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An improved synthesis of noroxymorphone

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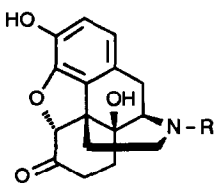
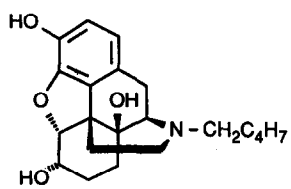
Abstract: A brief synthesis of noroxymorphone is described which involves the oxidation of 3-*O*-^{t}butyldimethylsilylmorphine by manganese dioxide. The initial product is the corresponding morphinone which is further oxidised to the 14-hydroxymorphinone. After hydrogenation the 7,8-dihydro-14-hydroxymorphinone is acetylated and *N*-demethylation of the 14-*O*-acetylated product is achieved using vinyl chloroformate as the reagent. The overall yield from morphine is 40-45%.

The introduction of a 14-hydroxyl group into morphines often increases their potency[1-4], thus 14-hydroxy-7,8-dihydromorphinone (1) (oxymorphone) and nalbuphine (2)[5] are more powerful analgesics than morphine (3). Other 14-hydroxymorphines, such as noroxymorphone (4), are important intermediates for well known drugs such as the narcotic antagonist naloxone (5) and nalmexone (6), and naltrexone (7)[6] which show mixed agonist and antagonistic effects.



(1, R=Me)
(4, R=H)
(5, R=$CH_2CH{=}CH_2$)
(6, R=$CH_2CH{=}CMe_2$)
(7=$CH_2C_3H_5$)



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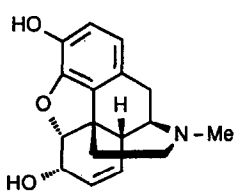
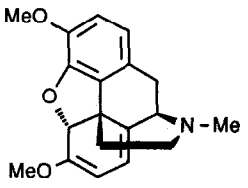


(3)

A commercial seven step synthesis of noroxymorphone commences from the alkaloid thebaine (8)[7], however, the overall yield is variable and thebaine is expensive. Another route uses codeine (9)[8] as the starting material and requires seven steps. Although codeine is readily available, this approach has not found favour in industry.

A new synthesis of noroxymorphone is clearly needed and for this we have selected morphine as the starting material. Not only is this the commonest opium alkaloid, it also lacks an *O*-methyl group thus avoiding *O*-demethylation later in the synthesis: a step which is potentially troublesome on a large scale and which is common to the two existing approaches. Morphine, selectively protected as the 3-^{t}butyldimethylsilyl (TBDMS) derivative (10), was dissolved in reagent grade chloroform and the solution stirred at room temperature with commercially available active manganese dioxide[9]. After 20 min., the reagent and the solvent were removed to afford the morphinone (11) in 90% yield, after chromatography. Continuation of the oxidation for 48 hours produced the silylated hydroxymorphinone (12) in 35% yield. This yield can be improved to 59% and the time reduced to 3 hours if silica gel is added to the reaction mixture and the vigorously stirred suspension is heated at 38-40° C[10].



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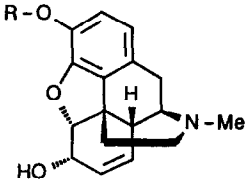
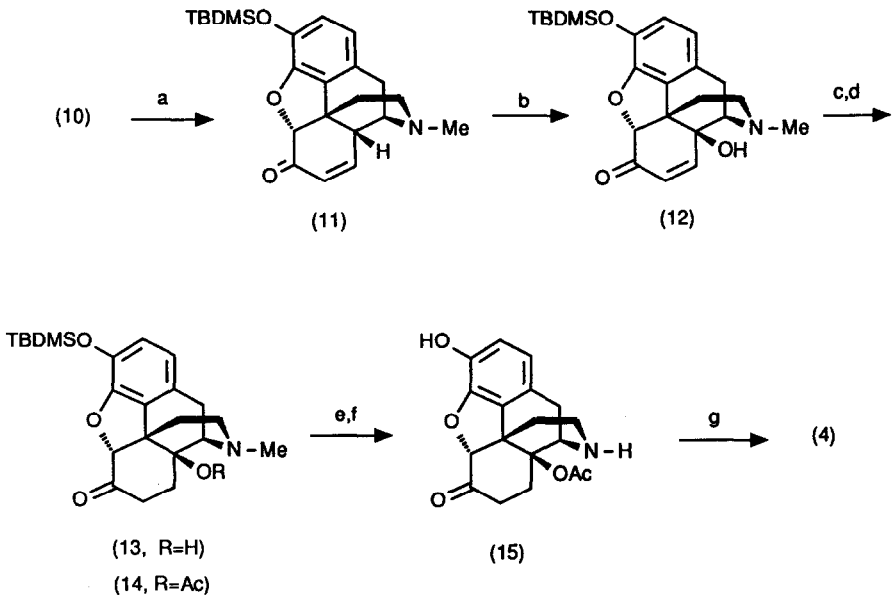


