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SYNTHESIS OF 7,8-DIDEHYDRO-3,4-DIMETHOXY-17-METHYLMORPHINAN-6-ONE AND THE REGIOSELECTIVE REDUCTION OF THE KETO FUNCTION

(Chemistry of Opium Alkaloids, Part XXIV)*

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ABSTRACT

7,8-Didehydro-3,4-dimethoxy-17-methylmorphinan-6-one (2) was prepared by reductive opening of the epoxy bridge of codeinone, followed by methylation with Rodionow's reagent. Reduction of the title compound with sodium tetrahydroborate in the presence of cerium(III) chloride afforded a mixture of 7,8-didehydro-3,4-dimethoxy-17-methylmorphinan-6α-ol (3) and -6β-ol (4) in a ratio of 4:1 from which the 6α-epimer was crystallized and converted into the acetate (7).

INTRODUCTION

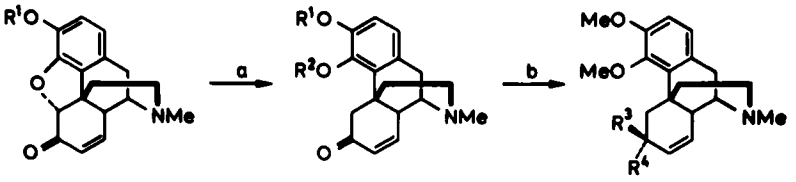
In our search for new synthetic pathways to morphinan-6,8-dienes, we investigated the synthesis of 3-benzyloxy-7,8-didehydro-4-methoxy-17-methylmorphinan-6-one (1)[1]. This compound may be used as starting material for the preparation of morphinan-6,8-dienes *via* the reduction of 1 to the morphinan-6α-ol, followed by the introduction of the diene system by analogy with the synthesis of 6-demethoxythebaine from codeine[2].

In order to study the regio- and stereoselective reduction of 7,8-didehydromorphinan-6-ones we used 7,8-didehydro-3,4-dimethoxy-17-methylmorphinan-6-one (2) as a model compound.

We wish to report here a simple synthesis of 2 from codeinone (5), and the results of the reduction of this model compound by a variety of reducing agents (Scheme 1). Results show the formation of 7,8-didehydromorphinan-6α-ol 3 and 7,8-didehydromorphinan-6β-ol 4, both of which are suitable intermediates for further studies on the synthesis of morphinan-6,8-dienes.

RESULTS AND DISCUSSION

Model compound 2 can be prepared in two steps from readily accessible codeinone (5). The reductive opening of the epoxy bridge of 5 was accomplished selectively using zinc dust at 0 °C. The similar conversion of 1 proceeded better when activated zinc dust was used at room temperature. One can note that compound 5 is more reactive than the corresponding 3-benzyloxy analogue 1 with respect to both the scission of the 4,5α-epoxy bridge and the hydrogenation of the C-7/C-8 double bond.



5: R^1 = Me

1: R^1 = CH_2Ph, R^2 = Me
2: R^1 = R^2 = Me
6: R^1 = Me, R^2 = H

3: R^3 = H, R^4 = OH
4: R^3 = OH, R^4 = H
7: R^3 = H, R^4 = OAc

a: 1. Zn/NH_4Cl, 2. $PhNMe_3Cl/NaOMe$; b: $NaBH_4/CeCl_3$

Scheme 1. Synthesis of 7,8-didehydro-3,4-dimethoxy-17-methylmorphinan-6-ols (3 and 4) from codeinone (5).

Treatment of 5 with zinc dust and aqueous ammonium chloride in acetone afforded quantitatively 7,8-didehydro-4-hydroxy-3-methoxy-17-methylmorphinan-6-one (thebainone-A, 6). The free phenolic hydroxyl group of thebainone-A was methylated in order to avoid interference with hydride reagents and to protect it from oxidation. This was effected with Rodionow's reagent (trimethylphenylammonium chloride and sodium methoxide), giving 2 in 92% yield. To prevent the formation of tarry oxidation products the reaction was carried out in a nitrogen atmosphere. The reduction of 2, which was purified by recrystallization, was carried out with sodium tetrahydroborate in absolute ethanol in the presence of anhydrous cerium(III) chloride, and afforded in 84% yield a mixture of 7,8-didehydro-3,4-dimethoxy-17-methylmorphinan-6α-ol (3) and the 6β-epimer (4) in a ratio of 4:1. The major epimer was isolated by crystallization from ethyl acetate, and it proved to be the 6α-alcohol (3) according to 200 MHz ^1H NMR data. The most significant structural difference between the 6α-ol and the 6β-ol

is the position of the C-6 proton relative to the C-5 protons. We measured a coupling constant of 1.4 Hz between the 5β proton and the C-6 proton. This is in agreement with the structure of the α-epimer in which the dihedral angle between H-5β and H-6β is approximately 60°, as depicted in Scheme 2. In the β-epimer the dihedral angle between H-5β and H-6α is about 180°, which would correspond with a coupling constant of 5-10 Hz.

