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A NEW SYNTHETIC APPROACH TO BENZOMORPHANS

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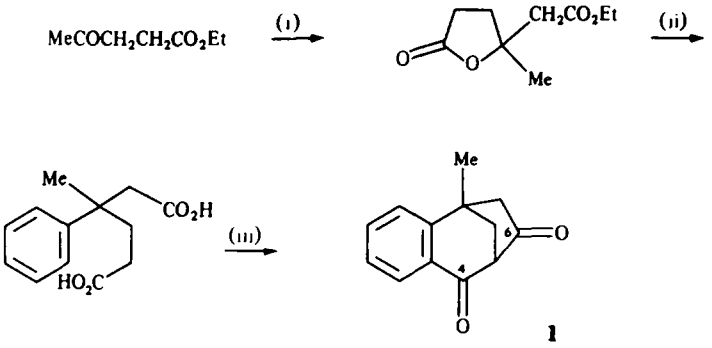
Abstract—A new approach to the synthesis of benzomorphan derivatives is exemplified by the obtention of 3,6-dimethyl-benzomorphan from the readily available 1-methyl-2,3-benzobicyclo-[3,2,1]octane-4,6-dione.

The valuable analgesic activities displayed by a variety of benzomorphan derivatives have ensured a continuing interest in their synthesis.[1,2] This paper describes a new approach to the synthesis of 3,6-dimethyl-benzomorphan (**12**) which should be capable of extension to the preparation of a variety of other substituted benzomorphans and morphinans.

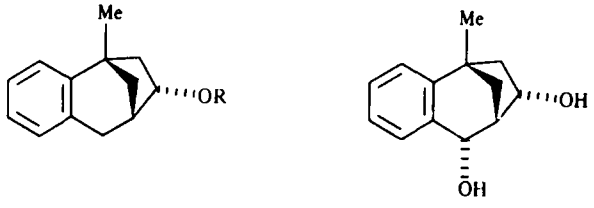
The starting point for the present synthesis was the benzobicyclooctanedione (**1**).[3] The previously described preparation of **1**, commencing from ethyl levulinate and ethyl bromoacetate is outlined in Scheme 1 and in our hands proceeded in 28% overall yield. The subsequent conversion of **1** into the benzomorphan ring system depended upon the establishment of a convenient method for selectively removing the 4-keto group.

Reduction of the diketone (**1**) with LAH–$AlCl_3$ gave a mixture of the alcohol (**2a**) and the diol (**3**). As in the case of similar reductions reported in this paper the stereochemistries assigned to **2a** and **3** are based upon the presumption that formal addition of hydride to carbonyl groups occurs from the less sterically hindered side. Since standard oxidative methods failed to provide a satisfactory conversion of alcohol (**2a**) into the ketone (**4**) it was clearly necessary to identify a means of converting **1** to **4** which avoided



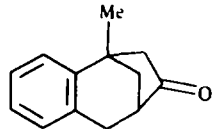
(i) $BrCH_2CO_2Et/Zn$; (ii) $C_6H_6/AlCl_3$; (iii) PPA

Scheme 1.



2a R = H
2b R = Ac

3



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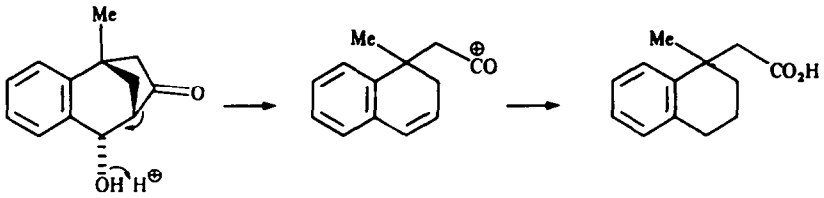
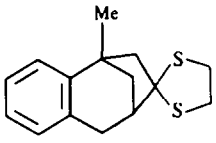


5 6

7 8

Scheme 2.



