Synthesis of racemic 3-hydroxy-*N*-methyl-6-oxomorphinan (Chemistry of opium alkaloids, Part XIV)*

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(Received February 25th, 1980)

Abstract. The preparation of racemic 3-hydroxy-*N*-methyl-6-oxomorphinan (**5**) by acid-catalysed cyclization of 1-(4-hydroxybenzyl)-1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline (**4**) and its 4'-methyl ether **6** is described. The corresponding *N*-formyl derivatives did not give the desired cyclization.

Introduction

3-Hydroxy-*N*-methyl-6-oxomorphinan (Scheme, **5**) may be of use as an intermediate in syntheses of narcotic analgesics. Elimination of the 6-oxo substituent of (–)-**5** yields levorphanol[1], which is used as a synthetic analgesic. Introduction of an oxygen bridge between C4 and C5 in (–)-**5** should give access to morphine and derivatives. An unsuccessful attempt was made to form the oxygen bridge via introduction of an hydroxyl group at C4, with C2 protected by bromine substitution. In this case an unexpected 2,4-shift of the bromine atom was observed[2].

(–)-3-Hydroxy-*N*-methyl-6-oxomorphinan (**5**) was initially obtained from (–)-dihydrothebainone[2], which in turn had been prepared from natural material. A total synthesis of **5** has been described by *Maeda* et al.[3]; the octahydroisoquinoline obtained from 3-(hydroxymethyl)-4-methylpyridine was cyclised using phosphoric acid. The overall yield of this seventeen-step synthesis was low. We report herein a much shorter synthesis of racemic **4** via a Bischler–Napieralski cyclization of *N*-(3-methoxyphenylethyl)-4-benzyloxy-phenylacetamide to **1**. Racemic **5** was obtained from **4** by cyclization using Maeda's method[3].

Results and Discussions

The syntheses of the 1,2,3,4,5,8-hexahydroisoquinolines **4** and **8** are similar to those described for other 1-benzylhexahydroisoquinolines[4,5]. Compound **4** was also prepared *via* **7** by reductive *N*-methylation using formaldehyde and sodium cyanoborohydride. As the experiment of Maeda shows that the 4-methoxybenzyl compounds give reasonable results thus **4** and **8** were methylated to **6** and **9**, respectively. The cyclization of the *N*-methylisoquinolines **4** and **6**, and of the *N*-formylisoquinolines **8** and **9**, was attempted, using orthophosphoric acid (85% and 100%), polyphosphoric acid and sulfuric acid (80% and 96%) in the temperature range 20–140°C.

The reaction mixtures were analysed for **5** and/or its *O*-methylated derivative using HPLC; **5** was only detected for cyclization of **4** and **6** in orthophosphoric acid (85%) at 140°C. It is noteworthy that formation of the morphinan skeleton is dependent on the substitution pattern. *N*-Acyl-1-(4-hydroxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline can be converted smoothly into levorphanol[6]. The corresponding 6-methoxy compound needs drastic conditions and gives

* For Part XIII: see ref. 2.

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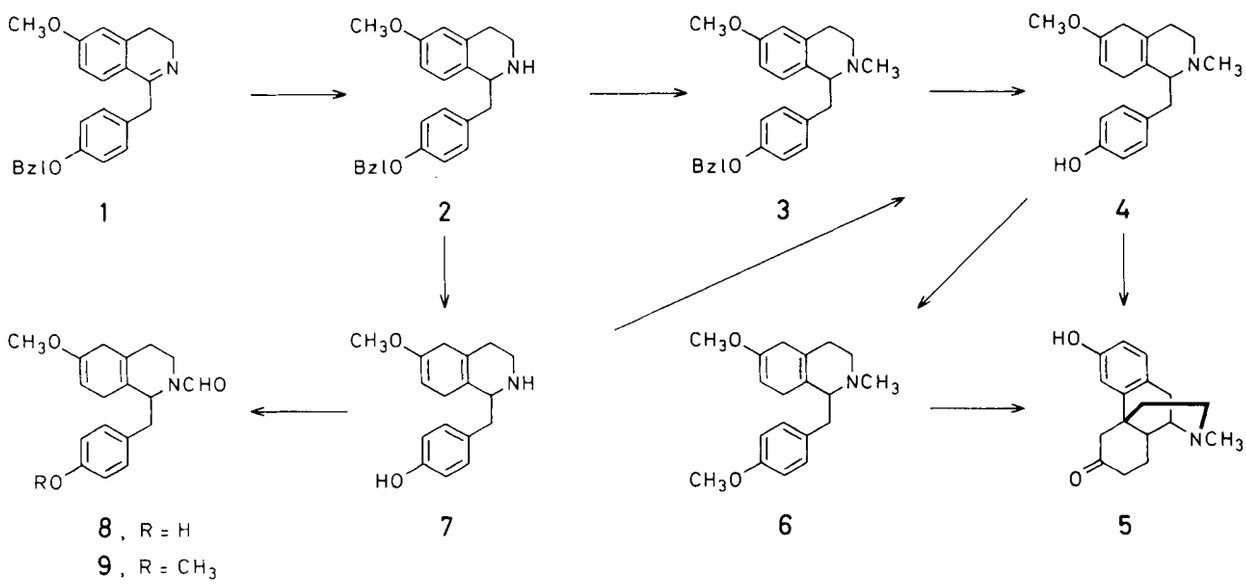