3: α - epimer 4: β - epimer

Scheme 2. Newman projections along the C-5/C-6 axis of the epimeric 7,8-didehydromorphinan-6-ols 3 and 4, respectively.

Using silicagel chromatography only a mixture of 3 and 4, enriched in 4, was isolated from the mother liquor. Due to the presence of the α-epimer, the coupling constant between H-5β and H-6α of 4 could not be determined unambiguously.

The α-epimer 3 was converted into the acetate 7 with acetic anhydride and triethylamine in the presence of the acylation catalyst 4-dimethylaminopyridine (DMAP)[3]. The allylic acetate 7 may be an intermediate in an alternative synthetic route to morphinan-6,8-dienes in which acetic acid is eliminated with the aid of tetrakis(triphenylphosphino) palladium(0)[4].

For the preparation of the morphinan-6,8-diene according to the procedure described for codeine[2], 2 should be reduced stereoselectively to 3. Therefore, various reducing agents have been examined for the improvement of the stereoselectivity. Lithium tetrahydridoaluminate, aluminium hydride, and diisobutylaluminium hydride gave the above mentioned epimeric mixture of 3 and 4 in about the same ratio of 4:1. Sodium tetrahydroborate/cerium(III) chloride in absolute ethanol gave the best results, regarding both the stereoselectivity and the simplicity of the procedure. The advantageous effect of cerium(III) ions on this reduction can be attributed to the Ce^{3+}-catalyzed formation of bulky triethoxyhydroborate ions[5] with which the reduction takes place from the least hindered side of the morphinan molecule, *i.e.* the β-face. It was expected that increasing the size of the reducing species would enhance the stereoselectivity. However, by employing 1-propanol or 2-propanol as solvent the conversion was slow and incomplete. Other reducing agents such as lithium tri(*tert*-butoxy)hydridoaluminate, lithium tri(*sec*-butyl)hydroborate (L-Selectride), 9-bora-bicyclo[2.2.1]nonane (9-BBN) and diborane did not improve the stereoselectivity either, under the circumstances examined.

EXPERIMENTAL

Reactions were monitored by thin layer chromatography on deactivated silica, Merck F254 Kieselgel, with dichloromethane/methanol/concentrated ammonia 85:15:0.1 as the eluent. Detection took place with UV light (λ = 254 nm) and iodine vapour. Gibb's reagent was used to detect compounds with phenolic hydroxyl groups[6]. Analytical HPLC was performed on a reversed-phase column (10 x 0.8 mm, Nucleosil C18, 10 µm) using a Waters Associates M-6000 chromatographic pump. Detection took place with an ERMA ERC 7510 RI-detector. Water/methanol/trifluoroacetic acid 50:50:0.1 was used as the eluent. 60 MHz ^{1}H NMR spectra were recorded on a Varian T60 NMR spectrometer, using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. 200 MHz ^{1}H NMR spectra were recorded by Dr. *J.A. Peters*, using a Nicolet NT 200 WB spectrometer. Infrared spectra were recorded on a Beckman IR 4210 spectrophotometer, using KBr discs. Mass spectra were recorded on a Varian MAT 311A mass spectrometer by Mrs. *A.H. Knol-Kalkman*, Mr. *H.M.A. Buurmans* and Dr. *B. van de Graaf*. Optical rotations were measured on a Perkin-Elmer P141 polarimeter, using a mixture of chloroform/ethanol 9:1 as the solvent. Melting points are uncorrected and were determined on a Büchi 510 melting point apparatus.

7,8-Didehydro-4-hydroxy-3-methoxy-17-methylmorphinan-6-one (thebainone A, 6)
Thebainone A (6) was obtained from codeinone (5) according to ref. 1.

