Synthesis and Reactivity of 6-Carbamoyl-5-phenyl-2,3,5,6-tetrahydro-1*H*-1,4-ethanobenzo[*f*]quinoline. X-Ray Molecular Structure of (4a*R**,5*S**,6*R**,10b*R**)-5-Phenyl-2,3,4a,5,6,10b-hexahydro-1*H*-1,4-ethanobenzo[*f*]quinolin-6-yl Acetate

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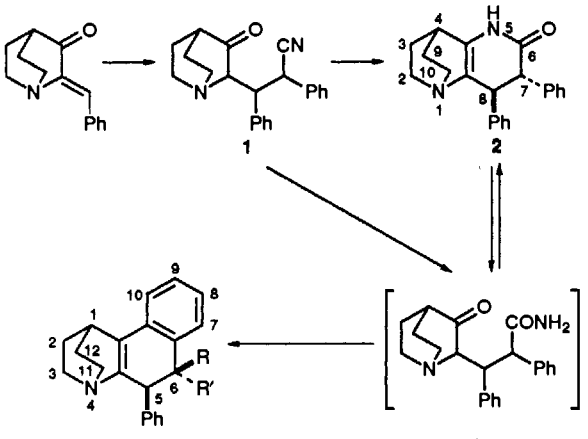
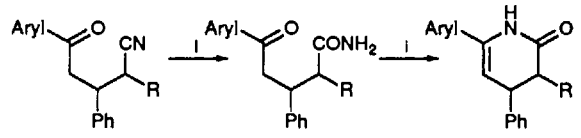
Cyclocondensation of 2-(2-cyano-1,2-diphenylethyl)quinuclidin-3-one **1** in the presence of sulfuric acid gave an intramolecular phenylation instead of lactam formation. The cyclic product was hydrogenated to give 6-carbamoyl-5-phenyl-2,3,4a,5,6,10b-hexahydro-1*H*-1,4-ethanobenzo-[*f*]quinoline. On treatment with $LiAlH_4$ the carbamoyl group was stereospecifically replaced by a hydroxy group. The alcohol was acetylated and the structure was confirmed by X-ray crystallography. The hydroxylation reaction is believed to proceed *via* a carbonitrile intermediate. In the presence of air the nitrile can be converted to a ketone which is then reduced to the alcohol with an overall retention of configuration.

We are currently synthesizing derivatives of perhydronaphthyridine as potential NK_1-receptor antagonists.[1] In this report we describe studies on the cyclization of 2-(2-cyano-1,2-diphenylethyl)quinuclidin-3-one† **1**,[1] which was synthesized by addition of the lithium salt of phenylacetonitrile to 2-benzylidenequinuclidin-3-one (Scheme 1).



Scheme 1

γ-Cyano ketones, which are structural analogues of compound **1**, form dihydropyridines in HCl/HOAc or in conc. H_2SO_4. This reaction is believed to proceed *via* the corresponding amido ketones which result from a partial hydrolysis of the γ-cyano ketones (Scheme 2).[2-4] When similar conditions were applied to compound **1** (conc. H_2SO_4 for several hours at room temperature) the unexpected product **4a** was formed in 65–80% yield (Scheme 1). The structure of product **4a** was identified as follows: The GLC-MS spectrum of compound **4a** gave peaks at *m/z* 330 (14%, M^+) and 286 (100,



Scheme 2 *Reagent:* i, H^+

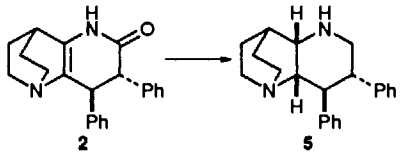
$M^+ - CONH_2$) and the ^1H NMR spectral properties were characteristic for a 'quinuclidin-2-ene' derivative. The two protons in the primary amido group appeared as two broad singlets at δ 5.26 and 6.18 which disappeared after addition of CD_3OD. The GLC-IR spectrum showed two N–H bands at 3530 and 3422 cm^{-1}, respectively, and a carbonyl band at 1718 cm^{-1}. The presence of a primary amido function in compound **4a** was also indicated by its conversion into the corresponding methyl ester by using methanolic HCl.

