

The reaction of thebaine (1) with lithium dimethylcuprate yields 7β-methyldihydrothebaine-φ (2). Acid hydrolysis of 2 gave mixtures of 7,8-didehydro-7,17-dimethyl-4-hydroxy-3-methoxy-*B/C-cis*- (**4a**) and -*B/C-trans*- (**4b**) morphinan-6-ones which, after separation, were hydrogenated to the saturated ketones **5a,b**. The B/C ring junctures in **5a,b**, respectively, were determined by mass spectral and chemical studies. Reaction of dihydrothebaine (**6**) or dihydrocodeinone enol acetate (**8**) with Me_2CuLi gave 4,5-epoxy cleaved 7β-methylmorphinane derivatives, some of which could be converted to **5a**.

We have recently reported that reaction of codeinone with lithium dialkylcuprates yields mainly 8β-alkylated-dihydrocodeinones.[2] A 4,5-epoxy cleaved product, thebainone A,[3] was found as a minor constituent of these reaction mixtures, particularly in the reaction of codeinone with lithium dimethylcuprate. With the goal of preparing compounds for further synthetic work in which the 4,5-epoxy bond has been cleaved,[4,5] we investigated the reaction of lithium dimethylcuprate with thebaine (**1**). We have unexpectedly found that this reaction yields 7β-methyldihydrothebaine-φ (**2**).

Addition of a benzene solution of **1** to 1.2 equiv of ethereal lithium dimethylcuprate gave **2** as the major product (>90% by TLC), which was obtained in crystalline form as the monochloroform solvate. Chromatography of the mother liquors allowed isolation of the minor product, the 7α-methyl isomer **3**, in about 4% yield. The NMR signal for the 7β-methyl group of **2** was observed as a doublet, centered at δ 1.17, whereas the corresponding signal for **3** was observed at δ 1.08. This difference in position for the 7-methyl signal is due to the anisotropic effect of the aromatic A ring and reflects our earlier observations.[1,5] This anisotropic effect is also responsible for the low-field position (δ 6.13) observed for H-5.[6]

Treatment of **2** with aqueous acetic acid at 90–100 °C gave an approximately 3:1 mixture of the *B/C-cis* (**4a**) and *B/C-trans* (**4b**) α,β-unsaturated ketones (Scheme I) whereas hydrolysis with 5% hydrochloric acid gave a 94% yield of **4b**. Conditions could not be found which gave exclusively the cis isomer **4a** which corresponds to the natural morphine B/C configuration. Catalytic reduction of these separated isomers gave the 4-hydroxy-6-ones **5a** and **5b**. The assignment of B/C ring junctures in **5**, and thus in **4**, was initially based on the characteristic *m/e* 59 ion which is found only in the mass spectrum of ring C saturated *cis*-morphinanes and the relative abundance of molecular ions (trans > cis).[7] Final confirmation of this assignment was demonstrated by conversion of **8** to **5a** as described below.

It was reported some years ago that both dihydrothebaine (**6**)[8] and dihydrocodeinone enol acetate (**8**)[9] react with methyl Grignard reagents. These reactions yield, after workup including acid hydrolysis, mainly 5-methyldihydrothebainone (5,17-dimethyl-4-hydroxy-3-methoxymorphinan-6-one) together with a small percentage of the corresponding 7-methyldihydrothebainone.[10] In view of this result, we further examined the reaction of Me_2CuLi with these substrates. Only methylation at the 7 position was observed in our reactions.

Reaction of **6** with Me_2CuLi gave the 4-hydroxy-5,6-didehydro-6-methoxy-7β-methyl compound **7** in about 77% yield. Mild acid hydrolysis of **7** gave the saturated ketone **5a**, identical with material prepared from **4a**. A mixture of four products was obtained upon reaction of **8** with Me_2CuLi under similar conditions followed by mild basic workup. Two isomeric 6-oxo compounds were obtained in about equal amounts. One of these was **5a** (NMR δ 0.87 (7α-methyl)) while the other was presumed to be the less stable (axial) 7β methyl compound **9**. NMR confirmation of this supposition was obtained when a $CDCl_3$ solution of **9** upon treatment with CF_3COOH converted to a spectrum identical with that of **5a**. 5,6-Didehydro-7-methyl compound **10** and the product of epoxy bond cleavage without alkylation **11** were also obtained in this reaction. Thus, Me_2CuLi reacts with **6** and **8** in a manner opposite to that of methyl Grignard.