(9, R=Me)
(10, R=^{t}BuMe$_2$Si)

Ultrasonification of the cold reaction mixture serves only to bring about extensive decomposition of the products, and the use of either carefully purified chloroform, or activated manganese dioxide[11] has no beneficial effect. Iodosobenzene failed to oxidise the silylated morphine (10), but selenium dioxide in dioxane gave the morphinone (11) in 14.6% yield. Selenium dioxide and ^{t}butyl hydroperoxide yielded the morphinone (10%) and the 14-hydroxymorphinone (12) (10%), whereas oxidation with tetrapropyl ammonium perruthenate/*N*-methylmorpholine-*N*-oxide[12] afforded only the silylated morphinone (11), but in 86% yield.

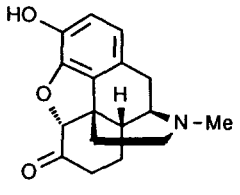
The 14-hydroxymorphinone (12) was hydrogenated at atmospheric pressure over Pd/C as catalyst and the product (13) was protected as the 14-acetoxy derivative (14). *N*-Demethylation and *O*-desilylation were then effected through treatment with vinyl chloroformate[13-15] . In this process the *N*-vinylcarbamate was isolated as an intermediate and *N*-deprotected simply by treatment with hot methanol containing hydrochloric acid. Finally, the product 14-acetoxynoroxymorphone (15), as the hydrochloride salt, was *O*-deacetylated to give noroxymorphone (4) by hydrolysis with 25% aqueous sulphuric acid at reflux and basification with ammonia. The overall yield for last the four steps was 78%. A similar sequence using 1-chloroethyl chloroformate[16]

instead of vinyl chloroformate afforded noroxymorphone in 68% yield.

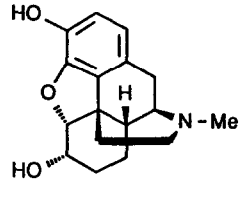


Scheme 1. Reagents: (a) $MnO_2/CHCl_3/20°$ C/20min; (b) $MnO_2/CHCl_3/SiO_2/38$-40° C/3 h; (c) $H_2/Pd/C$; (d) Ac_2O; (e) vinyl chloroformate/DCM; (f) HCl/MeOH; (g) H_2SO_4/H_2O

The new synthesis has been repeated several times on a 10g scale with reproducible results (overall yields from morphine 40-45%). It offers a considerable improvement on existing syntheses of noroxymorphone, both in methodology and brevity and may prove to be valuable on a much larger scale.



(16)



(17)

Hydromorphone (7,8-dihydromorphinone) (16) is 3-4 times more effective as an analgesic than morphine. This compound is normally synthesised from morphine in 69% yield through reduction to dihydromorphine (17) and Oppenauer oxidation[17]. As an extension of our work we have devised a more convenient preparation of hydromorphone from 3-TBDMS-morphone (11). The latter compound was hydrogenated over Pd/C catalyst at atmospheric pressure to give the 7,8-dihydro derivative which, without isolation, was *O*-desilylated to give hydromorphone in an overall yield of 83%. This route may also have commercial value since it involves very few chemical operations.

EXPERIMENTAL

Petrol refers to petroleum ether b.p. 60-80° C. Merck DC-alufolien Kieselgel 60 F_{254} sheets containing fluorescent indicator were used in TLC analyses, and flash column chromatography was carried out using Amicon Matrex or Merck 9385 silica gel. ^1H and ^{13}C NMR spectra were recorded on a JEOL GX FT 270 (270 MHz) spectrometer. In the latter case the spectrometer was operated at 67.8 MHz and 90 and 135 DEPT pulse sequences were used to aid multiplicity determinations. Chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded using a VG 7070E instrument with a VG 2000 data system. Electron ionisation (E.I.) spectra were produced using an ionising potential of 70 eV. Chemical ionisation (C.I.) was employed using ^{i}butane as the reagent gas.

