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THE SYNTHESIS AND STEREOCHEMISTRY OF SOME PYRIDO[3,4-d]CARBAZOLE DERIVATIVES

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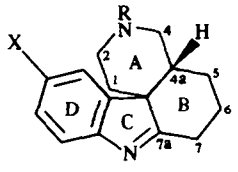
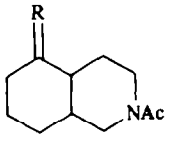
Abstract—Pyrido[3,4-d]carbazole derivatives have been synthesised from N-acetyl-5-oxodecahydroisoquinoline by the Fischer indole synthesis, and their stereochemistry established by ^{1}H-NMR spectroscopy. In contrast to experience with simpler systems, cyclisation in acetic acid gave only the alternative pyrido[3,4-a]-carbazole, and the desired pyrido[3,4-d]carbazole formation occurred only in the presence of sodium acetate.

The elucidation of the topology of 5-hydroxytryptamine (5-HT) receptor sites should be facilitated by the availability of analogues of 5-HT in which the aminoethyl side-chain is constrained to adopt a well-defined disposition relative to the indole moiety. The pyrido[3,4-d]carbazole derivatives (**19** and **22**) were of particular interest for this purpose and their synthesis is described in this paper. The approach used was based upon earlier brief reports[1,2] of the formation of **1** from N-acetyl-5-oxodecahydroisoquinoline and phenylhydrazine.

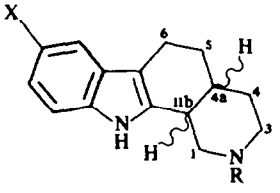
While no difficulties were encountered in repeating the synthesis of N-acetyl-5-hydroxydecahydroisoquinoline (**3**) from isoquinoline, the procedure recommended[3] for its oxidation to **4** proved unsatisfactory. A good yield of **4** was obtained using an equivalent amount of ruthenium tetroxide as oxidant, but when the reaction was conducted for economic reasons on a catalytic basis with sodium metaperiodate as co-oxidant a much lower yield resulted. Eventually it was established that oxidation of **3** in acetone with chromic acid would give **4** in 91% yield. In contrast to the earlier reports,[1,2] we found that the indolisation of the phenylhydrazone of **4** in glacial acetic acid gave predominantly the isomeric pyrido[3,4-a]carbazole (**5**). Saturation of the acetic acid medium with hydrogen chloride has been claimed[4] to increase ring closure in the desired direction (i.e. **1**) in related systems. However, application of this method also gave mainly **5**, as did replacing the hydrogen chloride with zinc chloride. These observations are in line with more recent conclusions[6] that in such situations the use of highly acidic conditions in the Fischer indole reaction favours indole rather than indolenine formation. The converse effect of decreasing the acidity of the cyclisation medium does not appear to have been studied. Consequently the effect of adding sodium acetate to the acetic acid reaction medium was investigated and indeed found to result in the formation of the desired **1** together with **5** in a 3:2 ratio. This result prompted a semiquantitative study of such effects on the popular model system provided by the phenylhydrazone of 2-methylcyclohexanone. In agreement with previous work[5] the carbazolenine (**7**) rather than the carbazole (**8**) was the major product of cyclisation in acetic acid and addition of sodium acetate caused only a minor increase in the yield of **7**.



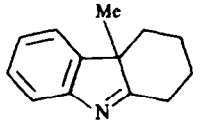
1 X = H, R = Ac
2 X = OCH_2Ph, R = CO_2Et



3 R = H, OH
4 R = O



5 X = H, R = Ac
6 X = OCH_2Ph, R = CO_2Et



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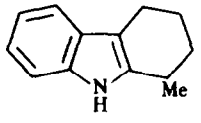

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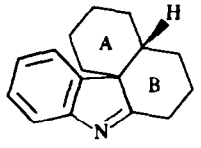

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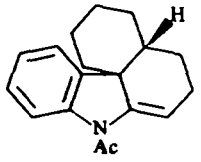