When compound **1** was treated with H_2SO_4 for longer periods of time and at elevated temperature, the epimer **4b** was produced. Compound **4b** was completely converted into epimer **4a** under alkaline conditions. ^1H NMR spectra of the hydrochlorides of **4a** and **4b** in D_2O exhibited an ABCD coupling pattern (two broad doublets and two broad triplets with coupling constants of ~7.5 Hz) of four aromatic protons which indicated that one of the phenyl moieties was *ortho* disubstituted (the other aromatic hydrogens appeared in two narrow multiplets corresponding to 2 and 3 protons, respectively). One of the aromatic doublets (10-H) exhibited strong NOE enhancement on irradiation of the bridgehead 1-H. The stereochemistries of the epimers were determined by a comparison of the coupling constants for J_{H5-H6} (1.3 Hz for **4a**, 7.6 Hz for **4b**) with the expected dihedral angles derived from semiempirical (AM1) calculations (−86° and +44°, respectively). The coupling constant in compound **4a** (1.3 Hz) implies that the substituents adopt dipseudoaxial positions. This result was corroborated by the AM1 calculations which showed that the dipseudoaxially substituted conformer is more stable than the dipseudoequatorially substituted (ΔH_f 9.3 kJ mol^{-1}).

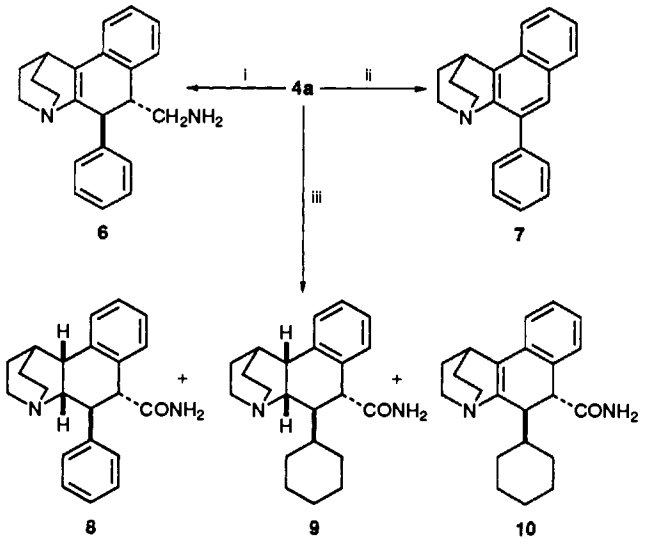
Only a few examples have been reported of an acid-catalysed cyclocondensation involving a keto group and a non-activated benzene nucleus under mild conditions.[5] In fact, such reactions

† *Systematic name*: 3-(3-oxoquinuclidin-2-yl)-2,3-diphenylpropanonitrile.

usually require prolonged reaction times at elevated temperatures.[6-10] When compound **1** was submitted to fairly mild reaction conditions (1 h in H_2SO_4 at 0 °C) compound **4a** was still a major product. However, the reaction mixture was complex and also contained unchanged substrate **1**, the corresponding amide **3**, and lactam **2** (Scheme 1); chromatography of the mixture on silica yielded an equimolar mixture of compounds **2** and **4a**, which was not separated as the compounds eluted together. The presence of lactam **2** was deduced from spectral data [GLC-MS *m/z* 330 (90%, M^+) and GLC-(FT)IR: 3431 (N–H) and 1712 cm^{-1} (C=O)] and from the following chemical correlations: reduction of the mixture of compounds **2** and **4a** with diborane in tetrahydrofuran (THF) provided an equimolar mixture of compounds **5**[1] and **6** (Scheme 3). These products were separated and fully characterized. Reduction of pure amide **4a** using the same conditions provided only amine **6** with no trace of the naphthyridine **5** (Scheme 3). Thus, the perhydronaphthyridine **5**, the structure of which was previously determined by X-ray analysis,[1] could originate only from lactam **2**.



