Synthesis of 6-Methoxymethylmorphinol

M.U. VALHARI[1], A.U. RAHMAN[1], M.U. MEMON[2], F.C. NACHNANI[1] AND M. Y. KHAN[1]
[1]*Department of Organic and Natural Products Chemistry, Institute of Chemistry, University of Sindh, Jamshoro,*
[2]*Department of Pharmacy, University of Sindh, Jamshoro, Pakistan*

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Summary: An allyl ether of 14-hydroxycodeinone (2) was investigated as an intermediate for the preparation of analogues of (10) or (11) of cyclohexenodihydrocodeinones (9). The reactions involve an aromatising degredation of 14-hydroxycodeinone through the methine base (4) to yield 6-methoxymethylmorphinol (6, R = Me) with the elimination of the side chain, a process not reported with any 14-substituted codeinone.

Introduction

Electrophilic attack takes place either at C-7 or C-14 position of thebaine (1) molecule which is both a diene and dienolether. Thus bromination of thebaine afforded 14-bromocodeinone [1] and hydroxylation, normally with peracids gave 14-hydroxycodeinone [2] (2). Both reactions were previously investigated by Lutz and Small [3] who claimed 40% yield, Fel'dman and Lyutenberg [4] 75% yield and Seki [5] 85% yield for the hydroxylation reaction using modified conditions. The stereochemistry at C-14 in 14- hydroxycodeinone [6] and 14-hydroxydihydrocodeinone have been assigned from the infrared spectra. The products arise from a 1,4 addition to the diene system followed by hydrolysis at the enolether group of thebaine, whereby tertiary alcoholic hydroxyl group is introduced at C-14; and a carbonyl group at C-6 in the final product.

Results and Discussion

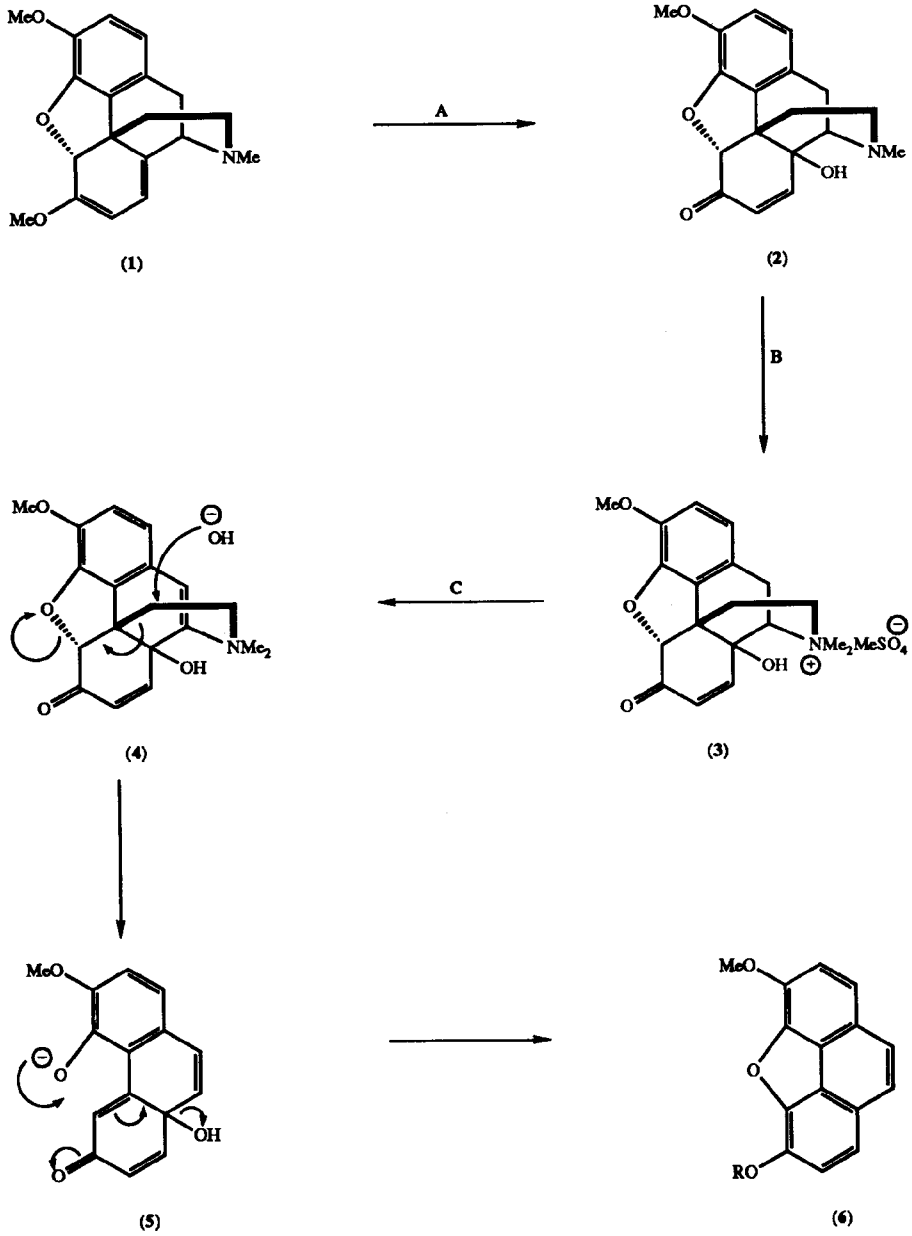
The infrared parameters of the hydroxyl group and the nitrogen atom indicated [7], that the nitrogen is difficult to quaternize because of the hydrogen bond. The reaction of α-chloroacetylchloride with 14-hydroxycodeinone eventually afforded a lactone, and the compound forms a well-defined copper complex. The C-14 substituent was therefore assigned the β- configuration.

