Acetamides of 1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocine (Benzomorphan), 5,6,7,8,9,10-Hexahydro-6,9-methanobenzocyclo-octene, and 6,7,8,9,10,11-Hexahydro-7,10-methanocyclo-octa[*b*][1]benzothiophene as Potential Selective Opioid Analgesics

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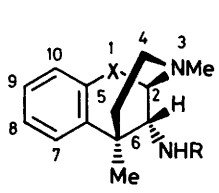
The acetate of 5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclo-octen-11-one oxime (**13**) was reduced with zinc dust in a mixture of acetic acid and acetic anhydride, to give exclusively *syn*-11-acetamido-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclo-octene (**3**). By contrast, the acetate (**17**) of 6,7,8,9,10,11-hexahydro-7,10-methanocyclo-octa[*b*][1]benzothiophen-12-one oxime (**16**) gave a mixture of the *syn*- (**6**) (28% yield) and *anti*-12-acetamido-derivatives (**10**) (25%). The three amides (**3**), (**6**), and (**10**) were hydrolysed with acid to the corresponding amines (**4**), (**7**), and (**11**) and reduced with lithium aluminium hydride to the corresponding *N*-ethyl derivatives (**5**), (**8**), and (**12**) respectively. Reduction with sodium borohydride in methanol of 6,7,8,9,10,11-hexahydro-7,10-methanocyclo-octa[*b*][1]benzothiophen-12-one (**15**) gave exclusively the *syn*-alcohol (**9**). 11α-Acetamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**1**) was prepared by reduction in acetic acid–acetic anhydride of 3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-11-one (**19**) oxime, prepared by adaptation of a procedure due to Belleau.

Separation of the desirable pain-killing properties of the opioid analgesics from their less desirable side-effects, such as addiction, respiratory depression, and tolerance, has become an achievable goal following recognition that some compounds can exhibit specificity for the different opioid receptors.[1] Reports (*e.g.* refs. 2 and 3) that opioid activity has been observed with some amides of diverse chemical structure prompted us to synthesize an amide derivative (**1**) of benzomorphan and to convert the oximes whose syntheses are described in our preceding paper[4] into the corresponding amides, (**3**), (**6**), and (**10**).

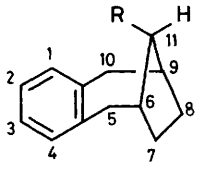
5,6,7,8,9,10-Hexahydro-6,9-methanobenzocyclo-octen-11-one oxime (**13**) was heated in a mixture of acetic acid and acetic anhydride (3:2) to convert it into the oxime acetate, which was isolated (78% yield) and treated subsequently with zinc dust in a mixture of acetic acid and acetic anhydride (3:2).[5] This gave the *syn*-amide (**3**) (65.5% yield) exclusively.† Previously, Bélanger *et al.*[6] reduced the oximes (**13**) and (**14**) to the corresponding *syn*-amines with hydrogen in acetic acid in the presence of Adam's catalyst. Hydrogenation of the oxime (**13**), however, with 10% palladium–charcoal in acetic acid, either at atmospheric pressure or at 60 or 100 psi, failed in our hands to give the amine (**4**). Other methods for reducing oximes to amines, *e.g.* use of sodium in ethanol[7] or methanol, failed also.

By contrast, when the oxime (**16**) of 6,7,8,9,10,11-hexahydro-7,10-methanocyclo-octa[*b*][1]benzothiophen-12-one (**15**) was converted similarly into the oxime acetate (**17**) (completion of reaction indicated by TLC) and this ester was reduced (without isolation in this case) by addition of zinc dust, it gave a mixture of the isomeric *syn*- (**6**) (28% yield) and *anti*-amides (**10**) (25%), separable by chromatography on silica. Attempted purification of the oxime acetate (**17**) by chromatography resulted in its hydrolysis to the oxime (**16**). The two isomers, (**6**) and (**10**), have different m.p.s and different NH stretching frequencies in their IR spectra, at 3 250 (*syn*) and 3 270 cm^{-1} (*anti*), respectively. In

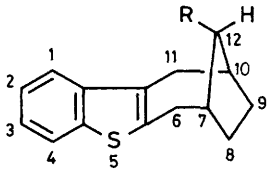
† *Syn* and *anti* refer to the relative orientation of the methano bridge substituent with respect to the aromatic ring.