The mechanism of reaction of lithium dialkylcuprates with various substrates remains a subject of vigorous investigation.[11] Our observed reaction of Me_2CuLi with enol ethers derived from the morphine alkaloids may proceed either by electron transfer or nucleophillic addition. Alkylation of the intermediates involved in these reactions takes place stereospecifically from the less hindered β face of the molecule.

The novel method for the introduction of a C-7 methyl group into the morphinane nucleus has allowed us to extend our previous studies aimed at determining the effect of alkyl substitution in the C ring of opiate derivatives on analgesic–narcotic antagonist activity. These studies will be reported elsewhere.[12]

Experimental Section

Methods have previously been described.[2] Processing in the usual fashion implies that the organic phases were washed with dilute NH_4OH, dried ($MgSO_4$), and evaporated at 40 °C. The residue was further dried at 50–60 °C under high vacuum. Column chromatography was carried out over silica gel G (E. Merck), using the indicated amount of gel and the indicated $CHCl_3$–MeOH mixtures containing 0.5–1% (v/v) concentrated NH_4OH as eluant. NMR spectra were recorded in $CDCl_3$ unless otherwise stated.

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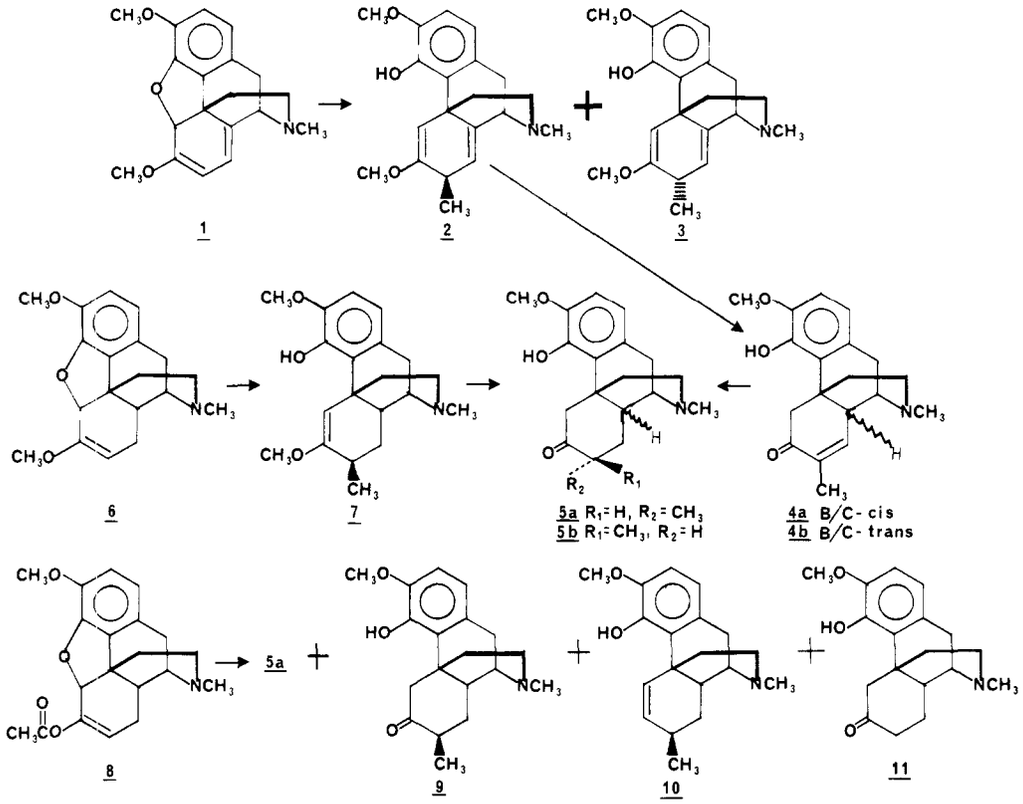
0022-3263/80/1945-4026$01.00/0

Scheme I



This method was also used to confirm the presence and amount of solvent of crystallization. Optical rotations were determined by using a Perkin-Elmer Model 241 polarimeter. Mass spectra were determined by using a Hewlitt-Packard 5985A GC/MS system and are reported as m/e (relative intensity). Only selected, significant peaks are reported.