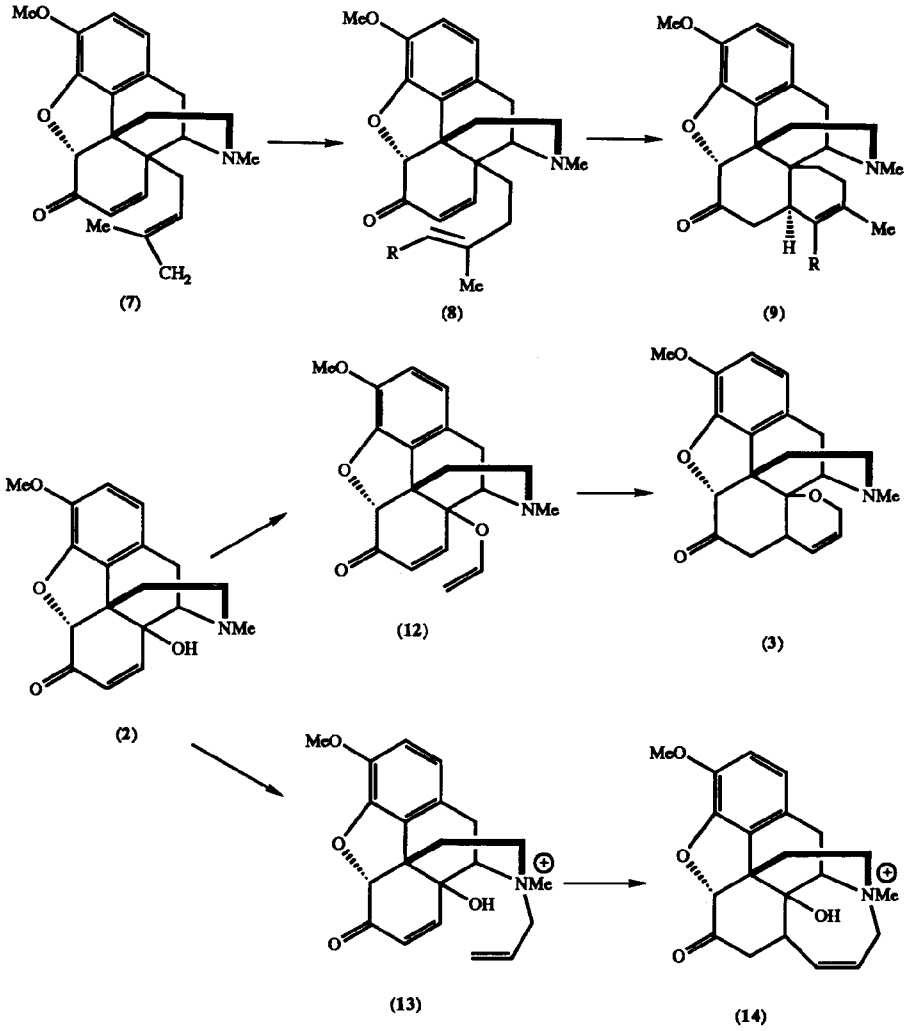
Accordingly, we prepared 14-hydroxy codeinone (2) by treating thebaine (1) with glacial acetic acid and 30% hydrogen peroxide, as previously described [4]. The yield of the brown crystalline powder was 70%, purification was achieved by dissolving the product in boiling chloroform, cooling and diluting with ethanol, to give a crystalline product m.p. 275-276° (dec.). The infrared spectrum showed a single broad hydroxyl band 3325 cm^{-1}. In the ^{1}H-NMR spectrum, the alkene protons H-7 and H-8 resonate at low field δ 6.13 and 6.53, this is due to the unsaturation in α/β position to the carbonyl function.