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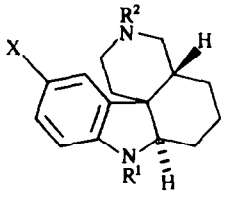
The pyrido[3,4-d]carbazole (**1**) was obtained as a solid, m.p. 151–152°, although reported[1,2] as an oil. The proton decoupled ^{13}C-NMR spectrum showed resonances for 17 C atoms indicating that only one of the two possible stereoisomers had been formed. The ^{1}H-NMR spectrum of **1** showed singlets at δ 2.18 and 2.22 for the acetyl protons, as a consequence of restricted rotation which coalesced to a single resonance on heating to 120°. Duplicate sets of resonances were also obtained for the protons attached to C-2 and C-4. Examination of Dreiding models shows that the geometrical relationship between the protons on C atoms 4 and 4a, and between those on C atoms 6 and 7, depends upon the mode of fusion of rings A and B and their conformation. The possible relationships are indicated in the table and diagram. The observed values of $J_{4(eq),4a} = 1.6$ Hz and $J_{4(ax),4a} = 3.2$ Hz are in best accord with the relationship shown in the Newman Projection I, rather than II or III where coupling constants of 10–13 Hz would be expected. Similarly, the 13.5 Hz coupling constant observed for H-7 is typical of the transdiaxial relationship depicted in projection IV. Additionally, the coplanarity required for the long-range coupling of 1.6 Hz between $H_{2(eq)}$ and $H_{4(eq)}$ is precluded in both the AB-*cis* and *trans*-fused all-boat conformations. Taken together the spectral data indicate an AB-*cis* ring fusion for **1** with ring A adopting a chair conformation. Ring B could have either a chair or boat conformation although examination of molecular models suggests that there would be lower internal repulsions if ring B were to adopt a chair rather than a boat conformation. An analogous AB-*cis* stereochemistry has been suggested[2] for the product (**9**) of indolisation of *trans*-α-decalone on account of its ease of conversion to **10**.

In contrast to the regiospecific formation of **1** the accompanying octahydropyrido[3,4-a]carbazole (**5**) was obtained as a 4:1 mixture of the two possible stereoisomers, which were not readily separable. The ^{1}H-NMR spectrum of the mixture displayed *inter alia* two pairs of resonances for the N-acetyl groups at δ 1.99, 2.02, 2.03 and 2.94 which coalesced to two singlets at 120°, and two broad singlets at δ 10.71 and δ 10.75 for the indolic N—H's.



11 X = H, R^1 = H, R^2 = Ac
12 X = H, $R^1 = R^2$ = Ac
13 X = NO_2, R^1 = H, R^2 = Ac
14 X = NO_2, $R^1 = R^2$ = H
15 X = NO_2, R^1 = H, R^2 = CO_2Et
16 X = NH_2, R^1 = H, R^2 = CO_2Et
17 X = OH, R^1 = H, R^2 = CO_2Et
18 X = $NHSO_2Me$, R^1 = H, R^2 = CO_2Et
19 X = $NHSO_2Me$, R^1 = H, R^2 = Me
20 X = OCH_2Ph, R^1 = H, R^2 = CO_2Et
21 X = OCH_2Ph, R^1 = H, R^2 = Me
22 X = OH, R^1 = H, R^2 = Me

Reduction of the imine group of **1** with sodium borohydride and subsequent acetylation yielded **12**. The assigned stereochemistry at C_{7a} is based upon the well established[7,8] preferential addition of hydride to the less stereochemically hindered face in such systems. Nitration of **12** in conc sulphuric acid by additon of potassium nitrate, followed by partial acid hydrolysis gave the 11-nitro derivative (**13**). The remaining N-acetyl group was removed by alkaline hydrolysis to give **14**, which was then converted to **15** by reaction with ethyl chloroformate in pyridine. Catalytic hydrogenation of **15** reduced the nitro group forming the amine (**16**), and this was reacted with methanesulfonyl chloride in pyridine yielding **18**. Subsequent reduction of **18** with lithium aluminium hydride gave **19**. This compound was of special interest as the methanesulphonamido group is a useful bioisosteric replacement for a phenolic OH group.[9]

Neither oxidation of **11** with potassium nitrosodisulphonate[10] nor decomposition of the diazonium salt derived from the amine (**16**) proved suitable for the introduction of an 11-OH group. Consequently, 2-carbethoxy-5-oxodecahydroisoquinoline was condensed with *p*-benzyloxyphenylhydrazine to give the hydrazone, which was indolised in glacial acetic acid containing sodium acetate to give **2** and **6**. Successive reduction of **2** with sodium borohydride and lithium aluminium hydride provided **21**. Catalytic hydrogenolysis of the benzyl group then gave **22**.