3,6-Dimethoxy-7β,17-dimethyl-4-hydroxy-5,6,8,14-tetradehydromorphinane (2). To a solution of Me_2CuLi, prepared from CuI (23.18 g, 125 mmol) and MeLi (250 mmol, 126 mL of a 1.8 M solution in Et_2O containing LiBr), in Et_2O (500 mL) stirred in an ice–salt bath under an argon atmosphere was added rapidly in a thin stream a solution of **1** (31.14 g, 100 mmol) in C_6H_6 (500 mL). The resulting suspension was stirred for 1 h in the cold, then poured into saturated NH_4Cl solution (600 mL), and stirred for 15 min. The organic layer was separated and the aqueous phase adjusted to pH 13–14 by use of 50% NaOH. The aqueous phase was extracted with $CHCl_3$ and the organic phases were processed in the usual manner. Evaporation gave a foam which crystallized from $CHCl_3$ with the addition of hexane to give 33.20 g (74%) of **2** as the $CHCl_3$ solvate, mp 97–100 °C. Recrystallization from the same solvent pair gave pure **2**·$CHCl_3$: mp 98–101.5 °C; NMR δ 7.30 (s, 1, $CHCl_3$), 6.65 (m, 2, H-1 and H-2), 6.13 (s, 1, H-5), 5.47 (d, 1, H-8, $J_{7,8}$ = 3 Hz), 3.86 (s, 3-OCH_3), 3.63 (s, 6-CH_3), 2.33 (s, NCH_3), 1.17 (d, 3, 7β-CH_3, $J_{7H,7CH_3}$ = 7 Hz), ~6.20 (exchangeable 4-OH); mass spectrum, m/e 327 (M^+, 54), 312 (100).

Anal. Calcd for $C_{20}H_{25}NO_3$·$CHCl_3$: C, 56.46; H, 5.87; N, 3.13. Found: C, 56.27; H, 5.82; N, 3.07.

3,6-Dimethoxy-7α,17-dimethyl-4-hydroxy-5,6,8,14-tetradehydromorphinane (3). The mother liquor obtained above was evaporated to a dry residue and chromatographed (500 g, 15:1:1%). After elution of additional **2** (2.46 g), **3** (1.36 g, 4%) was obtained as a foam; NMR δ 6.69 (m, 2, H-1 and H-2), 6.08 (br s, 1, H-5), 5.57 (d, 1, H-8, $J_{7,8}$ = 4 Hz), 3.87 (s, 3-OCH_3), 3.65 (s, 6-OCH_3), 2.42 (s, NCH_3), 1.08 (d, 3, 7α-CH_3, $J_{7H,7CH_3}$ = 7 Hz).

7,8-Didehydro-7,17-dimethyl-4-hydroxy-3-methoxy-*B*/*C*-*cis*- (4a) and -*B*/*C*-*trans*- (4b) morphinan-6-ones. A. To HOAc (150 mL), preheated in an oil bath to 90 °C, was added **2**·$CHCl_3$ (10.00 g, 22.4 mmol) and the mixture kept between 90–100 °C for 40 min. The cooled solution was made basic by the addition of NH_4OH and extracted with several portions of $CHCl_3$. Processing in the usual fashion gave a residue (8.36 g) which was chromatographed (500 g, 20:1:0.5%). Eluted first from the column was **4b** (1.61 g, 23%) obtained as a tan glass: NMR δ 6.65 (3, H-1, H-2, and 4-OH), 6.26 (br s, 1, H-8), 4.10 (d, 1, H-5α, J = 17 Hz), 3.85 (OCH_3), 2.36 (NCH_3), 1.86 (m, 3, 7-CH_3); mass spectrum, m/e 313 (M^+, 56), 176 (100).

Next eluted was **4a** which was obtained as crystals (5.07 g, 72%) after evaporation. Recrystallization from EtOAc gave white needles of **4a**, mp 183–185 °C, which were found to contain 0.33 mol of EtOAc by NMR and elemental analysis: NMR δ 6.58 (H-1 and H-2), 6.40 (br s, 2, H-8 and 4-OH), 4.30 (d, 1, H-5α, J = 15 Hz), 3.76 (OCH_3), 2.40 (NCH_3), 1.60 (m, 3, 7-CH_3); mass spectrum, m/e 313 (M^+, 74), 176 (100), 109 (59).

Anal. Calcd for $C_{19}H_{23}NO_3$·$0.33C_4H_8O_2$: C, 71.25; H, 7.55; N, 4.09. Found: C, 71.21; H, 7.58; N, 3.98.

B. Compound **2**·$CHCl_3$ was hydrolyzed at 90–100 °C as above, but with 5% aqueous HCl. The residual foam was chromatographed to yield, after evaporation of appropriate fractions, 6.60 g (94%) of **4b** as a foam followed by 0.40 g (6%) of **4a**. Two crystallizations of **4b** from Et_2O gave 3.0 g of shiny tan crystals, mp 135–138 °C after drying at 50 °C in high vacuum, which were found to contain 0.33 mol of Et_2O by NMR and elemental analysis.