Reagents: B_2H_6, THF

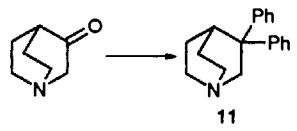


Scheme 3 *Reagents:* i, B_2H_6, THF; ii, $LiAlH_4$, THF; iii, H_2/Pt

Compound **2** was gradually converted into compound **4a** when treated with sulfuric acid, either diluted or concentrated. Most likely, this conversion occurs *via* a ring opening, leading to the amide **3** (Scheme 1). The N^1–C^{8a}–C^{4a} fragment in lactam **2** does not have a nucleophilic β-carbon.[11,12] Instead, C-4a is strongly electron-deficient as a result of the inductive effect from the protonated nitrogen. This facilitates hydrolytic cleavage of the C^{4a}–N^5 bond.

Intramolecular Friedel–Crafts acylation of the phenyl group in compound **3** seems to proceed irreversibly, resulting in a high yielding transformation into epimers **4a** and **4b**. Phenylation of C-3 in quinuclidin-3-one is also favoured intermolecularly since quinuclidin-3-one yields 3,3-diphenylquinuclidine **11** on treatment with $AlCl_3$ in benzene (Scheme 4).

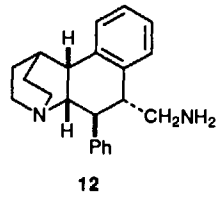
Hydrogenation of amide **4a** with Adams catalyst led to the same difficulties as previously reported for the hydrogenation of 1,4-ethanonaphthyridones;[1] we observed an incomplete



Scheme 4 *Reagents:* $AlCl_3$, benzene

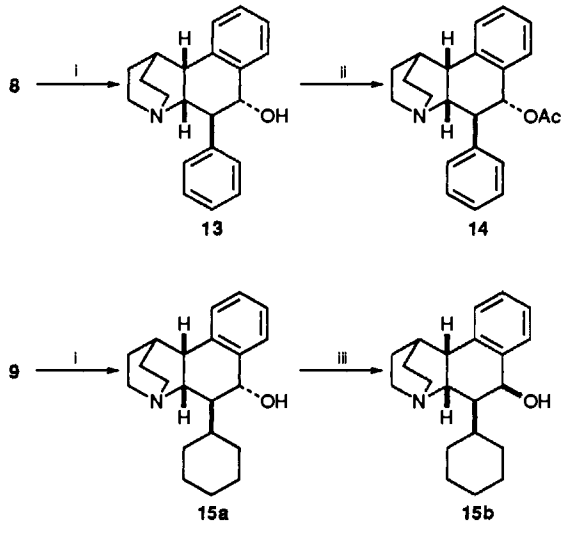
conversion and a competitive reduction of the C-5 phenyl group to a cyclohexyl group, and three products (**8**, **9** and **10**) were observed and characterized (Scheme 3). Relative stereochemistries of compounds **8** and **9** were assigned on the basis of NOE experiments which revealed a spatial proximity of 4a-H, 6-H, and 10b-H, whereas irradiation of 5-H caused no NOE-enhancement of these signals. The large values of $J_{H10b-H4a}$, J_{H4a-H5} and J_{H5-H6} (~ 11.2–11.5 Hz) are compatible only with the assigned structures of compounds **8** and **9**, since these dihedral angles are close to either 0° or 180° according to MM2-calculations.

Reduction of the carbamoyl functionality in compounds **4a** and **8** to the corresponding methylamino group by using borane proceeded smoothly to yield compounds **6** (Scheme 3) and **12**,



respectively. However, reduction of amide **4a** with lithium aluminium hydride in THF resulted in a decarbamoylation to give compound **7** in 14% yield.