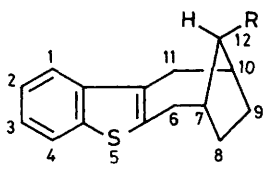
(**1**) R = Ac
(**2**) R = H



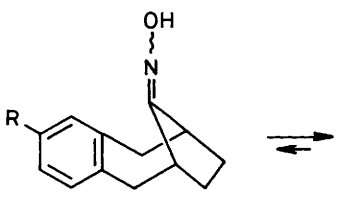
(**3**) R = NHAc
(**4**) R = NH_2
(**5**) R = NHEt



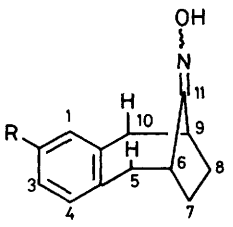
(**6**) R = NHAc
(**7**) R = NH_2
(**8**) R = NHEt
(**9**) R = OH



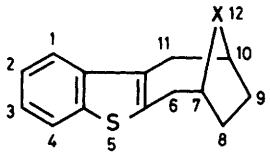
(**10**) R = NHAc
(**11**) R = NH_2
(**12**) R = NHEt



(**13a**) R = H
(**14a**) R = OMe



(**13b**) R = H
(**14b**) R = OMe



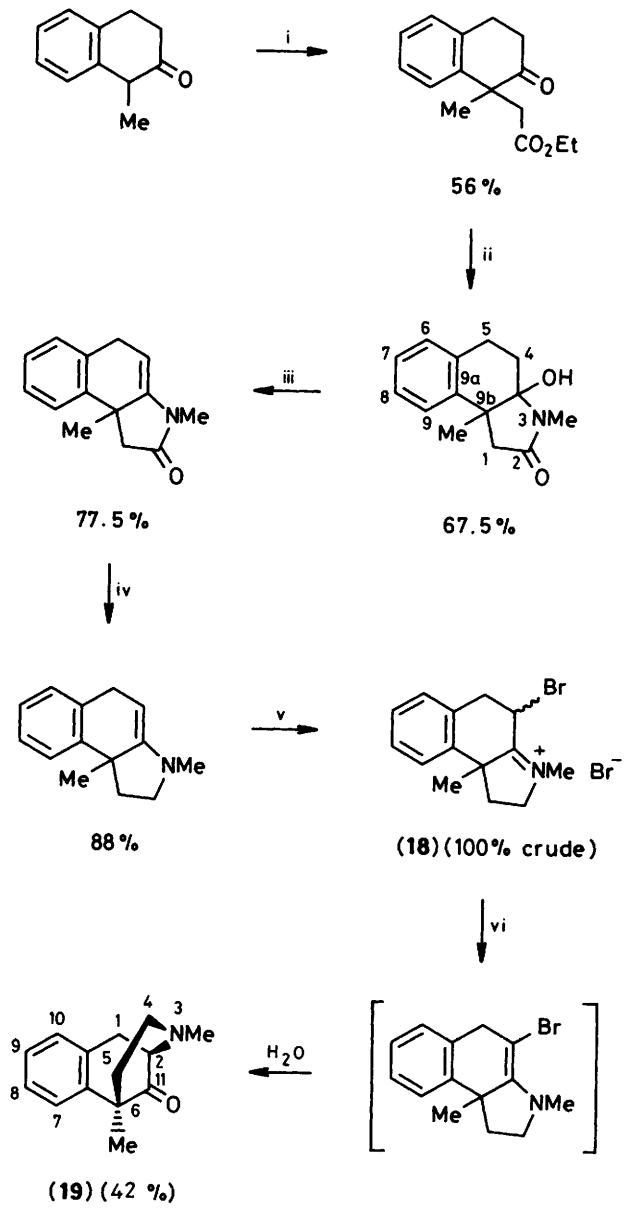
(**15**) X = C=O
(**16**) X = C=N〰OH
(**17**) X = C=N〰OAc