*Scheme Synthesis of 3-hydroxy-*N*-methyl-6-oxomorphinan* (**5**).

5 in a moderate yield. Activation of the benzylic moiety at position 3 by a hydroxyl group leads to smooth formation of the morphinan derivative.

In acidic solution the enol ether in **6** is hydrolyzed to the compound used by *Maeda* et al. for acid-catalysed ring closure. In this case concomitant demethylation of the aromatic methoxy group of **6** occurs. Cyclization of **4** gave fewer by-products than cyclization of **6**. Racemic 3-hydroxy-*N*-methyl-6-oxomorphinan (**5**) was obtained and found to be identical to (–)-**5** prepared from (–)-dihydrothebainone on the basis of TLC, HPLC, MS, and ^1H and ^{13}C NMR spectroscopy.

The IR spectra (KBr disc) of racemic and (–)-**5** were markedly different. Racemic **5** crystallizes as an internal salt and consequently the hydroxyl peak was absent from the IR spectrum, whereas ammonium peaks were present. The high melting point of racemic **5** is also consistent with salt formation.

Experimental part

Mass spectra were measured by Dr. *P. J. W. Schuyl* and Mrs. *A. H. Knol-Kalkman* using a Varian-Mat 311 A mass spectrometer. ^{13}C NMR spectra were obtained using a Varian CFT-20 spectrometer [spectral width 5000 Hz, pulse width 5 μs, 8 K, acquisition time 0.8 s, pulse delay = acquisition time]. The ^{13}C-chemical shifts were measured in ppm from internal tetramethylsilane (TMS). ^1H NMR spectra were measured using a Varian T-60 spectrometer. The compounds were dissolved (10% w/v) in deuteriochloroform and/or hexadeuteriodimethyl sulfoxide. TMS was used as internal standard. Infrared spectra were obtained from KBr discs using a Beckman IR 4210 spectrophotometer. Analytical HPLC was performed on a reverse-phase column (15 cm × 0.4 cm I.D., Nucleosil C_{18}, 7 μm or 30 cm × 0.4 cm I.D., Polygosil 60, 10 μm, C_{18}) with mixtures of methanol and water, containing 5 mmol/l of heptanesulfonate and 2% of acetic acid (ion-pair method)[7] with detection at 280 nm. TLC was performed on deactivated silicagel (Merck F-254) with dichloromethane/methanol/2 *N* ammonia 85 : 15 : 2 as the mobile phase; the compounds were detected by UV (254 nm) and iodine vapour. Combustion analyses were performed by Mr. *H. M. A. Buurmans*. Organic layers of extractions were dried over sodium sulfate.

N-(3-Methoxyphenylethyl)-4-benzyloxyphenylacetamide

A solution of 4-benzyloxyphenylacetic acid[8] (117 g, 0.48 mol) and 2-(3-methoxyphenyl)ethylamine[9] (77 g, 0.51 mol) in *p*-xylene (600 ml) containing molecular sieve (3A) was boiled under reflux for 8 h. After cooling, the amide crystallized and was washed with petroleum ether (b.p. 40–60°C, 300 ml). More amide (3 g) was recovered from the mother liquor, affording a total of 172.5 g (0.46 mol, 95%). A small sample was recrystallized twice from ethanol: m.p. 95–96°C, calcd. for $C_{24}H_{25}NO_3$ (375.47): C 76,77; H 6.71; N 3.73, found C 76.9; H 6.8; N 3.9. ^1H NMR ($CDCl_3$): δ 2.67 (t, *J* 6 Hz, 2H, CH_2); δ 3.42 (q, *J* 6 Hz, 2H, CH_2); δ 3.42 (s, 2H, CH_2CO); δ 5.01 (s, 2H, CH_2O); δ 6.50–7.10 (m, 7H, H(Ar)); δ 7.35 (s, 5H, H(Ar)).