On treatment with $LiAlH_4$ at room temperature, compound **8** remained unchanged for several hours, but heating of the mixture to reflux in the presence of air afforded a new product **13** in ~ 50–65% yield (Scheme 5). The assigned structure of product



Scheme 5 *Reagents and conditions:* i, $LiAlH_4$, THF (O_2); ii, Ac_2O; iii, acetone, 40–50 °C

13 is supported by spectral and analytical data. The system of five coupled methine protons 1-H, 10b-H, 4a-H, 5-H, and 6-H in the ^1H NMR spectrum of the alcohol **13** exhibited a coupling pattern similar to that in the precursor **8** but the 6-H signal was shifted downfield by 1.1 ppm. NOE experiments showed that the relative stereochemistry was retained. The molecular ion was observed at *m/z* 305 in the GLC-MS spectrum, and a hydroxy group was identified in the GLC-(FT)IR spectrum of compound **13** (3620 cm^{-1}). In addition, compound **13** was acetylated to give

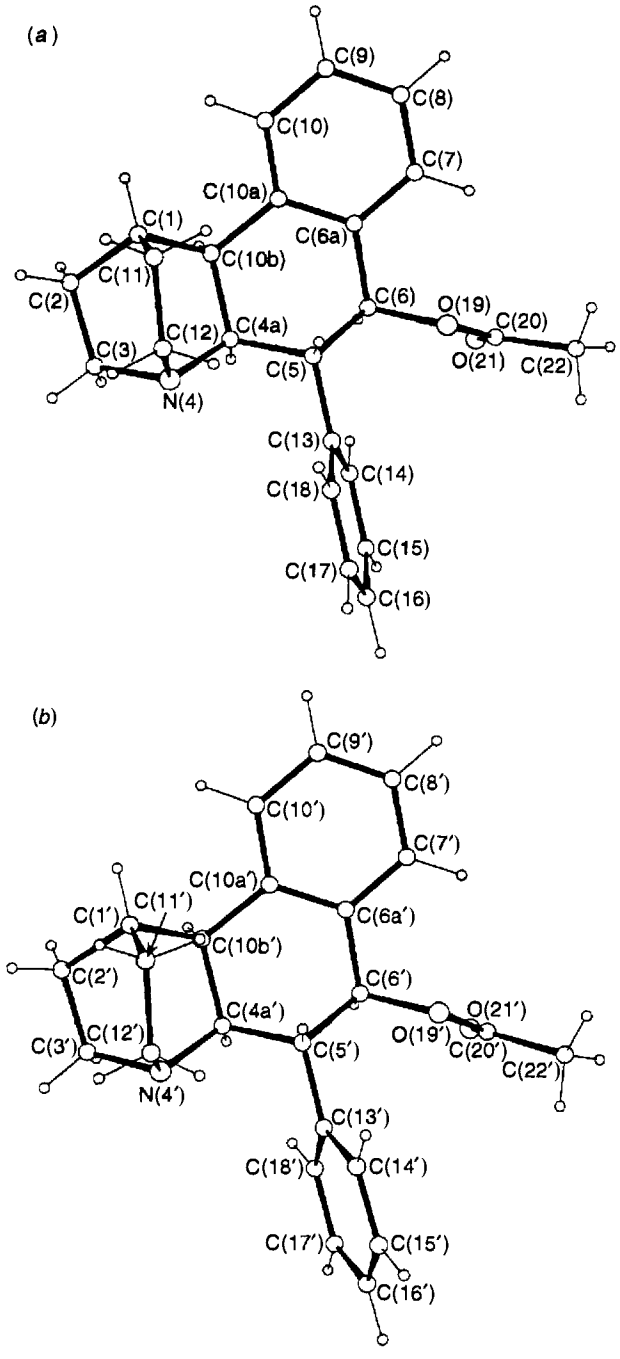


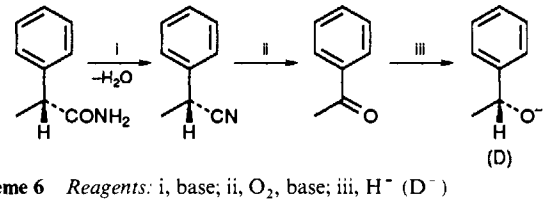
Fig. 1 Perspective views of acetate **14** as two crystallographically independent molecules (*a*) unprimed and (*b*) primed with crystallographic labelling of the atoms

ester **14**, in which the doublet due to 6-H was deshielded by 1.4 ppm (δ 6.12). The X-ray analysis of acetate **14** (Fig. 1) verifies the assignment of the structure of this compound, and also, indirectly, that of the precursors **4a**, **8** and **13**.