the ^{1}H NMR spectrum of the *anti*-isomer (**10**) the signal at δ 4.10 for H-12 is a doublet, *J* 8.0 Hz, through coupling with the adjacent NH proton at δ 7.05 whose signal is similarly split into a doublet, *J* 8.0 Hz. The dihedral angle between H-12 and the bridgehead protons, H-7 and H-10, is zero in molecular models. By contrast, the signal at δ 4.52 for H-12 in the ^{1}H NMR spectrum of the *syn*-isomer (**6**) appears more complex owing to coupling with the adjacent NH proton (*J* 8.0 Hz) at δ 6.95 and also with the equatorial bridgehead protons, H-7 and H-10. The mass spectra differ for these two isomers also. In both cases the molecular ion peak can be observed at *m/z* 285. Fragmentation by loss of acetamide (−MeCONH$_2$, *m/z* 59) is difficult for the *syn*-isomer (**6**), with its axially positioned acetamido-group, and the molecular ion peak is also the base peak in this case. However, loss of acetamide occurs readily from the *anti*-isomer (**10**), with its equatorially positioned acetamido-group, resulting in the appearance of a fragment ion peak at *m/z* 226 which fragments further by loss of *m/z* 65, to give the base peak at *m/z* 161. The different stereochemical configurations of the B/C-rings in morphinanones have been established similarly by differences in their fragmentation patterns.[8]

Bélanger *et al.*[6] have established by ^{1}H NMR spectroscopy and X-ray analysis that the parent ketone from which oxime (**13**) is derived exists predominantly in the boat conformation. Exclusive formation of the *syn*-amine (**4**) on reduction of the oxime (**13b**) was accounted for by steric hindrance to approach of the reagent from the side of the aromatic ring by the axially orientated H-5 and H-10 protons. This argument is clearly not applicable to analogous reduction of the oxime acetate (**17**) which yields both amide isomers, (**6**) and (**10**). A possible explanation for the difference in the behaviour of the oximes (**13**) and (**16**) on reduction (*via* their acetates) is that an appreciable amount of the chair conformer of the latter exists in solution in equilibrium with its boat conformer, thus allowing access by the reagent across the face of the aromatic ring to produce the *anti*-isomer (**10**). However, reduction of the parent ketone (**15**) with sodium borohydride in methanol gave exclusively the *syn*-alcohol (**9**) (66% yield), (cf. refs. 9 and 10), which suggests that this explanation may be an oversimplification. The structure of the alcohol (**9**) was established by the presence in its ^{1}H NMR spectrum of a triplet, *J* 8.0 Hz, for H-12 which is coupled to the bridgehead protons, H-7 and H-10.

Reduction of the amides (**3**), (**6**), and (**10**) with lithium aluminium hydride in anhydrous tetrahydrofuran gave the corresponding *N*-ethyl-derivative (**5**) (58% yield), (**8**) (34%), and (**12**) (29%), whilst their hydrolysis with 4M hydrochloric acid gave the corresponding amine (**4**) (72% yield), (**7**) (44%), and (**11**) (31%), respectively. Reduction and hydrolysis of the *anti*-amide (**10**) were noticably slower than corresponding reactions of the *syn*-amide (**6**), presumably owing to steric hindrance. For the *syn*-amine (**7**) the molecular ion peak is the base peak whereas, in the case of its *anti*-isomer (**11**), the equatorially positioned amine group on C-12 is readily lost and the molecular ion is no longer the base peak.

Amide (**1**) was prepared in 18% yield by hydrogenation of 3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-11-one (**19**) oxime in a mixture of acetic acid and acetic anhydride in the presence of Adam's catalyst.[11] This reaction was carried out on ten times (600 mg) the scale reported in the literature[11] which resulted in difficulties during isolation of the product.



Scheme. *Reagents:* i, NaH, DMF, N_2, $BrCH_2CO_2Et$; ii, $MeNH_2$, EtOH; iii, *p*-$MeC_6H_4SO_3H$, PhMe; iv, $LiAlH_4$, Et_2O, N_2; v, Br_2, CH_2Cl_2, −60 °C; vi, Al_2O_3 (Merck G, Type E), Me_2SO, H_2O.

Previously we[12] have described an improved procedure for the synthesis of the benzomorphanone (**19**) but in this work we adapted the procedure recently reported by Belleau and his co-workers[13] for the synthesis of analogues of this ketone. The results are summarised in the Scheme. For rearrangement of the bromoiminium salt (**18**) we used TLC grade alumina in preference to ammonium carbonate,[13] which failed in our hands to effect this conversion.