3-(^{t}Butyldimethylsilyl)morphine (10)

Morphine (1.42 g, 5 mmol) was added to dry ethanol (40 cm^3) containing sodium metal (0.13 g, 1.1 equivalent per mol of morphine) and the resulting solution was evaporated under reduced pressure. The residue was redissolved in benzene (20 cm^3) and evaporated to give a colourless powder. This was dissolved in dry THF (40 cm^3) and TBDMSCl (1.10 g, 7.3 mmol) dissolved in dry THF (5 cm^3) was added slowly under nitrogen. The reaction mixture was left overnight at room temperature. Next day the solvent was removed, the residue dissolved in chloroform, washed with water and the solvent evaporated to give the title compound (1.98 g, 99% yield) as colourless needles, m.p. 201-203° C (EtAc); R_f 0.35 ($CHCl_3$: MeOH 9:1); δ_H ($CDCl_3$) 0.16 and 0.19 (2 x 3H, 2 x s, 2 x Si-CH_3), 0.98 (9H, s, Si-^{t}Bu), 1.8 - 2.6 (4H, m, 15-H_2 and 16-H_2), 2.28 (1H, dd, J_{gem} = 18.7 and $J_{10,9}$ = 6.2 Hz, 10-Hα), 2.44 (3H, s, N-CH_3), 2.60 (1H, m, 14-H), 2.81 (1H, br.d, 6-OH), 3.02 (1H, d, J = 18.6 Hz, 10-Hβ), 3.40 (1H, q, $J_{9,10}$ = 6.4 Hz, 9-H), 4.16 (1H, m, 6-H), 4.85 (1H, dd, $J_{5,6}$ = 6.0 Hz and $J_{5,7}$ = 1.1 Hz, 5-H), 5.30 (1H, m, 8-H), 5.70 (1H, m, 7-H), 6.40-6.60 (2H, AB system, J = 8.2 Hz, 1-H and 2-H); *m/z* (E.I.) 399 (70%, M^+), 342 (100, M-^{t}Bu).

3-^{t}Butyldimethylsilylmorphinone (11)

(a) using manganese dioxide as oxidant

A solution of 3-(TBDMS)morphine (0.28 g, 0.7 mmol) in chloroform (50 cm^3) was stirred with manganese dioxide (2.8 g, 10 weight equivalents) at room temperature for 20 min. The mixture was filtered through a pad

of silica gel (2-3 mm deep) and washed with warm chloroform. The filtrate and washings were evaporated to give 3-(TBDMS)morphinone as an oil, which was purified by flash column chromatography eluting with DCM:MeOH (98:2). Yield = 0.26 g, 91%; R_f 0.43 ($CHCl_3$:CH_3OH 9:1); δ_H ($CDCl_3$) 0.1 and 0.18 (2 x 3H, 2 x s, 2 x Si-CH_3), 0.97 (9H, s, Si-^{t}Bu), 2.40 (1H, dd, J = 18.6 and 5.1 Hz, 10-Hα), 2.46 (3H, s, N-CH_3), 2.57 (1H, m, 14-H), 3.09 (1H, d, J = 18.7 Hz, 10-Hβ), 3.41 (1H, m, 9-H), 4.66 (1H, s, 5-H), 6.07 (1H, d,d $J_{8,7}$ = 10.3 and $J_{8,14}$ = 2.8Hz, 8-H), 6.63 (1H, d, J = 10.4 Hz, 7-H), 6.52 - 6.64 (2H, dd, J = 8.2 Hz, 1-H and 2-H); *m/z* (%): (Low E.V. E.I.) 397 (100, M^+), 340 (90, [M-^{t}Bu]$^+$).

(b) using tetrapropyl ammonium perruthenate (TPAP) and N-*methylmorpholine* N-*oxide as oxidant*

TPAP (10 mg, 5 mol%) was added to a stirred mixture of 3-(TBDMS)morphine (10), (0.18 g, 0.45 mmol), *N*-methylmorpholine *N*-oxide (0.8 g, 0.7 mmol, 1.5 equivalents) and powdered 4 Å molecular sieves (0.20 g) in dry dichloromethane (3 cm^3). The reaction mixture was protected under nitrogen and then left stirring for 2 hours. It was then added to the top of a short column of silica (5 cm length, 1 cm diameter) and eluted with ethyl acetate. The solution was evaporated to give pure 3-(TBDMS) morphinone (11) (0.16 g, 86% yield).