Anal. Calcd for $C_{19}H_{23}NO_3$·$0.33C_4H_{10}O$: C, 72.23; H, 7.85; N, 4.14. Found: C, 72.30; H, 7.52; N, 4.33.

7α,17-Dimethyl-4-hydroxy-3-methoxy-*B*/*C*-*cis*-morphinan-6-one (5a). A solution of **4a**·$0.5C_4H_8O_2$ (22.0 g, 61 mmol) in 95% EtOH (200 mL), containing concentrated HCl (12 mL) and 10% Pd/C (2.0 g), was hydrogenated at an initial pressure of 50 psi until uptake of H_2 ceased. The mixture was filtered from the catalyst and the filtrate evaporated to a small volume. The residue was diluted with H_2O, made basic with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ extracts were processed to give a thick syrup which crystallized on addition of EtOAc. The crystals were collected and air-dried to give 14.4 g (74%) of **5a** as white needles, mp 163–165 °C: NMR δ 6.55 (H-1 and H-2), 6.40 (br, 4-OH), 4.22 (d, H-5α, J = 13 Hz), 3.77 (OCH_3), 2.38 (NCH_3), 0.87 (d, 3, 7α-CH_3, J = 6.5 Hz); mass spectrum, m/e 315 (M^+, 32), 178 (100), 150 (15), 115 (16), 59 (12). Recrystallization of **5a** from acetone gave the hemiacetone solvate of **5a**, mp 166–167 °C (lit.[8] mp 168–168.5 °C), $[\alpha]_D$ −55° (c 1.0, $CHCl_3$) (lit.[8] $[\alpha]_D$ −57° [c 1.0, EtOH]). The oxime of **5a** melted at 190–191 °C (lit.[8] 191–192 °C).

Anal. Calcd for $C_{19}H_{25}NO_3$·$0.5CH_3COCH_3$: C, 71.48; H, 8.19; N, 4.07. Found: C, 71.69; H, 8.27; N, 4.12.

7α,17-Dimethyl-4-hydroxy-3-methoxy-*B*/*C*-*trans*-morphinan-6-one (5b). Compound **4b** was hydrogenated in a similar manner to that reported for **4a**. Workup gave a foam which was chromatographed to give **5b** as a foam: NMR δ 6.68 (H-1 and H-2), 6.20 (br, 4-OH), 4.09 (s, 0.5, 1/2 doublet for H-5α), 3.87 (unsymmetrical s, 3.5, 1/2 doublet for H-5α, OCH_3), 2.32 (NCH_3), 1.02 (unsymmetrical d, 3, 7β-CH_3, J = 5 Hz); mass spectrum, m/e 315 (M^+, 80), 272 (55), 244 (100), 178 (76), 122 (53), 115 (31), 59 (0). Conversion to the HCl salt followed by two crystallizations from MeOH-EtOAc gave an analytical sample of **5b**·HCl, mp sinters 142-145 °C, melts 222-224 °C.

Anal. Calcd for $C_{19}H_{25}NO_3$·HCl: C, 64.86; H, 7.45; N, 3.98. Found: C, 64.47; H, 7.73; N, 4.21.

5,6-Didehydro-3,6-dimethoxy-7β,17-dimethyl-4-hydroxymorphinane (7). A solution of Me_2CuLi (12.5 mmol) was prepared in Et_2O (75 mL) as previously described. To this was added rapidly dropwise a solution of dihydrothebaine (**6**, 3.13 g, 10 mmol) in benzene (75 mL) and the reaction mixture was stirred for 1 h in the ice bath. The mixture was poured into saturated NH_4Cl solution, stirred for 30 min and then adjusted to pH 11 with NH_4OH. Extraction with $CHCl_3$ followed by processing in the usual fashion gave 3.76 g of a foam which was chromatographed (400 g, 10:1:1%). Fractions containing the major product, homogeneous by TLC, were combined and evaporated to give **7** (2.54 g, 77%) as a foam; NMR δ 6.60 (s, H-1 and H-2), 6.13 (br, 4-OH), 5.68 (s, 1, H-5), 3.83 (3-OCH_3), 3.58 (6-OCH_3), 2.40 (NCH_3), 1.18 (m, 3, 7β-CH_3).

Hydrolysis of 7 to 5a. Compound **7** (2.54 g, 7.7 mmol) in 1 N HCl (30 mL) was heated on the steam bath for 30 min. The cooled solution was made basic with NH_4OH and extracted with $CHCl_3$. Processing followed by evaporation gave a crystalline residue. Recrystallization from acetone gave **5a**·0.5C_3H_6O (1.29 g, 48%), mp 166-167 °C, identical with material prepared above.