Experimental

The instruments used and the general experimental conditions used are described in the preceding paper.[4]

The following compounds were prepared by literature procedures: phenacetyl chloride (from commercially available phenylacetic acid) (88%), b.p. 108–110 °C at 16–18 mmHg (lit.,[14] 94% and 122 °C at 70 mmHg); 3,4-dihydronaphthalen-2(1*H*)-one (2-tetralone) (72%), b.p. 106 °C at 1.5 mmHg (lit.,[15] 70%); 1-methyl-3,4-dihydronaphthalen-2(1*H*)-one (70%), b.p. 134–136 °C at 1.5–2.0 mmHg (lit.,[16] 81% and 138–142 °C at 20.0 mmHg); and 2-nitro-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclo-octen-11-one (**20**) (45%), m.p. 144–146 °C (lit.,[6] 58% and 145–146 °C).

11-*Hydroxyimino*-5,6,7,8,9,10-*hexahydro*-6,9-*methanobenzocyclo-octen*-11-*yl Acetate*.—A mixture of the oxime (**13**) (3.02 g, 15.0 mmol), acetic acid (30 ml), and acetic anhydride (20 ml) was heated under reflux for 30 min, then cooled, diluted with dichloromethane (150 ml), washed with water (2 × 100 ml), and dried ($MgSO_4$). Distillation of the solvents gave the *ester* (2.83 g, 78%), m.p. 103–104 °C (from ethyl acetate–light petroleum), ν_{max} 1 660 (C=N) and 1 755 cm^{-1} (C=O); δ($CDCl_3$) 1.10–1.85 (4 H, m, 7- and 8-H_2), 2.15 (3 H, s, COMe), 2.95 (4 H, t, 5- and 10-H_2), 3.05 (1 H, m, 6- or 9-H), and 3.60 (1 H, m, 6- or 9-H) (Found: C, 74.0; H, 7.1; N, 5.8. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.05; N, 5.8%).

11-syn-*Acetamido*-5,6,7,8,9,10-*hexahydro*-6,9-*methanobenzocyclo-octene* (**3**).—Zinc dust (*ca.* 7.0 g) was added portionwise to a stirred mixture of the oxime ester (2.43 g, 10.0 mmol), prepared as described in the preceding experiment, acetic acid (30 ml), and acetic anhydride (20 ml), at such a rate that the exothermicity of the reaction was kept under control and until the yellow colour of the starting material had disappeared. The resulting mixture was stirred for a further 6 h, then cooled and diluted with dichloromethane (100 ml). The mixture was filtered and the filtrate was washed with water (2 × 100 ml) and dried ($MgSO_4$). Distillation of the solvents gave the *acetamido-compound* (**3**) (1.5 g, 65.5%), m.p. 178–179 °C (from ethyl acetate), ν_{max} 1 635 (C=O) and 3 300 cm^{-1} (NH); δ($CDCl_3$) 1.15 (2 H, m, 7- or 8-H_2), 1.68 (2 H, m, 7- or 8-H_2), 2.00 (3 H, s, COMe), 2.60 (4 H, m, 5- and 10-H_2), 2.94–3.10 (2 H, m, 6- and 9-H), 4.25 (1 H, br s, 11-H), 6.20 (1 H, br s, NH), and 7.05 (4 H, s, ArH) (Found: C, 78.6; H, 8.2; N, 5.9%; M^+, 229. $C_{15}H_{19}NO$ requires C, 78.7; H, 8.4; N, 6.1%; M^+, 229).

11-syn-*Amino*-5,6,7,8,9,10-*hexahydro*-6,9-*methanobenzocyclo-octene* (**4**) *Hydrochloride*.—A mixture of the 11-acetamido-compound (**3**) (2.29 g, 10.0 mmol) from the previous experiment and 4M hydrochloric acid (50 ml) was heated under reflux for 5 h, then (after cooling) treated with activated charcoal (5 g) and filtered hot. Distillation of the solvent and cooling gave the product (**4**) (1.6 g, 72%), m.p. 290–293 °C (from methanol) (lit.,[6] 283–285 °C) (Found: C, 64.8; H, 8.4; N, 5.5. Calc. for $C_{13}H_{20}NCl{\cdot}H_2O$: C, 64.6; H, 8.3; N, 5.8%).