EXPERIMENTAL

IR spectra were recorded for liquid films or Nujol mulls on a Unicam SP200 spectrophotometer, and UV spectra for ethanol solns on a Pye-Unicam SP800A spectrophotomer. NMR spectra were recorded at 60 MHz on a Perkin–Elmer R12B or Bruker WP60FT spectrometer, and at 250 MHz by the ULIRS service at King's College. Mass spectra were obtained by the ULIRS Mass Spectrometry service at Q.E.C. (MS30).

Preparation of N-acetyl-5-oxodecahydroisoquinoline (**4**)

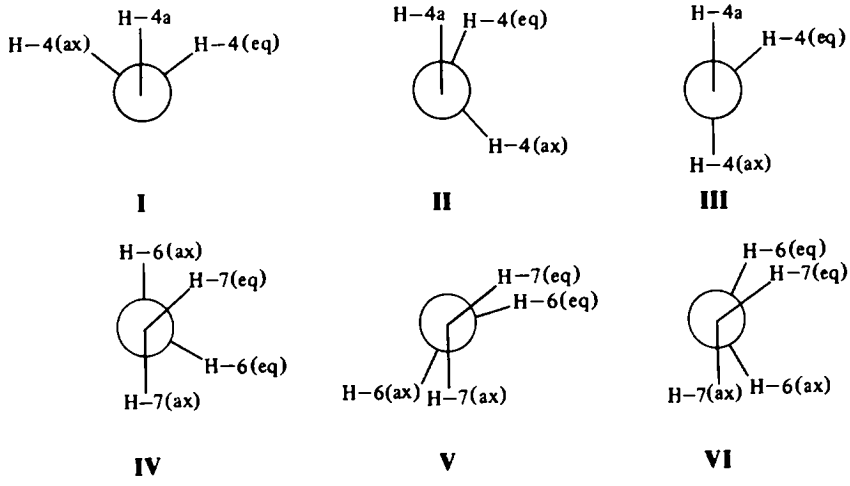
(a) A soln (38 ml) of chromic acid prepared from CrO_3 (26.7 g), conc H_2SO_4 (23 ml) and water (100 ml) was added dropwsie to an acetone soln (750 ml) of N-acetyl-5-hydroxydecahydroisoquinoline[3] (74.7 g) until the orange–brown colouration persisted. The mixture was stirred overnight, unreacted chromic acid destroyed by addition of a few drops of isopropanol and anhyd K_2CO_3 added. The acetone soln was decanted and the green residual solid extracted with acetone. The combined extracts were dried (Na_2SO_4) and evaporated to give a residue which was distilled to give the pure **4** (67 g, 91%), b.p. 0.5 180–184° (lit.[3] b.p. 0.7 154–157°). (Found: C, 67.52; H, 8.86; N, 7.60. Calc for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17%); IR 1700, 1640 cm^{-1}; ^{1}H-NMR δ 1.40–2.40 (m, 10H, 5 × CH_2), 2.10 (s, 3H, $COCH_3$), 2.80–4.00 (m, 3H, 3 × CH), 4.60–5.10 (m, 1H, CH). The compound was further characterised by conversion to the 2,4-dinitrophenylhydrazone, m.p. 217–219° from EtOH (lit.[3] m.p. 218–219°).

(b) To the alcohol **3** (0.9 g) in CCl_4 (50 ml) was added a CCl_4 soln of ruthenium tetroxide obtained by oxidising ruthenium dioxide (0.6 g) with sodium metaperiodate (1.6 g) in a CCl_4–water system. The mixture was stirred for 8 hr, the black ruthenium dioxide filtered off, and the CCl_4 evaporated to give the crude ketone (0.6 g, 67%).

(c) The alcohol (**3**, 0.9 g) was dissolved in CCl_4 (50 ml) and to this was added ruthenium dioxide (0.1 g) and a soln of sodium metaperiodate (1.5 g) in water (20 ml). The mixture was stirred for 36 hr, the CCl_4 layer separated and evaporated to give the crude ketone (0.35 g, 39%).

Table 1.