As 14-alkenylcodeinones of structure (7) can be easily converted into cyclohexano dihydrocodeinone (9) by acids, presumably by way of the transient intermediates (8) [12]. Attempts have been made to prepare the dihydropyranoishydrocodeinones (10) and (11) by similar acid-catalysed cyclizations of the alkenyl ethers (12), (13) and 14-hydroxycodeinone (2). In a preliminary study of the *O*-alkylation or *N*-alkylation of 14-hydroxy codeinone (2) without the loss of the side chain, the above was treated with potassium hydroxide and allyl bromide in dimethylsulphoxide for 2 hr. The reaction gave two crystalline products melting at 135-136° and at 131-133° for the above products. The ^{1}H-NMR spectral data of compound (10) fully agreed with the structure but regarding the product (11) due to the inappropriate parameters obtained, the structure remains unknown.

We considered the aromatisation of 14-hydroxylcodeinone methine (4), for its synthesis from 14-hydroxycodeinone by Freund and Speyer [2] gave insufficient details for a direct conversion.

It was decided to methylate the 14-hydroxycodeinone with dimethylsulphoxide instead of methyl iodide. Methylation of 14-hydroxycodeinone (2) with methyl sulphate, afforded a quaternary metho-salt of 14-hydroxy- codeinone (3), and hot aqueous alkali readily degraded the metho-salt to the methine base (4). The base was treated with potassium hydroxide and methyl iodide in dimethyl sulphoxide. The only identifiable product from this reaction was 6-methoxylmethylmorphinol (6, R = Me). This product was identified by the UV spectra, which was very similar to that of methylmorphinol (6, R = H). The ^{1}H-nmr spectrum (2H, s, δ 7.68, C-9 and C-10; 4H quartet δ 7.62 (C-1 and C-8), δ 7.37 (C-3 and C-7), $J_{1,2}$ and $J_{7,8}$ = 9Hz; (6H, s, C-3, 6-OMe). For such a base to be converted into a phenanthrene the nitrogen containing side chain must be removed by a process of analogous to those involved in the acetolysis of thebaine methiodide [8], codeinone methiodide [9], and α- codeimethine [10] and in the degradation of α-codeimethine to methylmoprhinol by treating





with sodium ethoxide [11], which are initiated by attack at C-15 by acetate ion and ethoxide ion respectively.

Attack of the methine base (4) by hydroxide ion could be followed by elimination with loss of oxygen function at C-5 or C-14. Loss of hydroxyl ion from C-14 would involve *cis*-elimination and the give the phenate ion (5). Examination of the model of this ion shows that the negatively charged oxygen atom lies above the plane of C-5 and C-6 double bond on the same side as C-14 hydroxyl group, thus facilitating the displacement by the S_N2 reaction mechanism of the latter to give the phenol (6, R = H). The phenol must then be methylated by some quaternary salt in the reaction involving methyl iodide (a process of which there are several precedents in the morphine group).

Experimental

All metling points were taken on a Kofler hot-stage appratus and are uncorrected. ^1H NMR were recorded by a Varian EM-360A spectrometer (60 MHz) in solution of $CDCl_3$ with TMS as internal reference. Infrared spectra were recorded as KBr discs or in chloroform solution by means of Perkin Elmer 177 grating spectrometer.