Compound **14** crystallizes as two crystallographically independent molecules. The conformation of the fused ring system of compound **14** can be described by means of the ring-puckering parameters, based on the deviation of the ring atoms from a main ring plane.[13] As seen in Fig. 1*a* and 1*b* the two molecules are geometrically similar. Ring B [C(4a)–C(5)–C(6)–C(6a)–C(10a)–C(10b)]* adopts a strongly distorted half-chair conformation with an approximate two-fold axis through the C-5–C-6 bond, and with the two substituents pseudoequatorially oriented in both molecules. The corresponding bond distances and bond angles in the two molecules of compound **14** agree with each other within experimental error, and no anomalous values have been observed.

The cyclohexyl analogue **9** was converted into the *trans*-alcohol **15a** in 51% yield by treatment with $LiAlH_4$. Compound **15a** appeared to be relatively unstable and isomerized to its 5,6-*cis*-epimer **15b** during recrystallization from acetone. Compound **15b** exhibited a similar mass spectrum (*m/z* 311, M^+) to that shown by its C-6 epimer **15a** but the chemical shifts and, in particular, the coupling constant values in ^1H NMR spectra of compounds **15a** and **15b** were distinctly different. The epimerization of compound **15a** to compound **15b** was probably catalysed by traces of acid, as no *trans–cis* conversion was observed in the reduction reaction yielding compound **15a** or during the work-up procedure.

In order to study further the above transformations, resulting in a replacement of the carbamoyl group with a hydroxy substituent (Scheme 5), we carried out some additional experiments; when the reaction with $LiAlH_4$ was performed under nitrogen, other products were predominantly formed from intermediate amides **8** and **9**. These products exhibited M^+ peaks of 18 mass units lower than that of the starting material (*m/z* 314 and 320 respectively) and an IR absorption characteristic for carbonitriles (2230 cm^{-1}). The transformation of sterically hindered primary amides into carbonitriles as a first step in the reduction with $LiAlH_4$ (or even $NaBH_4$) has been observed previously.[14–16] The carbonitriles were smoothly converted into alcohols (**13** and **15a**) with $LiAlH_4$ in THF in the presence of air. This conversion may be best explained by a stepwise mechanism, in which an oxidative elimination of the cyano group in the basic reaction medium should play a key role (Scheme 6). Numerous examples in the literature of oxidative decyanations of benzylcarbonitriles by O_2 in the presence of a base (to yield phenyl ketones *via* α-cyano peroxides)[17–20] provide support for this assumption. Presumably, the sterically hindered environment around the amide functions of compounds **8** and **9** prevent reduction with $LiAlH_4$. Instead nitriles are formed, which can be further converted into the alcohols **13** and **15a** (Schemes 5 and 6). This hypothesis is corroborated by experiments in which $LiAlD_4$ was used to convert amides **8** and **9** into alcohols **13** and **15a** with a deuterium atom incorporated at C-6.



Scheme 6 *Reagents:* i, base; ii, O_2, base; iii, H^- (D^-)

Experimental

M.p.s were measured in open glass capillaries on a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were run on a JEOL JNM-EX 270 spectrometer for solutions in $CDCl_3$ and the chemical shifts were determined relative to internal tetramethylsilane. Assignments were made on the basis of ^1H–^1H and ^1H–^{13}C correlation NMR experiments. *J*-Values are given in Hz. The IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer (KBr tablets) and on a combined Hewlett-Packard GLC (5890)-FT/IR(5965B) unit. Mass spectral data together with GLC data were obtained with a combined Hewlett-Packard GC(5890)-MS(5791) unit. The high-resolution mass spectrum was run on a Finnegan Mat 90

* Crystallographic numbering scheme.

double-focusing instrument, equipped with an FAB saddle field gun. The reaction mixtures were monitored by TLC on aluminium sheets precoated with silica gel 60 F_{254} (E. Merck) in 10 or 20% MeOH–CH_2Cl_2 or with alumina in 2% MeOH/CH_2Cl_2. The elemental analyses were performed by MikroKemi AB, Uppsala, Sweden. The syntheses of compounds **1–3** and **5** are described elsewhere.[1] pH Values were measured with litmus paper.