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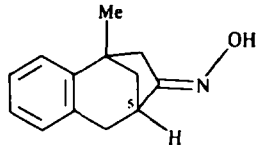
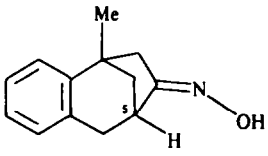
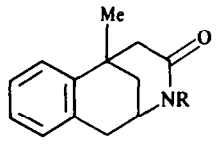


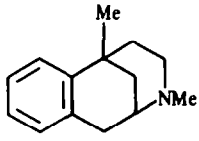
10a



10b



11a R = H
11b R = Me



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consequential reduction of the 6-keto group. Following a procedure successfully employed[4] for the selective removal of the 4-keto group of 2,3-benzobicyclo[3,3,1]nonane-4,6-dione the diketone (**1**) was hydrogenated in ethanol–acetic acid with a palladium on charcoal catalyst to give the 4-hydroxyketone (**5**), whose structure was immediately apparent from the replacement of the 1685 cm^{-1} carbonyl band of **1** by an OH band at 3455 cm^{-1}. Subsequent hydrogenolysis of **5** in acetic acid containing perchloric acid with a PtO_2 catalyst yielded a modest amount (24%) of the acetate (**2b**) together with the carboxylic acid (**6**) (50%). An attractive genesis for the acid (**6**) is indicated in Scheme 2. The structure of the acetate (**2b**) was established by its hydrolysis to the alcohol (**2a**). Accompanying reduction of the CO group also occurred when the hydroxyketone (**5**) was subjected to ionic hydrogenation with triethylsilane in a mixture of trifluoroacetic acid and dichloromethane, however, some of the desired ketone (**4**) was isolated in addition to a mixture of the trifluoroacetates of the epimeric 6-alcohols. The diketone (**1**) was not reduced under these conditions, but reduction did occur in trifluoroacetic acid alone, which gave solely the aforementioned epimeric fluoroacetates.

As none of these reductive methods were sufficiently selective we were reluctantly obliged to resort to protecting the more reactive 6-keto group. Reaction of

diketone (1) with 1,2-ethanedithiol resulted in the previously described[3] ethylenethioketal (7). This was readily reduced with diborane to the alcohol (8) which was then hydrogenolysed with triethylsilane in trifluoroacetic acid to 9. Deprotection of 9 with methyl iodide in aqueous acetonitrile gave the desired ketone (4) in an overall yield of 48% from 1.

The reaction of the ketone (4) with hydroxylamine gave a chromatographically separable mixture of two oximes. Comparison of their ^{1}H-NMR spectra showed that H-5 in the minor isomer was at appreciably lower field than in the major one, hence it was deduced that the minor isomer had the *Z*-configuration (**10b**) and that the major isomer had the desired *E* geometry (**10**). Beckmann rearrangement of the oxime (**10a**) in polyphosphoric acid gave the amide (**11a**). This amide could also be obtained, albeit in much lower yield, by a Schmidt reaction of the ketone (**4**) with hydrazoic acid in the presence of boron trifluoride etherate. Methylation of the amide (**11a**) with methyl iodide and sodium hydride gave the N-Me derivative (**11b**) which was subsequently reduced with lithium aluminium hydride. The sample of 3,6-dimethylbenzomorphan (**12**) thus obtained proved identical in all respects to material prepared[5] by the Grewe synthetic route.

EXPERIMENTAL

IR spectra were recorded for liquid films or Nujol mulls on a Unicam SP200 or a Perkin–Elmer 398 infrared spectrophotometer. NMR spectra were measured for $CDCl_3$ solns with internal TMS on a Perkin–Elmer R90 spectrometer. Mass spectra were obtained by the ULIRS Mass Spectrometry Service at QEC (MS25).

Reaction of **1** *with* LAH–$AlCl_3$. LAH (0.55 g) was added portionwise to a stirred suspension of $AlCl_3$ (4.5 g) in dry ether (30 ml) at 0°. Then the diketone **1** (0.95 g) was added in portions and the mixture subsequently heated under reflux for 2 hr. After cooling, the mixture was poured onto ice and HCl. The products were extracted with ether and the extracts washed with sat. brine before drying (Na_2SO_4). The residue obtained by evaporation of the ethereal extracts was chromatographed on silica gel with toluene–EtOAc (4:1) as eluent. The less polar product was the oily **2a** (34%): IR 3340 cm^{-1}; NMR δ 1.28 (3H, s, CH_3), 1.42–2.30 (6H, m, 3 × CH_2), 2.55 (1H, bs, OH), 2.61–2.87 (1H, m, H-5), 3.45–3.70 (1H, m, H-6), 6.97–7.42 (4H, m, ArH); MS *m/e* 188 (5), 170 (7), 145 (100), 129 (20), 128 (15), 117 (15), 115 (15). The more polar product was the oily **3** (41%): IR 3330 cm^{-1}; NMR δ 1.38 (3H, s, CH_3), 1.75–2.33 (4H, m, 2 × CH_2), 2.68–2.92 (1H, m, H-5), 3.86 (2H, bs, 2 × *OH*), 4.50–4.76 (1H, m, 6-H), 5.00 (1H, d, J = 4 Hz, H-4), 7.10–7.38 (3H, m, ArH), 7.62–7.86 (1H, m, 4'-H); MS *m/e* 204 (5), 186 (12), 158 (18), 142 (100), 128 (35), 116 (22).