1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**2**) via **1**

A suspension of *N*-(3-methoxyphenylethyl)-4-benzyloxyphenylacetamide (56.6 g, 151 mmol) in benzene (400 ml) was treated with phosphoryl chloride (72 g, 42.5 ml, 260 mmol) and boiled for 1 h. The mixture was evaporated, the residue dissolved in warm ethanol (150 ml) and the solution again evaporated yielding **1**.

To a cool, well-stirred solution of crude **1** in ethanol (850 ml), sodium tetrahydroborate (15.1 g, 380 mmol) was added in four equal portions during 2 h. After 1 h of stirring at 0°C and 3 h at room temperature, 2 N hydrochloric acid (180 ml) was added until pH 2. The mixture was diluted with ethanol (370 ml) and the boric acid filtered off. The filtrate was evaporated at reduced pressure. The residue was dissolved in water (400 ml) and made alkaline (pH 8–9) by addition of ammonia (50 ml). Chloroform extraction (1 × 250 ml and 2 × 100 ml), drying ($MgSO_4$), evaporation to dryness, and crystallization from ethanol afforded **2** (41.1 g, 115 mmol, 76%).

A small sample was recrystallized from ethanol: m.p. 126–127°C, calcd. for $C_{24}H_{25}NO_2$ (359.47): C 80.19; H 7.01; N 3.90, found C 80.2; H 7.1; N 3.8. ^1H NMR ($CDCl_3$): δ 1.70 (s, 1H, NH); δ 3.75 (s, 3H, CH_3O); δ 4.09 (dd, *J* 9 Hz, *J* 3.5 Hz, H(1)); δ 5.03 (s, 2H, $ArCH_2O$); δ 6.63–7.30 (m, 7H, H(Ar)); δ 7.40 (s, 5H, H(Ar)).

1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**3**)

In a nitrogen atmosphere platinum-on-carbon (5%, 1 g) and formaldehyde (37–40%, 16.5 ml) were added to **2** (4.7 g, 13.1 mmol) in methanol (200 ml). The solution was hydrogenated at 45°C for 10 h. The catalyst was then filtered off over hyflo and the filtrate evaporated under reduced pressure. The residue was taken up in some warm methanol and evaporated again. This was repeated once more and the residue was finally crystallized from ethanol (20 ml) yielding **3** (4.5 g, 12.0 mmol, 92%).

A small sample was recrystallized twice from ethanol: m.p. 75–76°C, calcd. for $C_{25}H_{27}NO_2$ (373.50): C 80.40; H 7.29; N 3.75, found C 80.3; H 7.4; N 3.9. ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, CH_3N); δ 3.66 (m, 1H, H(1)); δ 3.72 (s, 3H, CH_3O); δ 5.00 (s, 2H, $ArCH_2O$); δ 6.52–7.30 (m, 7H, H(Ar)); δ 7.38 (s, 5H, H(Ar)).

1,2,3,4,5,8-Hexahydro-1-(4-hydroxybenzyl)-6-methoxy-2-methylisoquinoline (**4**) *from* **3**

A solution of **3** (3.0 g, 8.04 mmol) in *tert*-butanol/tetrahydrofuran (40 ml, 1 : 1) was added dropwise during 15 min under nitrogen and at −60–−65°C to lithium (1.2 g, 170 mmol) in liquid ammonia (150 ml) and *tert*-butanol/tetrahydrofuran (90 ml, 1 : 1) in an apparatus as described in reference 10. After 2 h, TLC analysis showed a complete conversion. The excess of lithium was destroyed with methanol at −50°C. Ammonia and the other solvents were carefully distilled off, the latter at reduced pressure. The residue was dissolved in water and ammonium chloride (22.5 g) was added (pH 8). The solution was extracted with chloroform (3 × 100 ml). The chloroform extract was washed with water (50 ml), dried and evaporated affording **4** (2.2 g, 7.7 mmol, 96%, purity > 98% (HPLC)).

A small sample was crystallized twice from ethanol: m.p. 156–157°C, calcd. for $C_{18}H_{23}NO_2$ (285.39): C 75.75; H 8.12; N 4.91, found C 76.0; H 8.2; N 4.8. ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3N); δ 3.50 (s, 3H, CH_3O); δ 4.55 (b, 1H, H(7)); δ 6.06 (s, 1H, OH); δ 6.48 (d, $J_{2',3'}$ 8 Hz, 2H, H(3') and H(5')); δ 6.95 (d, $J_{2',3'}$ 8 Hz, 2H, H(2' and 6')).