(5R*,6S*)-5-*Phenyl*-2,3,5,6-*tetrahydro*-1H-1,4-*ethanobenzo*-[f]*quinoline*-6-*carboxamide* **4a**.—3-(3-Oxoquinuclidin-2-yl)-2,3-diphenylpropanonitrile **1** (2.0 g, 6.06 mmol) was added in portions to vigorously stirred, conc. sulfuric acid (10 cm^3), with the temperature kept at 15–20 °C with an ice-bath. The mixture was stirred at ambient temperature for 5–6 h while substrate **1** gradually dissolved. The mixture was diluted with water and made alkaline by slow addition of 20% NaOH at 50–70 °C. After cooling to room temperature the solution was extracted with $CHCl_3$ (3 × 100 cm^3). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a silica gel column with 20% MeOH in EtOAc as eluent to give *title compound* **4a** (1.48 g, 74%) as a yellowish foam; ν_{max}/cm^{-1} 1718 (C=O) and 3422 and 3530 (NH); δ_H 1.41–1.85 (4 H, m, 2- and 12-H_2), 2.22–3.10 (4 H, m, 3- and 11-H_2), 3.36 (1 H, ddd, each *J* 2.3, 1-H), 3.62 (1 H, d, *J* 1.3, 5-H), 4.28 (1 H, d, 6-H), 5.26 and 6.18 (2 H, 2 br s, NH_2) and 7.04–7.45 (9 H, m, ArH); δ_C 26.1 (C-1), 28.3 and 29.6 (C-2 and -12), 45.8 (C-6), 48.8 and 50.6 (C-3 and -11), 54.8 (C-5), 121.7, 126.8, 127.3, 127.5, 128.4, 130.3, 130.6, 132.3, 136.7, 140.7 and 149.9 (ArC, C-4a and -10b) and 175.0 (C=O); *m/z* 330 (M^+, 14%) and 286 (100) (Found: C, 76.2; H, 6.9; N, 7.9. $C_{22}H_{22}N_2O{\cdot}H_2O$ requires C, 75.9; H, 6.9; N, 8.0%).

Compound **4a** was also formed when its epimer **4b** (see below) (1.0 g, 3.03 mmol) was refluxed for 5 h in a solution of sodium methoxide (0.81 g, 15 mmol) in MeOH (10 cm^3). Purification as described above gave pure compound **4a** (0.83 g, 83%).

(5R*,6R*)-5-*Phenyl*-2,3,5,6-*tetrahydro*-1H-1,4-*ethanobenzo*-[f]*quinoline*-6-*carboxamide* **4b**.—Compound **1** (2.0 g, 6.06 mmol) was added in portions to stirred, conc. sulfuric acid (10 cm^3) kept at 20–50 °C. The mixture was heated at 70 °C for 1 h and was then kept for 5 days at ambient temperature. The solution was slowly poured into a cooled mixture of $CHCl_3$ (100 cm^3) and 15% aq. Na_2CO_3 (200 cm^3). The aqueous phase was extracted with $CHCl_3$ (2 × 100 cm^3). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel with 20% MeOH–EtOAc as eluent to give *title compound* **4b** (1.64 g, 82%) as a yellowish foam, δ_H 1.50–1.88 (4 H, m, 2- and 12-H_2), 2.02–3.15 (4 H, m, 3- and 11-H_2), 3.37 (1 H, m, 1-H), 3.82 (1 H, d, *J* 7.6, 5-H), 4.40 (1 H, d, 6-H), 4.86 and 5.43 (2 H, 2 br s, NH_2) and 7.02–7.44 (9 H, m, ArH); δ_C 26.0 (C-1), 28.3 and 29.3 (C-2 and -12), 46.9 (C-6), 49.6 and 50.9 (C-3 and -11), 54.7 (C-5), 121.4, 127.4, 127.5, 127.6, 128.0, 128.5, 128.7, 130.5, 132.3, 136.7, 138.1 and 149.9 (ArC, C-4a and -10b) and 173.8 (C=O); *m/z* 330 (M^+, 15%) and 286 (100) (Found: C, 77.7; H, 6.7; N, 8.0. $C_{22}H_{22}N_2O{\cdot}0.5$ H_2O requires C, 77.9; H, 6.8; N, 8.3%).