11-syn-*Ethylamino*-5,6,7,8,9,10-*hexahydro*-6,9-*methanobenzocyclo-octene* (**5**) *Hydrochloride*.—The acetamide (**3**) (2.29 g, 10.0 mmol) was added to a stirred suspension of lithium aluminium hydride (1.15 g, 30.0 mmol) in anhydrous tetrahydrofuran (100 ml) at ambient temperature and the mixture was stirred for a further 12 h. With cooling in an ice bath ice-cold water (1.1 ml) was added to the mixture followed by 2.5M sodium hydroxide (3.3 ml) and more water (3.3 ml). The precipitate was filtered off and to the filtrate in a separating funnel was added water (200 ml) and dichloromethane (150 ml). After shaking, the organic layer was separated, washed with water (2 × 100 ml), then dried ($MgSO_4$), and the solvents were removed by distillation. The viscous residue was dissolved in ethanolic hydrogen chloride, which gave the *hydrochloride salt* (1.5 g, 58%), m.p. 315–320 °C (from aqueous acetone) (Found: C, 71.2; H, 8.7; N, 5.4%; $M^+ - H^{35}Cl$, 215. $C_{15}H_{22}NCl$ requires C, 71.55; H, 8.8; N, 5.6%; $M - H^{35}Cl$, 215).

12-syn-(**6**) *and* 12-anti-*Acetamido*-6,7,8,9,10,11-*hexahydro*-7,10-*methanocyclo-octa*[b][1]*benzothiophene* (**10**).—A stirred solution of the oxime (**16**) (2.57 g, 10.0 mmol) in a mixture of acetic acid (60 ml) and acetic anhydride (40 ml) under nitrogen was heated for 2 h at 60 °C. Then zinc dust (*ca.* 7.0 g) was added portionwise and the mixture was stirred at 60 °C for 6 h. Dichloromethane (150 ml) was added and the mixture was filtered. The filtrate was washed with water (3 × 50 ml), then dried ($MgSO_4$), and distillation of the solvent gave a residue which was chromatographed on silica. Ethyl acetate–light petroleum (b.p. 40–60 °C) (3:2) eluted: (*i*) the syn-*isomer* (**6**) (0.8 g, 28% based on oxime), m.p. 204–206 °C (from ethyl acetate), ν_{max} 1 630 (C=O) and 3 250 cm^{-1} (NH); δ[$CDCl_3$–$(CD_3)_2SO$] 1.30–2.05 (4 H, m, 8- and 9-H_2), 1.90 (3 H, s, COMe), 2.50–3.22 (6 H, m, 6- and 11-H_2 and 7- and 10-H), 4.52 (1 H, m, 12-H), 6.95 (1 H, d, $J_{12\text{-H–NH}}$ 8.0 Hz, NH), and 7.20–7.80 (4 H, m, ArH) (Found: C, 71.3; H, 6.8; N, 4.7%; M^+, 285. $C_{17}H_{19}NOS$ requires C, 71.6; H, 6.7; N, 4.9%; *M*, 285); and (*ii*) the anti-*isomer* (**10**) (0.7 g, 25%), m.p. 209–210 °C (from ethyl acetate), ν_{max} 1 630 (C=O) and 3 270 cm^{-1} (NH); δ[$CDCl_3$–$(CD_3)_2SO$] 1.25–2.05 (4 H, m, 8- and 9-H_2), 1.90 (3 H, s, COMe), 2.58–3.30 (6 H, m, 6- and 11-H_2 and 7- and 10-H), 4.10 (1 H, d, $J_{12\text{-H–NH}}$ 8.0 Hz, 12-H), 7.05 (1 H, d, $J_{12\text{-H–NH}}$ 8.0 Hz, NH), and 7.20–7.80 (4 H, m, ArH) (Found: C, 71.05; H, 6.9; H, 4.65%; M^+, 285).

12-syn-*Ethylamino*-6,7,8,9,10,11-*hexahydro*-7,10-*methanocyclo-octa*[b][1]*benzothiophene* (**8**) *Hydrochloride*.—The *syn*-acetamido-compound (**6**) (1.43 g, 5.0 mmol) was added to a stirred suspension of lithium aluminium hydride (0.76 g, 20.0 mmol) in anhydrous tetrahydrofuran (100 ml) under nitrogen and the resulting mixture was heated at 100 °C for 2 h, then at ambient temperature for 4 h. With cooling in an ice bath, ice-cold water (0.75 ml) was added to the mixture followed by 10% aqueous sodium hydroxide (2.2 ml) and more water (2.2 ml). The precipitate was filtered off and the filtrate diluted with water (200 ml). Extraction with dichloromethane (3 × 50 ml) gave a residue which was added to ethanolic hydrogen chloride, to give the *hydrochloride salt* (0.52 g, 34%), m.p. 300–305 °C (decomp.) [from aqueous methanol (1:9)] (Found: C, 66.4; H, 7.2; N, 4.3%; $M^+ - H^{35}Cl$, 271. $C_{17}H_{22}ClNS$ requires C, 66.6; H, 6.9; N, 4.6%; $M - H^{35}Cl$, 271).