Catalytic hydrogenation of **1**. A soln of **1** (2.3 g) in EtOH (40 ml) and HOAc (9 ml) containing 10% Pd/C catalyst (0.2 g) was shaken with H_2 at 60 psi for 24 hr. The filtered soln was evaporated *in vacuo* and the residue chromatographed over silica gel with toluene–EtOAc (7:3) as eluent to give **5** (72%), m.p. 129–131°. (Found: C, 76.7; H, 6.9. Calc for $C_{13}H_{14}O_2$: C, 77.2; H, 7.0%); IR 3455, 1720 cm^{-1}; NMR δ 1.62 (3H, s, CH_3), 2.21 (2H, d, J = 4 Hz, H-8), 2.45 (2H, s, H-7), 2.63 (1H, bs, OH), 2.88–3.00 (1H, m, H-5), 5.14 (1H, d, J = 6 Hz, H-4), 7.20–7.38 (3H, m, ArH), 7.50–7.68 (1H, m, H-4'); MS *m/e* 202 (5), 143 (23), 142 (100), 141 (20), 128 (13), 115 (13).

Catalytic hydrogenation of **5**. A soln of **5** (0.9 g) in AcOH (30 ml) containing perchloric acid (1.2 ml) and PtO_2 (25 mg) was shaken with H_2 at 55 psi for 24 hr. The filtered soln was partially evaporated *in vacuo*, then neutralised with NH_4OH aq and extracted with $CHCl_3$. These extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography on silica gel with toluene–EtOAc (7:3) as eluent afforded the oily **2b** (24%). IR 1740 cm^{-1}; NMR δ 1.29 (3H, s, CH_3), 1.38–2.35 (6H, m, H-4, H-7 and H-8), 1.95 (3H, s, CH_3CO_2), 2.65–2.87 (1H, m, H-5), 3.80–4.15 (1H, m, H-6), 6.80–7.37 (4H, m, ArH); MS *m/e* 230 (2), 172 (8), 170 (18), 145 (100), 143 (23), 129 (30), 128 (22). Hydrolysis of **2b** with NaOH in aq EtOH gave **2a** (83%).

Further elution with toluene–EtOAc (4:1) provided **6** (50%), m.p. 67–69°. (Found: C, 76.6; H, 8.0. Calc for $C_{13}H_{16}O_2$: C, 76.4; H, 7.9%); IR 1710 cm^{-1}; NMR δ 1.42 (3H, s, CH_3), 1.60–2.90 (8H, m, 4 × CH_2), 7.05–7.35 (4H, m, ArH), 11.0 (1H, s, CO_2H); MS *m/e* 204 (12), 186 (12), 145 (100), 144 (35), 143 (21), 131 (30), 130 (29), 129 (65), 128 (42), 117 (18), 115 (32).

Ionic hydrogenation of **5**. A soln of **5** (1.2 g) and triethylsilane (1.4 ml) in trifluoroacetic acid (3 ml) and CH_2Cl_2 (5 ml) were stirred for 6 hr. Sat Na_2CO_3 aq was added and the aqueous mixture extracted with $CHCl_3$. The extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel with hexane–EtOAc (5:1) as eluent to give the epimeric trifluoro-acetates of **2a** (41%), the ketone **4** (27%) and unchanged **5** (32%). The ketone **4** crystallised from hexane–EtOAc, m.p. 110–112°. (Found: C, 83.3; H, 7.6. Calc for $C_{13}H_{14}O$: C, 83.8; H, 7.6%); IR 1745 cm^{-1}; NMR δ 1.62 (3H, s, CH_3), 2.02 (1H, d, J = 17 Hz, H-8), 2.25 (1H, d, J = 17 Hz, H-8), 2.30 (2H, s, H-7), 2.75–2.90 (1H, m, H-5), 2.94 (1H, dd, J = 16 and 2 Hz, H-4), 3.23 (1H, dd, J = 16 and 6 Hz, H-4), 7.00–7.40 (4H, m, ArH); MS *m/e* 186 (64), 171 (24), 153 (25), 144 (25), 143 (77), 142 (25), 141 (25), 129 (100), 128 (77), 105 (37).

