PARTIAL SYNTHESIS OF 3-DEOXYDIHYDROMORPHINE FROM (-)-4-HYDROXY-6-KETO-N-METHYLMORPHINAN[1]

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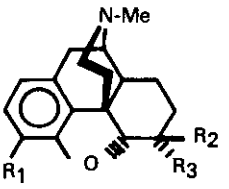
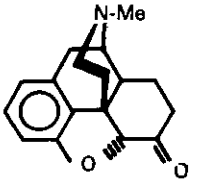
Abstract - Conversion of (-)-3-deoxydihydromorphine (2) into (-)-4-hydroxy-6-keto-N-methylmorphinan (5) and reconversion of 5 into 2 via the ketone 4 is described. The morphinan structure of 5 was proven by reduction to the known (-)-4-hydroxy-N-methylmorphinan (7).

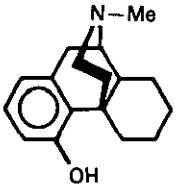
3-Deoxydihydromorphine (2) and 3-deoxydihydromorphinone (4), easily obtainable from dihydromorphine (1)[2], represent valuable intermediates for the preparation of a variety of antinociceptive 3-deoxyopioids.[2] In addition the ketone 4, with the ether bridge linked at the α-position of the carbonyl group, constitutes an important entry into the relatively unexplored class of 4-hydroxymorphinans.[3] Such a conversion could be accomplished as follows:





4

1. $R_1 = R_3 = OH$, $R_2 = H$
2. $R_1 = R_2 = H$, $R_3 = OH$
3. $R_1 = R_3 = H$, $R_2 = OH$



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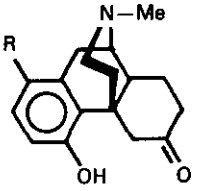

5. R = H
6. R = Br

Reduction of ketone 4 with freshly prepared aluminium amalgam[4] afforded the ketomorphinan 5 in 85-88% yield: mp 119-121°; $[\alpha]_D^{20}$ -142° (1.02, $CHCl_3$); ir (γmax, $CHCl_3$, cm^{-1}) 1710 (C=O), 3300 (OH); nmr (δ, $CDCl_3$) 6.94 (1H, dd, ArH, J = 8, 8 Hz), 6.64 (2H, m, ArH), 4.46 (1H, d, C_5-H, J = 13 Hz), 2.44 (3H, s, NCH_3); m/e 271 (M^+). 5·HBr·1/2 H_2O: mp 210-3°; $[\alpha]_D^{20}$ -38.2 (1.10, MeOH). Bromination of 5 with 1.1 mole of bromine in acetic acid afforded the bromoketone 6·HBr in 50% yield: mp 218-221°, $[\alpha]_D^{20}$ -43.2° (0.92, MeOH); ir (γ_{max}, KBr, cm^{-1}) 3300 (OH), 1705 (C=O); nmr (δ, CD_3OD) 7.31 (1H, d, ArH, J = 9.5 Hz), 6.63 (1H, d, ArH, J = 9.5 Hz), 4.30 (1H, d, C_5-H, J = 14 Hz), 2.97 (3H, s, NCH_3); m/e 349 (M^+), 351 ($M^+ + 2$). This bromination pattern is consistent with previously noted brominations[5] and with the spectral evidence. Bromination of 5 with 2.5 mole of bromine in acetic acid and reduction of the mixture of brominated materials over 10% Pd-C in acetic acid and sodium acetate[6] gave ketone 4 in 82% yield. The material thus obtained was identical in all respects to an authentic sample of 3-deoxydihydromorphinone (4).[2] The morphinan structure of 5 was confirmed by Wolff-Kishner reduction affording (-)-4-hydroxy-N-methylmorphinan (7) in 75-85% yield: mp 213-214.5° (lit.[3] 216-217°); $[\alpha]_D^{20}$ -35.4° 1.27, MeOH) [lit.[3] -35° (1.07, MeOH)]; ir (γ_{max}, $CHCl_3$, cm^{-1}) 3350, 3600 (OH); nmr (δ, $CDCl_3$) 6.95 (1H, dd, ArH, J = 8, 8 Hz), 6.65 (1H, d, ArH, J = 8 Hz), 6.42 (1H, d,ArH, J = 8 Hz), 3.48 (1H, d, C_5-H, J = 13 Hz), 2.39 (3H, s, NCH_3); m/e 257 (M^+). 7·HCl·EtOH: mp 282-4° (dec) lit.[3] 303-5°); $[\alpha]_D^{20}$ -17.4° (0.998, MeOH) [lit.[3] $[\alpha]_D^{25}$ -17.94° (0.958, MeOH)], and identical in all respects with a comparision sample prepared by total synthesis.[3,7]

Reduction of ketone 4 with sodium borohydride in methanol at room temperature afforded a mixture of two epimeric alcohols in a ratio of 3:2, which could be separated by preparative tlc on silica gel ($CHCl_3$:MeOH:NH_4OH = 90:10:1). The faster moving alcohol and also the major one was identical with 3-deoxydihydromorphine (2). The slower moving alcohol 3 was characterized as its hydrochloride salt, 3·HCl·1/2 H_2O: mp 310-2° (dec); $[\alpha]_D^{20}$ -159.7° (1.1433, CH_3OH); ir (γ_{max}, KBr, cm^{-1}) 3350 (OH); nmr (δ, CD_3OD) 7.37 (1H, t, ArH, J = 8 Hz), 6.76 (2H, dd, ArH, J = 8, 8 Hz), 4.32 (1H, d, C_5-H, J=8 Hz), 3.88 (1H, m, C<u>H</u>-OH), 2.95 (3H, s, NCH_3).

A selective high yield reduction of ketone 4 to 3-deoxydihydromorphine (2) was accomplished with lithium tri-<u>sec</u>-butylborohydride in tetrahydrofuran. This retrosynthesis of 3-deoxydihydromorphine (2) from the 4-hydroxy 6-keto-N-methylmorphinan (5) marks the latter an interesting intermediate for a total synthesis of 3-deoxyopioides.

References:

1. This work was presented by F. H. at the 20th Annual Meeting of the American Society of Pharmacognosy at Purdue University, July 29, 1979.

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5. H. L. Holmes in Manske "The Alkaloids", Vol. II, p. 48-49, 1952. A detailed examination of morphinans with varied substituents in the aromatic ring by ^{13}C NMR is in progress.

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7. We would like to thank Dr. E. Mohacsi from Hoffmann-La Roche Inc., Nutley, New Jersey, for providing a comparison sample of compound 4.

Received, 6th October, 1979