Ring conformation		Relevant Newman projections in diagram	
Ring A	Ring B	*cis*-AB Fusion	*trans*-AB Fusion
Chair	Chair	I, IV	—
Chair	Boat	I, IV	III, V
Boat	Chair	II, IV	—
Boat	Boat	I or III, V	III, VI



Preparation of **1** *and* **5**. Freshly-distilled phenylhydrazine (8.6 g) was added dropwise to N-acetyl-5-oxodecahydroisoquinoline (15 g) and the mixture stirred under N_2. The phenylhydrazone formed almost immediately. Anhyd NaOAc (12.6 g) and freshly distilled AcOH (250 ml) were added and the mixture heated at 60–70° for 2½ hr. Then the AcOH was evapd *in vacuo*, and 10% NaOH aq added to neutralise any remaining acid. The organic products were obtained by extraction with CH_2Cl_2, and the extracts washed with 10% NaOH and water. The CH_2Cl_2 soln was then extracted with 20% HCl, dried (Na_2SO_4) and evaporated to give a neutral fraction A. The HCl extracts were neutralised with 10% NaOH and reextracted with CH_2Cl_2 to provide a basic fraction B.

The neutral fraction A was chromatographed on silica in petroleum ether–acetone (4:5) to give **5** (4 g, 19%) as an oil which slowly crystallised, m.p. 157–159° (dec) from acetone–petroleum ether. IR 3300, 1630, 740, 690 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.04–1.98 (m, 5H), 1.99, 2.02, 2.04, 2.08 (4 × s, 3H, $NCOCH_3$), 2.34–2.50 (m, 1H), 2.55–2.82 (m, 3H), 2.87–3.30 (m, 1H), 3.87 and 4.51 (bd, 1H, H-4 (eq), J = 11.5 Hz), 3.99 and 4.64 (bd, 1H, H-1 (eq), J = 13.3 Hz), 6.93–7.00 (m, 2H, H-8 and H-9), 7.27–7.35 (m, 2H, H-7 and H-10), 10.71–10.75 (bs, 1H, NH); UV 256 (3.48), 261 (3.55), 2.77 sh (3.67), 282 (3.67), 292 sh (3.61) nm; MS 268 (M^+, 55), 219 (24), 196 (62), 182 (32), 180 (23), 168 (37), 167 (37), 43 (100). The carbazole gave a reddish-brown picrate (EtOH) m.p. 169–170° (decomp). (Found: C, 55.76; H, 4.67; N, 13.99. Calc for $C_{23}H_{23}N_5O_8$: C, 55.53; H, 4.66; N, 14.08%.)

The basic fraction B was chromatographed on silica in ether–acetone (10:3). Elution with EtOAc–isopropanol (5:2) provided **1** (6 g, 30%), m.p. 151–152°. (Found: C, 75.59; H, 7.52; N, 10.28. Calc for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.43%); IR 1640, 1590, 790, 770 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 250 MHz) δ 1.12 (dt d, H-1 (eq), J_{gem} = 13.3, $J_{1(eq),2(ax)} = J_{1(eq),2(eq)}$ = 3.4, $J_{1(eq),4a}$ = 1.6 Hz), 1.40–2.10 (m, 4H, H-5 and H-6), 2.18 and 2.22 (s, 3H, $NCOC\underline{H}_3$), 2.15–2.25 (m, 1H, H-4a), 2.32 (td, 1H, H-1 (ax), $J_{gem} \approx J_{1(ax),2(ax)}$ = 13.3, $J_{1(ax),2(eq)}$ = 5.0 Hz), 2.58 (td, 1H, H-7 (ax), $J_{gem} = J_{7(ax),6(ax)}$ = 13.3, $J_{7(ax),6(eq)}$ = 5.0 Hz), 2.85 (dddd, 1H, H-7 (eq), J = 13.5, 3.6, 2.1, 1.6 Hz), 3.17 (td, H-2 (ax), $J_{gem} = J_{2(ax),1(ax)}$ = 13.7, $J_{2(ax),1(eq)}$ = 3.4 Hz), 3.33 (dd, H-4 (ax), J_{gem} = 13.9, $J_{4(ax),4a}$ = 3.2 Hz), 3.65–3.81 (m, H-2 (ax) and H-4 (ax)), 3.86–4.0 (m, H-2 (eq) and H-4 (eq)), 4.68 (dt), H-4 (eq), J_{gem} = 13.9, $J_{4(eq),4a} = J_{4(eq),2(eq)}$ = 1.6 Hz), 4.86 (dddd, H-2 (eq), J_{gem} = 13.7, $J_{2(eq),1(eq)}$ = 3.4, $J_{2(eq),1(ax)}$ = 5.0, $J_{2(eq),4(eq)}$ = 1.6 Hz), 7.22 (t, 1H, H-11, J = 7.6 Hz), 7.41 (t, 1H, H-10, J = 7.6 Hz), 7.65 (d, 1H, H-12, J = 7.6 Hz), 7.75 (d, 1H, H-9, J = 7.6 Hz); ^{13}C-NMR (DMSO-d_6, 62.9 MHz) δ 21.3 (q), 25.0 (t), 27.2 (t), 28.3 (d, C-4a), 36.9 (t), 41.5 (t), 41.7 (t), 47.4 (t), 55.4 (s), 120.1 (d), 124.2 (d, 2 × C), 127.7 (d), 144.4 (s), 154.4 (s, C-8a), 168.7 (CO), 187.7 (s, C-7a); UV 257 (4.64), 284 sh (4.21), 290 sh (3.93) nm; MS 268 (M^+, 12), 225 (2), 196 (11), 182 (10), 168 (16), 167 (20), 43 (100). The compound gave a yellow pictrate (EtOH) m.p. 225–226° (decomp) (lit.[2] 224.5°).