The oily ester fraction appeared to be a mixture of the trifluoroacetate of **2a** and its 6-epimer. IR 1790 cm^{-1}; NMR δ 1.48 (3H, s, CH_3), 1.68–2.37 (4H, m, H-7 and H-8), 2.50–2.74 (1H, m, H-5), 2.75–3.30 (2H, m, H-4), 5.10–5.15 and 5.38–5.62 (1H, m, H-6), 7.01–7.29 (4H, m, ArH); MS *m/e* 284 (14), 170 (26), 155 (16), 142.5 (50), 128 (50), 86 (88), 85 (69), 84 (100), 83 (90).

Diborane reduction of **7**. A soln of BF_3-etherate (0.55 ml) in THF (10 ml) was added dropwise under N_2 to a stirred soln of **7** (2.3 g) in THF (30 ml) containing $NaBH_4$ (80 mg) at 0–5°. When addition was complete the mixture was stirred for 3 hr at room temp, prior to cautious dilution with water, and ether extraction. The extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated to give **8** (86%) as a gum. IR 3375 cm^{-1}; NMR δ 1.48 (3H, s, CH_3), 2.13 (2H, d, J = 4.5 Hz, H-8), 2.45 (2H, s, H-7), 2.81 (1H, bs, OH), 3.36 (4H, bs, —$S(CH_2)_2S$—), 3.42–3.55 (1H, m, H-5), 5.02 (1H, d, J = 3 Hz, H-4), 7.17–7.52 (3H, m, ArH), 7.72 (1H, d, J = 4 Hz, H-4'); MS *m/e* 278.

Ionic hydrogenation of **8**. A soln of **8** (0.17 g), triethylsilane (0.35 ml) and trifluoroacetic acid (0.55 ml) in CH_2Cl_2 (5 ml) was heated under reflux for 48 hr. The soln was cooled, sat Na_2CO_3 aq added and the organic product isolated by $CHCl_3$ extraction. The ethylenethioketal **9** (80%) was obtained as an oil. NMR δ 1.47 (3H, s, CH_3), 1.88–2.15 (2H, m, H-8), 2.46 (2H, s, H-7), 2.55–2.70 (2H, m, H-4), 2.78–3.00 (1H, m, H-5), 3.07–3.46 (4H, m, —$S(CH_2)_2S$—), 7.00–7.28 (4H, m, ArH); MS *m/e* 262 (23), 234 (28), 153 (20), 144 (48), 143 (100), 142 (34), 141 (37), 129 (57), 128 (90).

Deprotection of **9**. The ethylenethioketal **9** (65 mg) and MeI (1.5 ml) in a mixture of 20% aq MeCN (10 ml) and THF (3 ml) were heated at 55° for 5 hr. A soln of NH_4Cl was added and the organic solvents were evaporated *in vacuo*. The aqueous residue was extracted with EtOAc. These extracts were dried (Na_2SO_4) and evaporated to give **4** (87%).

Preparation of oximes **10a** *and* **10b**. A soln of **4** (0.32 g), hydroxylamine hydrochloride (0.4 g) and NaOAc (0.25 g) in 70% aq EtOH (10 ml) was heated under reflux for 2 hr. The soln was partially evaporated *in vacuo* and the remainder extracted with $CHCl_3$. The extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated *in vacuo* to give a mixture of **10a** and **10b**, which could be separated by chromatography on silica gel using toluene–EtOAc (4:1) as eluent. The *E*-oxime **10a** (49%) was a white crystalline solid, m.p. 138–141°. (Found: C, 77.1; H, 7.6. Calc for $C_{13}H_{15}NO$: C, 77.6; H, 7.5%); IR 3250