12-*anti*-Ethylamino-6,7,8,9,10,11-hexahydro-7,10-methanocyclo-octa[*b*][1]benzothiophene (**12**) Hydrochloride (29%) was prepared similarly; m.p. 315–320 °C (decomp.) [from aqueous methanol (1:9)] (Found: $M^+ - HCl$, 271).

12-syn-*Amino*-6,7,8,9,10,11-*hexahydro*-7,10-*methanocyclo-octa*[b][1]*benzothiophene* (**7**) *Hydrochloride*.—A stirred mixture of the *syn*-acetamido-compound (**6**) (1.43 g, 5.0 mmol), ethanol (50 ml), and 4M hydrochloric acid (50 ml) was heated under reflux for 6 h, then (after cooling) activated charcoal (2 g) was added and the solution was filtered hot. Ethanol was distilled off under reduced pressure and cooling of the remaining aqueous solution gave the *amine* (**7**) *hydrochloride* (0.62 g, 44%), m.p. 280–282 °C (from methanol) (Found: C, 64.1; H, 6.2; N, 4.9%; $M^+ - H^{35}Cl$, 243. $C_{15}H_{18}ClNS$ requires C, 64.4; H, 6.5; N, 5.0%; $M - H^{35}Cl$, 243).

12-anti-*Amino*-6,7,8,9,10,11-*hexahydro*-2,5-*methanocyclo-octa*[b][1]*benzothiophene* (**11**) *Hydrochloride* (31%) was prepared similarly; m.p. 281–284 °C (decomp.) [from aqueous methanol (1:9)] (Found: C, 64.1; H, 6.65; N, 4.5%; $M^+ - H^{35}Cl$, 243).

syn-12-*Hydroxy*-6,7,8,9,10,11-*hexahydro*-7,10-*methanocyclo-octa*[b][1]*benzothiophene* (**9**).—A mixture of sodium boro-

hydride (0.57 g, 15.0 mmol) and compound (**15**) (2.42 g, 10.0 mmol) in methanol (100 ml) was stirred at 25 °C for 4 h, then acetic acid (50 ml) was added followed by water (150 ml) and the product was extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with water (2 × 100 ml), then dried ($MgSO_4$), and distillation of the solvent gave the *alcohol* (**9**) (1.6 g, 66%), m.p. 125–126 °C [from ethyl acetate–light petroleum (2:3)], ν_{max} 3 350 cm^{-1} (OH); δ ($CDCl_3$) 1.10–1.80 (4 H, m, 8- and 9-H_2), 2.60–3.40 (6 H, m, 6- and 11-H_2 and 7- and 10-H), 4.36 (1 H, t, *J* 8.0 Hz, 12-H), and 7.00–7.60 (4 H, m, ArH) (Found: C, 73.6; H, 6.6%; M^+, 244. $C_{15}H_{16}OS$ requires C, 73.8; H, 6.6%; M^+, 244).