Reduction of **1**. A soln of **1** (3 g) in EtOH (10 ml) was added to $NaBH_4$ (0.63 g) in EtOH (10 ml) and the mixture stirred for 24 hr. The EtOH was evapd *in vacuo*, 20% NaOH added, followed by water (100 ml) and the organic product isolated by CH_2Cl_2 extraction. The resulting base (3 g) was acetylated by refluxing with Ac_2O (10 ml) for 4 hr, then cooled and poured into water. Neutralisation (Na_2CO_3) and CH_2Cl_2 extrn followed by flash chromatography over silica gel in EtOAc–isopropanol (8:2) gave **12** (2.3 g, 66%), m.p. 154–155° after softening 138–140°, from petroleum ether–MeOH. (Found: C, 72.74; N, 7.69; N, 8.91. Calc for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97%); IR 1650, 1630, 1600, 770, 760, 740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.10–1.90 (m, 8H), 2.0–2.25 (m, 1H), 2.10 and 2.17 (s, 3H, $NCOCH_3$), 2.35 (s, 3H, $ArNCOCH_3$), 2.25–2.50 (m, 1H), 2.78 (q, 1H, J = 13.1 Hz), 3.15–3.45 (m, 1H), 3.60–3.80 (m, 1H), 4.14–4.28 and 4.75–5.0 (br, 1H), 4.45–4.58 (bt, 1H, J = 13.3 Hz), 7.05–7.30 (m, 3H, H-10, H-11, H-12), 7.22–7.27 (m, 1H, H-9); MS 312 (M^+, 81), 270 (12), 225 (36), 212 (18), 184 (36), 183 (74), 170 (100), 143 (43), 130 (36), 83 (47).

Nitration of **12**. The finely powdered **12** (2.2 g) was added portionwise to conc H_2SO_4 (100 ml) with vigorous stirring.

The resulting soln was cooled to −3° and KNO_3 (0.78 g) added gradually over 45 min with stirring, which was continued for a further 2 hr at −3° and then for 4 hr at room temp. The mixture was then poured onto crushed ice (800 g) and the resulting mixture heated at 60–70° for 2½ hr. After cooling the pH was adjusted to 8 with conc NH_4OH and the organic product obtained by CH_2Cl_2 extraction. After washing the CH_2Cl_2 extracts with water, drying (Na_2SO_4) and evaporation the resulting residue was chromatographed on silica gel in Et_2O–EtOAc–MeOH (10:9:1) to give **13** (1.4 g, 61%), m.p. 242–243° (dec) from aq EtOH. (Found: C, 67.45; H, 6.75; N, 13.28. $C_{17}H_{21}N_3O_3$ requires: C, 64.74; H, 6.71; N, 13.32%); IR 3200, 1590, 1510, 1320, 850, 830, 820, 760, 740, 730, 700, 660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.30–1.90 (m, 8H), 1.96–2.10 (m, 1H), 2.11 and 2.16 (s, 3H, $NCOCH_3$), 3.27–3.70 (m, 3H), 3.80 (dd, 1H, H-7a, J = 8.5, J = 4.0 Hz), 4.51 (bs, 1H, NH), 4.03 (dd, H-4(eq), J = 13.6, 4.4 Hz), 4.58 (brd, H-2(eq), J = 13.6 Hz), 6.64 (d, 1H, H-9, J = 8.8 Hz), 8.08 (dd, 1H, H-10, J = 8.8, 2.2 Hz), 8.15 and 8.25 (d, 1H, H-12, J = 2.2 Hz); UV 232 sh (3.94), 265 sh (3.73), 393 (4.26) nm; MS 315 (M^+, 68), 298 (24), 256 (42), 254 (68), 228 (100).