3-(^{t}Butyldimethylsilyl)-14-hydroxymorphinone (12)

3-(TBDMS)morphine (10), (0.62 g, 1.56 mmol) in chloroform (80 cm^3) was stirred with manganese (IV) oxide (6.0 g, 10 weight equivalent) at 38-40°C, after 15 minutes TLC analysis ($CHCl_3$: MeOH 9:1) showed that the conversion into 3-*O*-silylmorphinone (11) (R_f 0.46) was almost complete. Silica gel (1.8 g, 3 weight equivalent Merck No 7736, Type 60H) was then added and the mixture was stirred vigorously at 38-40° C for 3 hours. The mixture was filtered and the residue washed with warm chloroform (200 cm^3) containing 1% methanol. The filtrate and washings were combined and evaporated to give the title compound (0.38 g, 59%) as an off-white solid. It was crystallised from ethyl acetate as colourless plates. R_f 0.55 ($CHCl_3$: CH_3OH 9:1); m.p. 222-224° C; δ_H ($CDCl_3$) 0.10 and 0.16 (2 x 3H, 2 x s, 2 x Si-CH_3), 0.95 (9H, s, Si^{t}Bu), 1.63-2.57 (4H, m, 15-Hα, 15-Hβ, 16-Hα, 16-Hβ), 2.35 (1H, dd, J = 18.7, 6.0 Hz, 10-Hα), 2.44 (3H, s, N-CH_3), 3.03 (1H, d, J = 5.9 Hz, 9-H), 3.20 (1H, d, J = 18.7 Hz, 10-Hβ), 4.67 (1H, s, 5-H), 6.16 (1H, d, J = 10.1 Hz, 8-H), 6.61 (1H, d, J = 10.1 Hz, 7-H), 6.53-6.64 (2H, AB system, J = 8.0 Hz, 1-H and 2-H); δ_H (DMSO): 5.4 (1H, br.s, 14-OH); δ_C ($CDCl_3$): 4.77 (Si-$\underline{C}H_3$), 4.64),(Si-$\underline{C}H_3$), 18.23 (Si-$\underline{C}Me_3$), 22.48 (C-15), 25.62 (Si-C($\underline{C}H_3$)$_3$), 29.55 (C-16), 42.55 (N-$\underline{C}H_3$), 45.12 (C-10), 46.71 (C-13), 64.16 (C-9), 67.79 (C-14), 86.86 (C-5), 119.46 (C-8), 122.54 (C-7), 125.46 (C-11), 130.55 (C12), 134.67 (C-1), 137.85 (C-4), 146.35 (C-3), 147.45 (C-2), 194.03 ($\underline{C}$=O); *m/z* (%): (Low E.I.) 413 (100, M^+), 356 (90, [M-^{t}Bu]$^+$)[Found; C, 66.5; H, 7.5; N, 3.35 $C_{23}H_{31}SiNO_4$ requires: C, 66.8; H, 7.5; N, 3.4%].

3-(^{t}Butyldimethylsilyl)-14-hydroxy-7,8-dihydromorphinone (13) [3-(^{t}butyldimethylsilyl)oxymorphone]

A mixture of the hydroxymorphinone (12), (0.20 g, 0.48 mmol) in absolute ethanol (50 cm^3) and Pd/C (10%, 0.1 g) was stirred under hydrogen for 2 hours. The mixture was filtered and the residue was washed with ethanol. The filtrate and the washings were combined and evaporated to give the title compound (0.20 g, quantitative yield). It was crystallised from ethyl acetate, m.p. 133-135° C; R_f = 0.49 ($CHCl_3$: CH_3OH 9:1); δ_H ($CDCl_3$) 0.19 and 0.26 (2 x 3H, 2xs, 2 x Si-CH_3), 0.98 (9H, s, Si-*t*-Bu), 1.52 (1H, m, 15-Hα), 1.67 (1H, m,

8-H_α), 1.97 (1H, m, 15-H_β), 2.20-2.60 (3H, m, 7-H_α, 7-H_β and 8-H_β), 2.53 (3H, s, N-CH_3), 2.67 (1H, m, 16-H_α), 2.68 (1H, dd, J = 18.5, 5.5 Hz, 10-H_α), 3.02 (1H, m, 16-H_β), 3.15 (1H, d, J = 18.5 Hz, 10-H_β, 3.20 (1H, m, 9-H), 4.63 (1H, s, 5-H), 6.55-6.66 (2H, q, AB system, J = 8.2 Hz, 1-H and 2-H); *m/z* (%): (E.I.) 358 (100, [M-^{t}Bu]$^+$), 315 (45), 415 (20, M^+).