1,2,3,4,5,8-Hexahydro-1-(4-hydroxybenzyl)-6-methoxy-2-methylisoquinoline (**4**) *from* **7**

Formaldehyde (37–40%, 1.7 ml) and sodium cyanoborohydride (0.44 g, 7.0 mmol) were added at 20°C to a suspension of **7** (1.20 g, 4.4 mmol) in acetonitrile (150 ml). After 30 min the *N*-methylation was complete (TLC). The solvent was evaporated *in vacuo*. The residue was dissolved in water and made alkaline with sodium carbonate (pH 9). Extraction with dichloromethane afforded **4** (1.18 g, 4.1 mmol, 94%, purity > 99% (HPLC)).

3-Hydroxy-N-methyl-6-oxomorphinan (**5**)

A solution of **4** (1.00 g, 3.5 mmol) in orthophosphoric acid (85%, 50 ml) was heated for 24 h at 135–140°C. The cooled mixture was diluted with water (75 ml) and heated for 2 h at 100°C. The cooled, dark-brown solution was added to a mixture of water (100 ml), chloroform (100 ml) and 2-propanol (30 ml). The mixture was made alkaline (pH 9) with concentrated ammonia. The organic layer was separated and the aqueous layer was extracted four times with chloroform/2-propanol (4 : 1). Evaporation of the combined organic layers yielded a product (0.96 g) which was purified by preparative liquid chromatography on a column (30 × 0.4 cm I.D.) packed with deactivated silicagel (Woelm). Dichloromethane/methanol/4 *N* ammonia (90 : 12 : 1) was used as the eluent. The fraction containing

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5 was collected, evaporated (136 mg, 0.5 mmol, 14%) and crystallized from methanol: m.p. 240–241°C. ^{1}H NMR, ^{13}C NMR, HPLC, and TLC data of (±)-**5** were identical with those of (−)-**5** prepared from natural starting material[2]. The IR spectrum of racemic **5** differs from that of (−)-**5**; (±)-**5** crystallizes as an internal salt; no O–H stretching at about 3600 cm^{-1} is observed, but absorption at 2680 and 2585 cm^{-1} indicates the presence of NH^+. ^{13}C NMR ($CDCl_3$ + 5% CD_3OD): δ 23.3 (10); δ 26.8 (8); δ 40.9, and δ 41.3 (7, 13, and 15); δ 42.5 (NCH_3); δ 43.2 (14); δ 46.2 (16); δ 51.3 (5); δ 57.4 (9); δ 112.6, and δ 114.6 (2, and 4); δ 126.7 (11); δ 129.1 (1); δ 138.3 (12); δ 155.9 (3); δ 211.0 (6).

1,2,3,4,5,8-Hexahydro-6-methoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (**6**)

Phenyltrimethylammonium chloride (855 mg, 5.0 mmol) and sodium methoxide (540 mg, 10.0 mmol) were added to a solution of **4** (710 mg, 2.5 mmol) in dioxane (8 ml). After heating at 70°C for 2 h, sodium hydride (100 mg, 4.2 mmol) was added. According to TLC the methylation was complete after 2 h. The solvent was evaporated *in vacuo*. The residue was taken up in water and evaporated *in vacuo* (5 ×) in order to remove dimethylaniline. Extraction with dichloromethane afforded **6** (m.p. 79–81°C, 744 mg, 2.5 mmol, 99%). ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3N); δ 3.54 (s, 3H, $CH_3O(6)$); δ 3.75 (s, 3H, $CH_3O(4')$); δ 4.60 (b, 1H, H(7)); δ 6.76 (d, $J_{2',3'}$ 9 Hz, 2H, H(3′ and 5′)); δ 7.15 (d, $J_{2',3'}$ 9 Hz, 2H, H(2′ and 6′)), IR (KBr): 1665 and 1692 cm^{-1} (C=C).

1,2,3,4,5,8-Hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (**7**)

In the same way as described for compound **4**, **2** (3.0 g, 8.3 mmol) was converted into **7** (2.2 g, 8.1 mmol, 97.7%). The latter compound crystallized from the final aqueous reaction mixture at 0°C. A small sample was recrystallized twice from ethanol: m.p. 194–195°C, calcd. for $C_{17}H_{21}NO_2$ (271.36): C 75.25; H 7.80; N 5.16, found C 75.2; H 7.8; N 5.4. ^{1}H NMR $CDCl_3$/DMSO-d_6): δ 3.53 (s, 3H, CH_3O); δ 4.67 (b, 1H, H(7)); δ 6.71 (d, $J_{2',3'}$ 8 Hz, 2H, H(3′ and 5′); δ 7.02 (d, $J_{2',3'}$ 8 Hz, 2H, H(2′ and 6′)).