Preparation of **19** *from* **13**. The compound **13** (0.9 g) was refluxed with KOH (5.6 g) in 1:1 aq MeOH (100 ml) for 24 hr and the cooled mixture poured into water (200 ml). The nitroamine **14** (0.6 g) was isolated by CH_2Cl_2 extraction, dissolved in pyridine (20 ml) and ethyl chloroformate (0.34 g) added dropwise to the stirred ice-cold soln. After 24 hr the pyridine was evaporated *in vacuo* and the residue partitioned between CH_2Cl_2 and water. The CH_2Cl_2 extract was dried (Na_2SO_4) and evaporated to give an oil, which was chromatographed over silica in Et_2O–EtOAc (5:3) to give **15** (0.8 g); IR 3250, 1680, 1540, 1310 cm^{-1}. This material in EtOH (50 ml) was hydrogenated at room temp for 48 hr with a H_2 pressure of 60 psi, in the presence of T-1 Raney Ni (0.2 g). The resulting soln was filtered, evaporated and the residue partitioned between CH_2Cl_2 and 2 M HCl. The acid layer was subsequently basified with 2 M NaOH and **16** isolated by re-extraction with CH_2Cl_2. The amine (0.6 g) in ice-cold pyridine (20 ml) was treated dropwise with methanesulphonyl chloride (0.26 g) and the mixture stirred for 24 hr. The bulk of the pyridine was then evaporated *in vacuo* and the residue partitioned between CH_2Cl_2 and water. The CH_2Cl_2 extract was dried (Na_2SO_4) and evaporated to give **18** which was purified by flash chromatography over silica in toluene–EtOAc–MeOH (10:4:1); IR 3200–3100, 1680, 1330, 1160 cm^{-1}. A THF soln of **18** was added dropwise to a suspension of LAH (0.12 g) in THF and the mixture refluxed for 8 hr before evaporation to dryness. Ether (10 ml) was added to the residue followed by 20% NaOH to destroy excess LAH. The ppt alumina was dissolved in 2 M NaOH and the organic product extracted into CH_2Cl_2, from which **19** was extracted into 2 M HCl. Basification of the acid extract with Na_2CO_3 and reextraction with CH_2Cl_2 provided the amine (0.2 g), which was dissolved in the minimum volume of MeOH and added to an Et_2O soln of HCl to give the very hygroscopic hydrochloride of **19**. (Found: C, 47.45; H, 6.69; N, 9.25. Calc for $C_{17}H_{25}N_3O_2S \cdot 2HCl \cdot H_2O$: C, 47.88; H, 6.85; N, 9.85%.) Recrystallisation from isopropanol–Et_2O gave the salt as a hemi-isopropanolate m.p. 150° (foaming) and then 220–238° (dec). (Found: C, 50.38; H, 7.29; N, 9.52. Calc for $C_{17}H_{25}N_3O_2S \cdot 2HCl \cdot \frac{1}{2}[(CH_3)_2CHOH]$: C, 50.68; H, 7.13; N, 9.58%); ^{1}H-NMR (D_2O) δ 1.20 (d, 3H, $(CH_3)_2CHOH$, J = 6.3 Hz) and 4.05 (sept, ½H, Me_2CHOH, J = 6.3 Hz), 1.25–2.30 (m, 8H), 2.80–3.80 (m, 5H), 3.00 (s, 3H, CH_3SO_2), 3.16 (s, 3H, NCH_3), 4.46 (dd, 1H, H-7a, J = 10.6 and 6.6 Hz), 7.25–7.50 (m, 3H, ArH).