3-(^{t}Butyldimethylsilyl-14-acetoxy-7,8-dihydromorphinone (14)

A mixture of 3-TBDMS-14-hydroxy-7,8-dihydromorphinone (13), (0.62 g, 1.4 mmol) and acetic anhydride (10 cm^3) was heated under reflux for 1.5 h. Excess reagent was removed and the residue was dissolved in wet chloroform (10cm^3). The solution was shaken with 2M ammonium hydroxide, the chloroform layer separated, and the aqueous phase extracted with chloroform (3x5cm^3). The organic phases were combined and evaporated to give a brown residue which was chromatographed eluting with chloroform to afford the title compound (0.63 g, 92%). This was crystallised from ethanol to give colourless needles, R_f 0.60 ($CHCl_3$: CH_3OH 9:1); m.p. 178 - 179° C; δ_H ($CDCl_3$) 0.18 and 0.26 (2 x 3H, 2xs, 2 x $SiCH_3$), 0.99 (9H, s, Si-*t*-Bu), 1.47 (1H, dd, J = 11.7, 4.2 Hz, 15-H_α), 1.66 (1H, td, J = 14.3, 4.0 Hz, 8-H_α), 2.00 (1H, dd, J = 18.5 and 5.6 Hz, 10-H_α), 2.18 (3H, s, N-CH_3), 2.25 (1H, dd, J = 11.8 and 3.4 Hz, 15-H_α), 2.32 (3H, s, $COCH_3$), 2.40 - 2.55 (3H, m, 7-H_α, 7-H_β and 8-H_β), 2.58 (1H, dd, J = 14.8 and 5.5 Hz, 16-H_α), 2.79 (1H, m, J = 14.3 and 2.7 Hz, 16-H_β, 3.18 (1H, d, J = 18.5 Hz, 10-H_β), 4.16 (1H, d, J = 5.3 Hz, 9-H), 4.58 (1H, s, 5-H), 6.55 - 6.66 (2H, dd, J = 8.2 Hz, 1-H and 2-H); *m/z* (%): (Low E.V. E.I.) 400 (100, [M-^{t}Bu]$^+$, 457 (50, M^+).

N-Vinyloxycarbonyl-3-(^{t}butyldimethylsilyl)-14-acetoxy-7,8-dihydronormorphinone

A solution of 3-(TBDMS)-14-acetoxy-7,8-dihydromorphinone (14), (0.30 g, 0.66 mmol) in 1,2-dichloroethane (10 cm^3) was heated under reflux with vinyl chloroformate (0.3 cm^3, 0.38 g, 5 equiv.) under nitrogen for 3 days. More vinyl chloroformate (0.2 cm^3 each time) was added after 25 and 50 h. When the reaction was complete solvent and excess reagent were removed under reduced pressure to give title compound, (0.33 g, 98%) as an off-white solid which was purified by flash column chromatography with chloroform as eluant. R_f 0.87 ($CHCl_3$: CH_3OH 9:1); υ_{max} cm^{-1} 3500 (br), 1698, 1640; δ_H ($CDCl_3$) 0.20 and 0.27 (2 x 3H, 2xs, 2 x Si-CH_3), 1.00 (9H, s, Si-*t*-Bu), 2.12 (3H, s, $COCH_3$), 4.50 (1H, m, 9-H), 4.62 (1H, s, 5-H), 4.81 (1H, m, CH=CH_2), 5.61 (1H, m, CH=CH_2), 6.59-6.72 (2H, dd, J = 8.1 Hz, 1-H and 2-H), 7.16 - 7.26 (1H, m, CH=CH_2); *m/z* (%): (C.I.) 71 (100, $C_2H_3CO_2$), 456 (73, [M-^{t}Bu]$^+$).

14-Acetoxy-7,8-dihydronormorphinone hydrochloride (14-acetylnoroxymorphone hydrochloride)

Method (a)

Dry hydrogen chloride gas was passed through a solution of *N*-vinyloxycarbonyl-3-(TBDMS)-14-acetoxy--7,8-dihydronormorphinone (0.300 g, 0.58 mmol) in dichloromethane (5 cm^3) for 1 h. The solution was evaporated and the residue was dissolved in methanol (10 cm^3) and heated under reflux for 2 h. The solvent was evaporated to give 14-acetylnoroxymorphone hydrochloride (0.205 g, 96%) R_f 0.72 ($CHCl_3$: MeOH 9:1); δ_H (CD_3OD) 2.31 (3H, s, $COCH_3$), 2.55 (1H, br.s, N-H), 3.26 (1H, m, 9-H), 4.93 (1H, s, 5-H), 6.69 - 6.78 (2H, dd, AB system, J = 8.2 Hz, 1-H and 2-H).