Reaction of Dihydrocodeinone Enol Acetate (7) with Me_2CuLi. A solution of **8** (6.40 g, 18.75 mmol) in benzene (100 mL) was added rapidly dropwise to a solution of Me_2CuLi (40 mmol), prepared in Et_2O (200 mL), at 0 °C under argon. The mixture was stirred for 1 h at 0 °C and poured into saturated NH_4Cl solution and the pH was adjusted to 10 with NH_4OH. After the mixture was stirred for 30 min, processing of the combined organic phase and $CHCl_3$ extracts gave a foam which contained four major compounds as indicated by TLC. The foam was chromatographed (750 g, 15:1:0.75%) and fractions were pooled on the basis of TLC.

First eluted was 5,6-didehydro-7β,17-dimethyl-4-hydroxy-3-methoxymorphinane (**10**, 1.48 g, 26%): NMR δ 6.63 (2.5, H-1, H-2, and 1/2 doublet for H-5), 6.46 (1/2 unsymmetrical doublet for H-5), 6.00 (4-OH), 5.55 (pair of d, 1, H-6, $J_{5,6}$ = 10 Hz, $J_{6,7}$ = 3.5 Hz), 3.83 (OCH_3), 2.45 (NCH_3), 1.05 (unsymmetrical d, 7-CH_3, J = 7 Hz). This material was converted to the HCl salt which was crystallized from EtOAc to give **10**·HCl, mp >250 °C dec.

Anal. Calcd for $C_{19}H_{25}NO_2$·HCl: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.70; H, 7.89; N, 4.07.

Next eluted was 7β,17-dimethyl-4-hydroxy-3-methoxymorphinan-6-one (**9**, 1.71 g, 28%); NMR δ 6.62 (H-1 and H-2), 4.10 (H-5α, J = 15 Hz), 3.82, 2.43, 1.21 (d, 7β-CH_3, J = 7 Hz). Two recrystallizations from EtOAc gave the hemi-EtOAc solvate of **9**, mp 163-165 °C, $[\alpha]_D$ -115° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{19}N_{25}NO_3$·0.5$C_4H_8O_2$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.44; H, 8.19; N, 3.87.

Continued elution gave **5a** (1.66 g, 27%) followed by **11** (0.65 g, 12%) which was identified by comparison with an authentic sample.

Acknowledgment. We are indebted to Drs. R. N. Schut and J. E. Villarreal for their continued interest and encouragement during the course of this work.

Registry No. 1, 115-37-7; 2, 74466-73-2; 3, 74466-74-3; 4a, 74466-75-4; 4b, 74497-87-3; 5a, 74497-88-4; 5b, 74497-89-5; 5b·HCl, 74497-90-8; 6, 57281-79-5; 7, 74466-76-5; 8, 466-90-0; 9, 74497-91-9; 10, 74466-77-6; 10·HCl, 74466-78-7; 11, 847-86-9.

Two New Germacranolides from *Melampodium leucanthum* and Their Reductive and Oxidative Rearrangements

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Received November 14, 1979

The isolation and structure elucidation of two new 4,5-dihydrogermacranolides, 9-acetoxymelnerin A and B, from *Melampodium leucanthum* Torr. and Gray (Compositae, Heliantheae) are reported. Reduction of the two germacranolides with sodium borohydride proceeds, besides saturation of the lactonic exocyclic methylene function, under 1(10) to 9,10 double bond rearrangment with the loss of the C-9 acetoxy group, a process which can be interpreted as a S_N' reaction. Pyridinium chlorochromate oxidation of the C-15 alcohol function of 9-acetoxymelnerin A provides the aldehyde as a minor product, the major product being a ketone formed by a C-4 to C-15 shift of C-5 of the ten-membered ring, resulting in an 11-membered-ring skeleton. The separation of the previously inseparable melnerin A and B mixture by reverse-phase high-pressure liquid chromatography is described, and the physical parameters of the pure compounds are reported.

In our biochemical systematic study of the genus *Melampodium* (Compositae, Heliantheae) we have in the past reported results of our populational analysis for sesquiterpene lactones in *M. leucanthum*. Our previous investigations of this chemically diverse species have led to the isolation of melampolides,[1-4] germacranolide dilactones,[5,6] and *cis,cis*-germacranolides.[6] Now we wish to describe the isolation, structure elucidation, and chemistry of two new 4,5-dihydrogermacranolides which are structurally related to melnerins A and B, compounds which have previously

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