Preparation of **2** *and* **6**. Compound **4** (19 g) and KOH (5.6 g) were refluxed in 1:1 aq MeOH (100 ml) for 6 hr. The cooled mixture was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was extracted in turn with 2 M HCl. These acidic extracts were basified with 2 M NaOH and then extracted with CH_2Cl_2 to give, after drying (Na_2SO_4) and evaporation, 5-oxodecahydroisoquinoline (10 g, 67%); IR 3300, 1700 cm^{-1}. This was dissolved in pyridine (50 ml) and ethyl chloroformate (9.6 g) added dropwise with stirring to the ice-cold soln. The reaction mixture was stirred for a further 24 hr and then most of the pyridine evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and the soln washed with 2 M H_2SO_4 and water, dried (Na_2SO_4), and evaporated to give an oil which was chromatographed on silica gel in toluene–EtOAc to give N-ethoxycarbonyl-5-oxo-decahydroisoquinoline (10 g, 76%); IR 1700–1680 cm^{-1}.

This ketone (6.5 g) and *p*-benzyloxyphenylhydrazine (6.2 g) were heated in EtOH containing a few drops of AcOH for 10 min. Then the EtOH was evaporated *in vacuo* and the oily hydrazone dissolved in AcOH (200 ml) and NaOAc (35 g) added. The mixture was heated at 70–75° for 24 hr and then the AcOH evaporated *in vacuo*. The residue was taken up in CH_2Cl_2 and the soln washed successively with 2 M NaOH and water, dried (Na_2SO_4), and evaporated to give a reddish-brown oil which was flash chromatographed on silica gel in toluene–EtOAc (5:3) to give successively **6** and **2**.

Compound **2** (1.7 g, 14%) was obtained as an oil which crystallised from acetone–petroleum ether, m.p. 119–121°. (Found: C, 74.22; H, 6.81; N, 6.94. Calc for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93%); IR 1680, 1620, 1600, 1590, 840, 780, 760, 740 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.05 (bd, 1H, H-1 (eq), J = 13.6 Hz), 1.30 (t, 3H, $\underline{CH_3}CH_2$, J = 7.0 Hz), 1.40–1.65 (m, 3H), 1.92 (qd, 1H, J = 13.2, 4.0 Hz), 2.12–2.22 (m, 1H), 2.28 (td, 1H, H-1 (ax), J = 13.6, 5.1 Hz), 2.52 (td, 1H, H-7 (ax), J = 13.6, 5.5 Hz), 2.79 (bd, 1H, H-7 (eq), J = 13.6 Hz), 3.20–3.60 (m, 2H, H-2 (ax) and H-4 (ax)), 4.19 and 4.20 (q, 2H, $Me\underline{CH_2}O$, J = 7.0 Hz), 4.00–4.40 (m, 2H, H-2 (eq) and H-4 (eq)), 5,07 (s, 2H, CH_2Ph), 6.98 (dd, 1H, H-10, J = 8.5 and 2.2 Hz), 7.36 (d, 1H, H-12, J = 2.2 Hz), 7.32–7.47 (m, 5H, C_6H_5), 7.53 (d, 1H, H-9, J = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 15.0 MHz) δ 14.2 (q), 25.6 (t), 26.8 (t), 27.6 (t), 28.9 (t), 39.8 (t), 41.8 (t), 45.2 (t), 55.8 (s, C-13), 61.5 (t, OCH_2), 70.9 (t, OCH_2Ph), 113 (d, 2 × C), 120.8 (d, C-2'), 127.6 (C-4'), 128.1, 128.7 (C-3'), 136.9 (C-1'), 145.5, 148.7, 156.3 (CO), 182.4 (C-7a); UV 273 (3.83), 282 sh (3.78) 297 sh (3.33), 307 sh (2.78) nm; MS 404 (M^+, 85), 313 (47), 241 (82), 91 (100).