Method (b)

A solution of *N*-vinyloxycarbonyl-3-(TBDMS)-14-acetylnoroxymorphone (0.10 g, 0.2 mmol) in methanol (5 cm^3) containing 3 drops of concentrated hydrochloric acid was heated under reflux for 1 h. The resultant solution on evaporation gave 14-acetylnoroxymorphone hydrochloride (0.07 g, 98%).

Noroxymorphone (4)

Method (a)

A mixture of 14-acetylnoroxymorphone hydrochloride (0.20 g, 0.55 mmol) and 25% dilute sulphuric acid (2 cm^3) was heated at 100-102° C under nitrogen for 5 h. The mixture was cooled to 0°C and basified with concentrated ammonia. A precipitate separated which was collected by centrifugation and then redissolved in minimum amount of dilute hydrochloric acid. The solution was cooled to 0° C, basified with concentrated ammonia and the solid which formed was collected, washed with cold water and dried to give noroxymorphone (0.14 g, 88%); δ_H (of the hydrochloride salt in D_2O) 1.65 (1H, dd, J_{gem} = 14.5 Hz and $J_{10,9}$ = 4.5 Hz, 10-H$_\alpha$), 1.74 (1H, m, 15-H$_\alpha$), 2.02 (1H, dm, J_{gem} = 14.1 Hz, 15-H$_\beta$), 2.28 (1H, m, J_{gem} = 14.8 Hz, 8-H$_\alpha$), 2.63 (1H, td, J_{gem} = 13.4 Hz and 4.9 Hz, 7-H$_\alpha$), 2.85 (1H, td, J = 13.2 Hz and 4.2 Hz, 7-H$_\beta$), 2.99 (1H, td, J = 14.8 Hz and 5.1 Hz, 8-H$_\beta$), 3.19 - 3.32 (3H, m, 10-H$_\beta$ and 16-H$_2$), 3.87 (1H, m, 9-H), 4.99 (1H, s, 5-H), 6.75 - 6.82 (2H, dd, AB system, J = 8.3 Hz, 1-H and 2-H); *m/z* (E.I.) 287 (100%, M^+). 202 (60); (C.I.) 288 (100, M + 1), 287 (70). This compound was identical in all respects to an authentic sample of noroxymorphone.

Method (b)

A mixture of 3-(TBDMS)-14-acetyloxymorphone, (0.110 g, 0.24 mmol) in 1,2-dichloroethane and 1-chloroethyl chloroformate (0.5 cm^3, 4.6 mmol) was heated under reflux under nitrogen for 2 days. The solvent and excess reagent were removed under reduced pressure and the residue was chromatographed eluting with chloroform solvent to yield *N*-(1-chloroethoxycarbonyl)-3-(TBDMS)-14-acetylnoroxymorphone (0.096 g, 73%). This was heated at reflux with methanol (5 cm^3) containing 3 drops of concentrated hydrochloric acid for 6 h. The solution was evaporated and the residue was heated under reflux with hydrochloric acid (6M, 5 cm^3) for 5 h. The resultant solution was cooled, basified with concentrated ammonia, noroxymorphone separated and was collected and purified as in method (a). Yield 0.047 g, 68%.

Hydromorphone (7,8-dihydromorphone) (16)

Hydrogen gas was bubbled through a solution of 3-TBDMS-morphone (11) (0.130g) in ethanol (30cm^3) containing 10% Pd/C (0.07g) for 1h. The catalyst was filtered off and the solvent removed to afford a glassy solid. This was redissolved in dry THF (2cm^3) and 1M ^{t}butylammonium fluoride in THF (0.5cm^3) was added. After 30 min, the solvent was removed, the residue redissolved in the minimum amount of 2M hydrochloric acid, and the solution then basified with conc. ammonium hydroxide. The precipitate of the title compound which separated was collected, dried, and crystallised from ethanol as colourless prisms. Yield 0.064g (83%),

m.p and mixed m.p. with an authentic sample 266-267° C[17].

ACKNOWLEDGEMENT

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9. Obtained from Aldrich Chemical Company Ltd.

10. At higher temperatures decomposition of the product becomes increasingly rapid.

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