14-hydroxycodeinone [4] (2)

The thebaine (1) (25.0g, 0.08 mole) was treated acetic acid (100 ml) at 55-60°, after which the mixture was stirred at 40° untill solution occurred, and the mixture was treated with 30% hydrogen peroxide (12.5 ml) added over 17-19 hrs. Most of the acetic acid was removed in vacuum at

40° and the residue warmed with water (125 ml), cooled to 5-10° and treated with concentrated ammonium hydroxide. The 14-hydroxycodeinone (2) was filtered off, washed with hot water, dried (19.12g, 76%) and recrystallised by dissolving the product in boiling chloroform, cooling and diluting with ethanol to give (2) (14.4g, 58%, m.p. 275-276° dec.). IR: ν_{max}(KBr) 3325 cm^{-1} (broad -OH stretch), 1678 cm^{-1} ($\alpha\beta$-unsaturated C=O).

^{1}H-NMR ($CDCl_3$): δ 2.41 (3H, s, N-CH_3); 3.8 (3H, s, OCH_3); 4.65 (1H, s, H_5-β) 6.13 (1H, d, H_7); 6.53 (1H, d, H_8); 6.6 (2H, s, H_1 and H_2).

14-Hydroxycodeinone methine (4)

14-hydroxycodeinone (2) (5.0 g, 0.015 mole) was dissolved in hot methyl sulphate (12.5 ml) on steam bath. The solution was cooled in ice and treated with diethylether (100 ml) to remove excess of methyl-sulphate. After removing the ether the residue was dissolved in water (35 ml) and boiled with 30% aqueous sodium hydroxide solution (50 ml) when a dark brown oily product was seaprated. It was extracted with chloroform from the alkaline media, well washed with water, dried and evaporated to give amorphous products, which was crystallised from pet.ether (80- 100°) (3.15 g, m.p. 190-192°). IR; ν_{max} ($CHCl_3$); 1680 cm^{-1} ($\alpha\beta$-unsaturated C=O).

6-Methoxy-3-methylmorphinol (6, R-Me)

14-hydroxycodeinone methine (4) (2.0g, 0.06 mole), methyl iodide (2.25 ml) and powdered potassium hydroxide (1.6 g) were stirred in dimethylsulphoxide (100 ml) for approximately 2.5 hr, it was poured in to water and the mixture extracted with ether. The extract, on evaporation, yielded the required product (6, R-Me) (1.2 g) as pale brown needles m.p. 126-128° from benzene.

^{1}H-NMR ($CDCl_3$): δ 4.26 (6H, s, C-3, 6-OMe): 7.37 (2H, d, H_2 and H_7); 7.62 (2H, d, H^1 and H^8); $J_{1,2}$ and $J_{7,8}$ = 9Hz) 7.68 (2H, s, H_9 and H_{10}). (Anal. Cacld: for $C_{16}H_{12}O_3$; C, 76.2; H, 4.8%, Found C, 75.9; H, 4.90%). The picrate was obtained as dark rusty needles m.p. 145-146° from ethanol.

(Anal. Calcd. for $C_{22}H_{15}N_3O_{10}$: C, 54.9; H, 3.14; N, 8.73%, Found C, 54.9; H, 3.20; N, 8.70%).

6,14-endo-Ethenol-7α-(1-hydroxy-1-methyl-ethyl) dihydrocodeine (7)

6,14-*endo*-Ethenol-7α(1-hydroxy-1-methyl-ethyl) tetrahydlrothebaine (10 g) was heated at 45-58° with (75 ml) of 6N hydrochloric acid for 6-8 hrs. The mixture was diluted and the base was precipitated with ammonia solution, collected and recrystallised from ethanol when the dihydrocodeine derivative (6.5 g) was obtained as white prisms m.p. 265-267°.

(Anal. Calcd. for $C_{23}H_{29}NO_4$: C, 72.0; H, 7.6; N, 3.7%, Found C, 72.6; H, 7.65; N, 3.8%).

The hydrochloride was obtained as white prism, m.p. 261-263° from ethanol.