Ethyl 1-*Methyl*-2-*oxo*-1,2,3,4-*tetrahydronaphthalen*-1-*yl Acetate*.—55% Sodium hydride in oil (3.6 g, 82.5 mmol) was placed under nitrogen in a 500 ml three-necked round-bottomed flask and washed several times with anhydrous toluene to remove the oil. Anhydrous *N*,*N*-dimethylformamide (DMF) (80 ml) was added and the flask was cooled in an ice bath. To the stirred suspension was added a solution of 3,4-dihydro-1-methylnaphthalen-2(1*H*)-one (12.8 g, 80.0 mmol) in anhydrous DMF (20 ml), the cooling bath was removed, and the mixture was stirred until gas evolution ceased (*ca.* 1.5 h). The flask was cooled again with an ice bath whilst a solution of ethyl 2-bromoacetate (14.0 g, 83.5 mmol) in anhydrous DMF (40 ml) was added dropwise. The resulting mixture was stirred for a further 1 h at ice-bath temperature, then overnight at ambient temperature. Water (300 ml) was added and the product was extracted with ether. The combined ethereal extracts were washed with water and dried ($MgSO_4$). Distillation of the solvent gave the *product* (11.02 g, 56%), b.p. 146–152 °C at 1.5–2.0 mmHg, ν_{max} 1 710 (ester C=O) and 1 730 cm^{-1} (ring C=O); δ ($CDCl_3$) 1.02 (3 H, t, CH_2CH_3), 1.39 (3 H, s, Me), 2.76 (2 H, m, 4-H_2), 3.10 (2 H, m, 3-H_2), 3.31 (2 H, s, CH_2CO_2Et), 3.90 (2 H, q, CH_2Me), and 7.20 (4 H, s, ArH) (Found: C, 73.1; H, 7.5. $C_{15}H_{18}O_3$ requires C, 73.2; H, 7.4%).

3a-*Hydroxy*-3,9b-*dimethyl*-3a,4,5,9b-*tetrahydro*-1H-*benz*[e]-*indol*-2(3H)-*one*.—A 13% ethanolic solution of methylamine (60 ml, 500 mmol) was added with stirring to ethyl 1-methyl-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl acetate (12.3 g, 50.0 mmol) at ambient temperature and the resulting mixture was kept for 5 days. Distillation of the solvent under reduced pressure gave the *product* (7.8 g, 67.5%), m.p. 143–144 °C (from ethyl acetate), ν_{max} 1 660 (C=O) and 3 200 cm^{-1} (OH); δ($CDCl_3$) 1.45 (3 H, s, 9b-Me), 2.03 (2 H, t, 5-H_2), 2.55 (2 H, m, 4-H_2), 2.70 (2 H, s, 1-H_2), 2.80 (3 H, s, NMe), 4.48 (1 H, br s, OH) and 6.90–7.30 (4 H, m, ArH) (Found: C, 72.85; H, 7.45; N, 6.2. $C_{14}H_{17}NO_2$ requires C, 72.8; H, 7.4; N, 6.0%).

3,9b-*Dimethyl*-5,9b-*dihydro*-1H-*benz*[e]*indol*-2(3H)-*one*.—A mixture of the foregoing 3a-hydroxy-3,9b-dimethyl-3a,4,5,9b-tetrahydro-1*H*-benz[*e*]indol-2(3*H*)-one (2.31 g, 10.0 mmol) and toluene-4-sulphonic acid (20 mg) in anhydrous toluene (100 ml) was heated under reflux for 4 h with azeotropic removal of water (Dean–Stark apparatus). The cooled solution was washed with water (2 × 50 ml) and dried ($MgSO_4$). Distillation of the solvent under reduced pressure gave the *product* (1.65 g, 77.5%), b.p. 129–130 °C at 0.05 mmHg, ν_{max} 1 680 (C=C) and 1 715 cm^{-1} (C=O); δ($CDCl_3$) 1.30 (3 H, s, 9b-Me), 2.80 (2 H, s, 1-H_2), 3.05 (3 H, s, NMe), 3.50 (2 H, d, 5-H_2), 5.18 (1 H, t, 4-H), and 7.25 (4 H, s, ArH) (Found: C, 78.15; H, 7.3; N, 6.3. $C_{14}H_{15}NO$ requires C, 78.8; H, 7.1; N, 6.6%).

3,9b-*Dimethyl*-2,3,5,9b-*tetrahydro*-1H-*benz*[e]*indole*.—A solution of the foregoing 3,9b-dimethyl-5,9b-dihydro-1*H*-benz-[*e*]indol-2(3*H*)-one (4.26 g, 20.0 mmol) in anhydrous ether (60 ml) was added during 20 min to a stirred suspension of lithium aluminium hydride (1.4 g, 36.8 mmol) in anhydrous ether (60 ml) under nitrogen at ambient temperature and the resulting mixture was stirred for a further 4 h, then cooled in an ice bath. Water (1.2 ml) was added followed by 10% aqueous sodium hydroxide (3.6 ml) and more water (3.6 ml). The precipitate was filtered off under nitrogen and washed with ether (2 × 40 ml). After drying ($MgSO_4$) the combined filtrate and washings, distillation of the solvents gave the air-sensitive product (3.5 g, 88%), b.p. 104–106 °C at 0.02 mmHg, ν_{max} 1 665 cm^{-1} (C=C); δ ($CDCl_3$) 1.20 (3 H, s, 9b-Me), 2.05 (2 H, m, 1-H_2), 2.30 (2 H, d, *J* 6.0 Hz, 5-H_2), 2.65 (3 H, s, NMe), 3.43 (2 H, m, 2-H_2), 4.30 (1 H, m, 4-H), and 7.10 (4 H, s, ArH) (Found: M^+, 199. Calc. for $C_{14}H_{17}N$: M^+, 199).