The isomeric **6** (1.4 g, 12%) had m.p. 148–150° from acetone–petroleum ether. (Found: C, 74.29; H, 7.03; N, 6.89%); IR 3380, 1680, 1620, 1600, 850, 820, 780, 760, 720 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.18 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.3 Hz), 1.20–1.40 (m, 1H), 1.43–1.75 (m, 3H), 1.97 (bd, 1H, J = 11.9 Hz), 2.40–2.54 (m, 2H), 2.66 (bt, 1H, J = 8.7 Hz), 2.58–3.04 (m, 2H), 4.03 (q, 2H, OCH_2Me, J = 7.3 Hz), 3.99–4.24 (m, 2H), 5.09 (s, 2H, CH_2Ph), 6.95 (dd, 1H, H-9, J = 8.3 and 2.7 Hz), 7.10 (d, 1H, H-7, J = 2.7 Hz), 7.30–7.60 (m, 6H, H-10 and C_6H_5), 11.70 (s, 1H, NH). It gave a reddish-brown picrate (EtOH), m.p. 168–170° (dec). (Found: C, 58.70; H, 4.60; N, 10.80. Calc for $C_{31}H_{31}N_5O_{10}$: C, 58.76; H, 4.93; N, 11.05%.)

Conversion of **2** *to* **22**. A soln of **2** (1.2 g) in EtOH (20 ml) was added to $NaBH_4$ (0.66 g) in EtOH (100 ml) and the stirred mixture refluxed for 5 days. The EtOH was evapd *in vacuo* and CH_2Cl_2 and 20% NaOH (3 ml) added to the residue. Further 2 M NaOH (50 ml) was added and the CH_2Cl_2 layer separated, washed with H_2O, dried (Na_2SO_4) and evapd to give an oil which was chromatographed over silica in toluene–EtOAc (5:3) to give successively **20** (0.8 g) and unchanged **2** (0.2 g). The reduction did not proceed at room temp. A soln of **20** in THF (10 ml) was added dropwise to LAH (0.11 g) in THF (50 ml) and the mixture refluxed for 24 hr. The THF was then evapd and ether (10 ml) added to the residue followed by a few ml of 20% NaOH. The ppt alumina was dissolved in 2 M NaOH (50 ml) and the organic products isolated by CH_2Cl_2 extrn. The crude product was chromatographed on silica in EtOAc–i-PrOH (5:2) and the desired **21** (0.4 g) eluted with EtOAc–i-PrOH–conc NH_4OH (25:10:1); IR (neat) 3350, 3010, 2900, 2850, 2800, 1600, 740, 700 cm^{-1}. This material was dissolved in MeOH (50 ml) and shaken with hydrogen at 50 psi for 24 hr in the presence of 10% Pd–C (0.1 g). The resulting soln was filtered and evapd to give crude **22** (0.25 g) as an oil which was purified by prep HPLC in MeOH and then converted to the hygroscopic hydrochloride, m.p. 290–292° (dec). (Found: C,

54.92; H, 7.67; N, 7.82. Calc for $C_{16}H_{26}N_2O \cdot 2HCl \cdot H_2O$: C, 55.62; H, 7.50; N, 8.01%); IR (KBr) 3600–3100, 2900, 2700–2400, 1630, 1600, 1480, 1380, 850, 830, 730, 720 cm^{-1}; ^{1}H-NMR (D_2O, 250 MHz) δ 1.70–1.85 (m, 2H), 1.85–2.02 (m, 1H), 2.21 (qd, 1H, J = 13.3, 3.7 Hz), 2.35 (bd, 1H, H-1 (eq), J = 14.7 Hz), 2.48–2.62 (m, 1H), 2.79 (td, 1H, H-1 (ax), J = 14.7, 4.6 Hz), 3.12 (td, 1H, J = 14.2, 6.0 Hz), 3.19 (s, 3H, N^+HCH_3), 3.26 (bd, 1H, J ≈ 14 Hz), 3.63 (td, 1H, H-2 (ax), J = 13.7, 2.7 Hz), 3.75–3.94 (m, 4H), 7.16 (dd, 1H, H-10, J = 8.7, 2.3 Hz), 7.54 (d, 1H, H-12, J = 2.3 Hz), 7.66 (d, 1H, H-9, J = 8.7 Hz); ^{13}C-NMR (D_2O, 62.9 MHz), δ 27.3, 27.5, 29.7, 30.4, 43.8, 46.9, 52.3, 55.8 (C-13), 57.3, 115.9, 119.0, 121.3, 137.5 (C-12a), 143.9 (C-11), 159.3 (C-8a), 194.6 (C-7a).

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