7,8-Didehydro-3,4-dimethoxy-17-methylmorphinan-6-one (2)
Trimethylphenylammonium chloride (10.79 g, 62.3 mmol) and sodium methoxide (7.4 g, 138 mmol) were added to a solution of 6 (9.82 g, 32.8 mmol) in 300 ml of anhydrous dioxane in a nitrogen atmosphere. The mixture was stirred vigorously and boiled under reflux. After 1 h the starting material had disappeared (TLC, Gibb's reagent and iodine vapour). The reaction mixture was cooled to room temperature and filtered. The residue was washed with 50 ml of warm dioxane and the combined filtrates were evaporated to dryness under reduced pressure. The brownish oily residue was dissolved in 5 ml of methanol. Then 100 ml of water was added and, subsequently, glacial acetic acid until the precipitate had dissolved again. This solution was extracted with hexane (5 x 50 ml) to remove the *N,N*-dimethylaniline (TLC, Gibb's reagent produces a bright blue colour with *N,N*-dimethylaniline). The aqueous layer was rendered alkaline with concentrated ammonia (pH > 11) and extracted with dichloromethane (4 x 50 ml). The combined extracts were washed with 2N ammonia (3 x 50 ml) and dried over sodium sulfate. After evaporation to dryness, a brownish oil was obtained which solidified upon trituration with ether (9.64 g, 30.8 mmol, 94%, pure according to HPLC).
The compound was recrystallized from ethyl acetate giving 3.47 g of 2. An analytical sample showed m.p. 158-159 °C, $[\alpha]_D^{25}$ -69° (*c* 1). MS: M^+ 313. ^{1}H NMR: δ 2.39 (s, 3H, NCH_3), 3.78 (s, 3H, 3-OCH_3), 3.90 (s, 3H, 4-OCH_3), 5.88 (dm, 2H, $J_{7,8}$ 9.7 Hz, H-7 and H-8), 6.72 (m, 2H, H-1 and H-2). IR: 1670 cm^{-1} (vs, C=O).

7,8-Didehydro-3,4-dimethoxy-17-methylmorphinan-6α-ol (3)
A solution of 5 g (13.4 mmol) of cerium(III) chloride heptahydrate in 25 ml of absolute ethanol and 15 ml of toluene was evaporated to dryness *in vacuo* to remove the water of crystallization. Sodium tetrahydroborate (1.0 g, 27 mmol) was added all at once to a stirred solution of the anhydrous cerium(III) chloride and 1.34 g (4.3 mmol) of 2 in 100 ml of absolute ethanol. After 20 min the starting material had disappeared (TLC), and the reaction was stopped by adding 100 ml of 2N ammonia (pH > 11). The mixture was filtered over hyflo and

the residue was washed with dichloromethane (15 ml). The filtrate was extracted with dichloromethane (3 x 15 ml). The combined extracts were washed with 2N ammonia (3 x 15 ml), then with saturated sodium chloride (15 ml) and, finally, dried over sodium sulfate. After evaporation of the solvent, 1.12 g (3.6 mmol, 83%) of a colourless product was obtained, according to HPLC a 4:1 mixture of two compounds.
Recrystallization from ethyl acetate yielded pure 3. M.p. 127-128 °C, $[\alpha]_D^{25}$ +87° (c 1). MS: M^+ 315. ^{1}H NMR: δ 1.71 (2 x d, 1H, $J_{5\alpha,5\beta}$ 14.6 Hz, $J_{5\alpha,6\beta}$ 5.3 Hz, H-5α), 2.35 (s, 3H, NCH_3), 3.48 (2 x t, 1H, $J_{5\beta,6\beta}$ 1.4 Hz, $J_{5\alpha,5\beta}$ 14.6 Hz, H-5β), 3.77 (s, 3H, 3-OCH_3), 3.92 (s, 3H, 4-OCH_3), 4.20 (m, 1H, H-6), 5.60 (d, 1H, $J_{7,8}$ 9.8 Hz, H-8), 5.78 (m, 1H, H-7), 6.74 (2 x d, 2H, J 10.3 Hz, H-1 and H-2). IR: 3280 cm^{-1} (br, 6α-OH).

6α-Acetoxy-7,8-didehydro-3,4-dimethoxy-17-methylmorphinan (7)

Acetic anhydride (250 µl) and triethylamine (250 µl) were added to a solution of 200 mg (0.64 mmol) of 3 in 4 ml of dichloromethane. 4-Dimethylaminopyridine (8 mg, 0.07 mmol) was added and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with 6 ml of dichloromethane and poured onto 15 g of crushed ice. The mixture was rendered alkaline with concentrated ammonia (pH > 11) and extracted with dichloromethane (3 x 10 ml). The combined extracts were washed with 2N ammonia (3 x 10 ml), then with saturated sodium chloride and, finally, dried over sodium sulfate. The solvent was evaporated under reduced pressure yielding 190 mg of a yellowish oil. Crystallization from ethyl acetate yielded 70 mg (0.2 mmol, 31%) of 7, m.p. 146-148 °C, $[\alpha]_D^{25}$ +35° (c 1). MS: M^+ 357. ^{1}H NMR: δ 1.80 (s, 3H, $OCOCH_3$), 2.38 (s, 3H, NCH_3), 3.73 and 3.78 (2 x s, 6H, 2 x OCH_3), 5.27 (m, 1H, H-7), 5.77 (m, 1H, H-8), 6.73 (s, 2H, H-1 and H-2). IR: 1728 (vs, C=O).

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