3,6-*Dimethyl*-1,2,3,4,5,6-*hexahydro*-2,6-*methano*-3-*benzazocin*-11-*one* (**19**).—The 3,9b-dimethyl-2,3,5,9b-tetrahydro-1*H*-benz[*e*]indole (2.98 g, 15.0 mmol), prepared as described in the preceding experiment, was treated with an equimolar amount of bromine in dichloromethane at −60 °C and the bromoiminium salt (**18**) produced (5.39 g, 15.0 mmol) was dissolved in water–dimethyl sulphoxide (1:3) (136 ml). Aluminium oxide (Merck G, Type E) (34.5 g) was added and the mixture was stirred under nitrogen at ambient temperature for 24 h. The precipitate was filtered off, and washed successively with ethanol (2 × 25 ml) and water (2 × 30 ml), and the combined filtrate and washings were diluted with water (250 ml), made alkaline by addition of 1M sodium hydrogen carbonate (75 ml), then extracted with ether (7 × 50 ml). The combined extracts were washed with water (2 × 75 ml), dried (Na_2SO_4), then evaporated to give the product (1.35 g, 42%) as an oil, b.p. 127 °C at 0.05 mmHg (lit.,[18] 122–127 °C at 0.05 mmHg), which solidified, m.p. 60–61 °C, ν_{max} 1 720 cm^{-1} (C=O); δ($CDCl_3$) 1.50 (3 H, s, 6-Me), 1.80–2.10 (2 H, m, 5-H_2), 2.50 (3 H, s, NMe), 2.60 (2 H, d, 1-H_2), 3.30 (2 H, t, 4-H_2), 3.45 (1 H, t, 2-H), and 7.15 (4 H, s, ArH) (Found: M^+, 215. Calc. for $C_{14}H_{17}NO$: M^+, 215).

11α-*Acetamido*-3,6-*dimethyl*-1,2,3,4,5,6-*hexahydro*-2,6-*methano*-3-*benzazocine* (**1**).—The ketone prepared as described in the preceding experiment was converted into its oxime (63%), m.p. 173–174 °C (lit.,[11] 78% and 175–176 °C) using the literature procedure. To this oxime (600 mg, 2.6 mmol) in acetic acid (50 ml) was added Adam's catalyst (200 mg) and the mixture was hydrogenated at 50 psi for 4 h. Then the catalyst was filtered off and washed well with dichloromethane. The combined filtrate and washings were washed with water (2 × 150 ml), then dried ($MgSO_4$). Distillation of the solvents gave a residue which was dissolved in a mixture of acetic acid (15 ml) and acetic anhydride (15 ml) and the resulting solution was warmed for 1 h. Distillation of the solvents gave a residue which was chromatographed on alumina. Ethyl acetate–light petroleum (3:2) eluted the 11α-acetamido-compound (120 mg, 18%), m.p. 191–192 °C (lit.,[11] 53% and 197–198 °C), ν_{max} 1 670 (C=O) and 3 250 cm^{-1} (NH); δ (at 300 MHz) ($CDCl_3$) 1.45 (3 H, s, 6-Me), 1.90 (3 H, s, COMe), 2.00–2.18 (4 H, m, 1- and 5-H_2), 2.45 (3 H, s, NMe), 2.76 (1 H, m, 2-H), 3.10 (2 H, m, 4-H_2), 4.26 (1 H, dd, $J_{11\text{-H-2-H}}$ 4.0, $J_{11\text{-H-NH}}$ 12.0 Hz, 11-H), 5.25 (1 H, m, NH), and 7.15 (4 H, s, ArH) (Found: M^+, 258. Calc. for $C_{16}H_{22}N_2O$: M^+, 258).

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