cm^{-1}; NMR δ 1.54 (3H, s, CH_3), 1.85 (1H, d, J = 14 Hz, H-8), 1.95 (1H, d, J = 14 Hz, H-8), 2.32 (1H, d, J = 18 Hz, H-7), 2.74 (1H, d, J = 18 Hz, H-7), 2.75–3.35 (3H, m, H-4 and H-5), 6.95–7.40 (4H, m, ArH), 8.94 (1H, bs, OH); MS *m/e* 201 (71), 184 (29), 183 (93), 181 (64), 170 (79), 169 (100), 168 (43), 167 (25), 166 (57), 155 (100), 154 (50), 153 (57), 143 (57), 142 (21), 141 (21), 129 (42), 115 (18).

The *Z*-oxime **10b** (19%) was obtained as a gummy solid. NMR δ 1.55 (3H, s, CH_3), 1.79 (1H, d, J = 14 Hz, H-8), 1.92 (1H, d, J = 14 Hz, H-8), 2.39 (1H, d, J = 18 Hz, H-7), 2.66 (1H, d, J = 18 Hz, H-7), 3.08–3.20 (2H, m, H-4), 3.50–3.65 (1H, m, H-5), 6.95–7.35 (4H, m, ArH), 9.00 (1H, s, OH).

Beckmann rearrangement of **10a**. The oxime **10a** (0.28 g) in polyphosphoric acid (26 g) was stirred for 1 hr at 120°. After cooling, the soln was poured onto ice, and the organic products extracted with $CHCl_3$. The residue obtained on evaporation was chromatographed on silica gel with toluene–EtOH (1:1) as eluent to give **11a** (61%) as a gum. IR 3210, 1670 cm^{-1}; NMR δ 1.41 (3H, s, CH_3), 1.84–2.00 (2H, m, H-11), 2.33 (2H, s, H-5), 2.75–3.35 (2H, m, H-1), 3.80–3.95 (1H, m, H-2), 6.90–7.40 (4H, m, ArH), 7.48 (1H, s, NH); MS *m/e* 201 (97), 186 (78), 144 (67), 143 (79), 142 (48), 141 (27), 129 (100), 128 (71), 115 (46).

N-*Methylation of* **11a**. The amide **11a** (0.32 g) and NaH (0.123 g) in toluene (5 ml) and DMF (8 ml) were stirred for 1 hr. Then MeI (0.15 ml) was added and the mixture left to stir overnight. After cautious addition of water the organic products were extracted with $CHCl_3$. The extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel with toluene–EtOAc (1 : 1) to give the **11b** (44%) as an oil. IR 1645 cm^{-1}; NMR δ 1.40 (3H, s, CH_3), 1.80–2.10 (2H, m, H-11), 2.35 (1H, d, J = 9 Hz, H-5), 2.72 (1H, d, J = 9 Hz, H-5), 2.93 (3H, s, NCH_3), 3.05 (1H, dd, J = 12 and 3.5 Hz, H-1), 3.35 (1H, d, J = 12 Hz, H-1), 3.73–3.88 (1H, m, H-2), 6.95–7.50 (4H, m, ArH); MS *m/e* 215 (85), 200 (100), 144 (35), 143 (35), 142 (26), 141 (20), 129 (67), 128 (50), 124 (36), 117 (36).

LAH *reduction of* **11b**. LAH (33 mg) was added portionwise over 10 min to a stirred soln of **11b** (142 mg) in ether (7 ml), and stirring then continued overnight. A little water (*ca* 0.5 ml) was added carefully and the precipitated alumina filtered off. The filtrate after addition of more ether, was extracted with 2 M HCl. The acid extracts were basified with ammonia and the liberated amine extracted into $CHCl_3$. These extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated to give **12** (54%). NMR δ 1.39 (3H, s, CH_3), 1.70–1.95 (4H, m), 2.03 (1H, td, J = 12, 3.4 Hz), 2.40 (3H, s, NCH_3), 2.38–2.53 (1H, m), 2.72 (1H, dd, J = 18 and 5.6 Hz), 3.05–3.20 (2H, m), 7.00–7.20 (4H, m, ArH); MS *m/e* 201 (69), 186 (100), 143 (31), 142 (45), 141 (45), 129 (38), 128 (55), 115 (48), 110 (55).

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