2-Formyl-1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (**8**)

A mixture of ethyl formate (30 ml, 440 mmol) and **7** (1.0 g, 3.7 mmol) in warm dioxane (40 ml) was boiled under reflux for 10 h. The product (0.8 g) crystallized after 2 days at 4°C. More of the product was recovered from the mother liquor, affording a total of 1.1 g (3.68 mmol, 99.7%, purity > 99% (HPLC)). A small sample was recrystallized from ethanol: m.p. 190–191°C, calcd. for $C_{18}H_{21}NO_3$ (299.37): C 72.22; H 7.07; N 4.68, found C 72.3; H 7.2; N 4.5. ^{1}H NMR (DMSO-d_6): δ 3.50 (s, 3H, CH_3O); δ 4.70 (b, 1H, H(7)); δ 6.75 (m, 4H, H(Ar)); δ 7.34 and δ 7.87 (2 × s, 1H, CHO, syn/anti).

2-Formyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline (**9**)*

Methyl iodide (0.09 ml, 1.4 mmol) and sodium hydride (60% in oil, 80 mg, 2.0 mmol) were added to **8** (600 mg, 2.0 mmol), dissolved in a mixture of tetrahydrofuran (20 ml) and *N,N*-dimethylformamide (4 ml). After 6 h of stirring another portion of methyl iodide (0.06 ml, 0.8 mmol) and sodium hydride (40 mg, 1.0 mmol) was added. The conversion was complete after 16 h (TLC). The solvents were evaporated *in vacuo* and the residue was taken up in water. Extraction with dichloromethane afforded **9** (m.p. 112–115°C, 445 mg, 1.4 mmol, 71%). ^{1}H NMR ($CDCl_3$): δ 3.56 (s, 3H, $CH_3O(6)$); δ 3.76 (s, 3H, $CH_3O(4')$); δ 4.21 (m, 1H, H(1)); δ 4.59 (m, 1H, H(7)); δ 6.90 (m, 4H, H(Ar)); δ 7.40 and δ 7.93)two signals due to syn-anti isomers, s, 1H, NCHO). High-resolution MS: 313.170 ± 6, calculated for $C_{19}H_{23}NO_3$: 313.167, IR (KBr): 1662 cm^{-1} (NCHO), 1700 cm^{-1} (C=C).

* The *N*-formyl *syn-anti* isomers of **8** and **9** could be separated by high-performance liquid chromatography (HPLC), using a reverse-phase octadecyl-silica column, see reference 7, p. 384. Semi-preparative HPLC yielded the pure rotamers. With Dr. H. van Koningsveld, we are presently engaged in assigning the *syn-anti* configuration to these rotamers by single-crystal X-ray crystallography.

The use of the 2,4-dinitrophenyl group in sugar chemistry re-examined*

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(Received April 2nd, 1980)

Abstract. The use of the tertiary base 1,4-diazabicyclo[2,2,2]octane, together with 1-fluoro-2,4-dinitrobenzene in the solvent DMF, proved to be an efficient method for the introduction of the 2,4-dinitrophenyl (DNP) group at different positions, including the anomeric centre of glucose and galactose. The introduction of the DNP ethers at the anomeric centre leads exclusively to the formation of β-DNP ethers. The latter derivatives can be easily converted with potassium carbonate in DMF into the α-DNP ethers. The X-ray analysis of 2,4-dinitrophenyl-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside is discussed. The DNP group can also be used as a protective group in the synthesis of a disaccharide (*i.e.* **8**) and as a UV probe to monitor (254 nm) and analyse (HPLC) sugar intermediates.

Introduction

As part of our programme[1] to broaden the domain of protective groups which may be suitable for the synthesis of oligosaccharides, we re-examined the use of the 2,4-dinitrophenyl group in sugar chemistry.

It is well known that the 2,4-dinitrophenyl (DNP) group plays an important role in the sequence analysis of peptides[2]. In sugar chemistry, the DNP group has been applied successfully to study solvolysis[3,4] and enzymatic reactions. For instance, 2,4-dinitrophenyl-β-D-galactopyranoside has been used extensively as a substrate for the enzyme β-galac-

* Dedicated to Prof. *J. F. Arens* upon the occasion of his retirement from the Chair of Organic Chemistry at the State University of Utrecht.

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