(Anal.Calcd. for $C_{23}H_{29}NO_4$. $HCl.H_2O$, C, 63.1; H, 7.4%, Found C 62.7; H, 7.9%).

5,14-etheno-18-isopropylidene thebainone (8)

6,14-endo-etheno-7α(1-hydroxy-1-methyleth-yl) tetrahydrothebaine (5g) was heated at 100° with 10N hydrochloric acid (15 ml) for 45-50 minutes during which time crystalline material separated. The mixture was diluted with water (15 ml) and cooled in ice, and the hydrochloride (2.5 g) was collected. This was dissolved in aqueous methanol, and the base was precipitated with ammonia. It was recrystallised readily from methanol and separated as off-white crystalls m.p. 138-140°, IR ν_{max} 1690 $cm.^{-1}$

The hydrochloride was obtained was white prism m.p. 320-321° from water. (Anal. Calcd. for $C_{23}H_{27}NO_3$.HCl, C, 68.7; H, 7.0%, Found C, 68.5; H, 7.4%).

7,8-Dihydro-5'-methyl cyclohex-4'-eno(1',2',: 8,14) codeinone (9)

6,14-endo-Etheno-7α-(1-hydroxy-1-methyl-ethyl) tetrahydro thebaine (2.5 g) was heated in hy drochloric acid (7 ml) on the steam bath for 90-100 minutes, during which time crystals separated. Water (8 ml) was added, and the solid matter was collected when compound (8) was obtained, m.p. 320-321°.

The combined filtrate and washing from the collection of this hydrochloride were neutralized

with aqueous sodium bicarbonate and the resulting base was isolated by extraction with chloroform. The solvent was removed and the syrup was dissolved in small methylene chloride and chromatographed on alumina. Combined elution of the column with methylene chloride, affrded material that was crystallised from n-hexane, yielding (750 mg) of the required material as prisms, m.p. 112-114°: IR ν_{max} 1730 cm.$^{-1}$ (Anal. Calcd. for $C_{23}H_{27}NO_3$: C, 75.6; H, 7.45%, Found C, 76.02; H, 7.8%).

O and N-alkylation synthesis of the dihydropyranodihydrocodeinones (10) and (11).

14-hydroxycodeinone (2) (2.0g, 0.006 mole), allyl bromide (2.25 g) and powdered potassium hydroxide (1.6 g) in dimethylsulphoxide (100 ml) were kstirred for approximately 2 hrs. The precipitated product was acidified with 2N hydrochloric acid and neutralized with soldium bicarbonate solution. It was isolated by ehter extract and shown by thin layer chromatography to consists of approximately 13.5% yield of compound (10) and N-allylmethyl ammonium salt (11). The mixture was dissolved in benzene and n- hexane and chromatographed on a column of alumina. The column was eluted with benzene, and 25 ml samples were collected, the composition of these being followed by thin layer chromatography. The first meterial eluted from column (250 mg) was obtained as a gum which crystallised on keeping for several hours. On recyrstallisation from aqueous methanol it was obtained as white prism m.p. 135-136°, IR: ν_{max} 1726 cm.$^{-1}$

^{1}H-NMR: δ 6.57 and 6.51 (2H, s, H_1 and H_2, $J_{1,2}$ = 9Hz); 5.72 and 5.37 (2H, s, H_{18} and H_{17}, $J_{17,18}$ = 10 Hz); 4.56 (1H, s, H-5); 3.82 (substituted OH function); 3.58 (3H, s, C-6 OMe); 3.20 (3H, s, C-19, OMe); 2.36 (3H, s, N-Me); 1.30 and 1.0 (3H, s, C-19, OMe); 2.36 (3H, s, N-Me); 1.30 and 1.0 (3H, s, C- 19, Me). (Anal. Calcd. for $C_{21}H_{23}O_4N$: C, 71.38; H, 9.09%, Found C, 71.41; H.9.1%).

The later part of the eluent was evaporated to give cyclized N- allyl ammonium salt (11) as white prism m.p. 131-133°; IR: ν_{max} 1730 cm.$^{-1}$ ^{1}H-NMR spectrometer did not resolved completely the above product and thus various protons present in the structure remained unknown and the elemental analysis reported as a allyl salt of hydrochloride.

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