(5R*,6S*)-6-*Aminomethyl*-5-*phenyl*-2,3,5,6-*tetrahydro*-1H-1,4-*ethanobenzo*[f]*quinoline* **6**.—Compound **4a** (0.5 g, 1.52 mmol) was added to a 1 mol dm^{-3} solution of diborane in THF (7.6 cm^3; 7.6 mmol) and the mixture was heated in a tightly closed vessel at 70–80 °C for 10 h. Methanol (5 cm^3) was slowly added at 5 °C and the volatile components were removed under reduced pressure. A solution of HCl (5% in 50% aq. ethanol; 20 cm^3) was added and the mixture was heated for 1.5 h at 50–60 °C. The solution was concentrated under reduced pressure, 1% aq. NaOH was added (to pH 9) and the mixture was extracted with $CHCl_3$ (2 × 30 cm^3). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The product was purified on alumina with a gradient of 0–2% MeOH in EtOAc as eluent to afford pure *title compound* **6** (0.3 g, 63%); m.p. 220 °C (decomp.); δ_H 1.42 (2 H, br s, NH_2), 1.50–1.89 (4 H, m, 2- and 12-H_2), 2.18–3.14 (4 H, m, 3- and 11-H_2), 2.77 (1 H, app br d, 6-H), 2.82–2.87 (2 H, m, CH_2NH_2), 3.29–3.34 (1 H, m, 1-H), 3.48 (1 H, app br s, 5-H) and 7.00–7.40 (9 H, m, ArH); δ_C 25.8 (C-1), 28.3 and 29.5 (C-2 and -12), 47.1 (C-6), 48.1 (CH_2NH_2), 48.8 and 50.7 (C-3 and -11), 52.0 (C-5) and 121.2, 126.4, 126.6, 127.0, 127.2, 128.3, 129.8, 131.4, 134.5, 136.0, 142.2 and 148.3 (ArC, C-4a and -10b); *m/z* 316 (M^+, 14%) and 286 (100) (Found: C, 79.1; H, 7.5; N, 8.2. $C_{22}H_{24}N_2{\cdot}H_2O$ requires C, 79.0; H, 7.8; N, 8.4%).

5-*Phenyl*-2,3-*dihydro*-1H-1,4-*ethanobenzo*[f]*quinoline* **7**.—Compound **4a** (0.20 g, 0.61 mmol) was added to a suspension of $LiAlH_4$ (0.07 g, 1.82 mmol) in THF (5 cm^3) and the mixture was stirred with full access to air for 3 days at room temperature. The reaction was quenched with ethanol (3 cm^3) and the resulting mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was partitioned between $CHCl_3$ and water. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel with 50% hexane–EtOAc as eluent to give *compound* **7** (24 mg, 14%) as an oil; δ_H 1.55–1.70 and 1.92–2.08 (4 H, m, 2-H and 12-H_2), 2.63–2.77 and 3.18–3.32 (4 H, m, 3- and 11-H_2), 3.98–4.03 (1 H, m, 1-H), 7.36–8.14 (9 H, m, ArH) and 7.79 (1 H, s, 6-H); δ_C 26.2 (C-1), 28.5 (C-2 and -12), 49.7 (C-3 and -11) and 121.9, 125.3, 125.6, 127.0, 127.9, 128.4, 128.8, 129.7, 131.8, 136.2, 139.1 and 140.7 (ArC and C-6) (Found: M^+, 285.1583. $C_{21}H_{19}N$ requires M, 285.1519).

Synthesis of (4aR*,5S*,6R*,10bR*)-5-*Phenyl*-2,3,4a,5,6,10b-*hexahydro*-1H-1,4-*ethanobenzo*[f]*quinoline*-6-*carboxamide* **8**, (4aR*,5S*,6S*,10bS*)-5-*Cyclohexyl*-2,3,4a,5,6,10b-*hexahydro*-1H-1,4-*ethanobenzo*[f]*quinoline*-6-*carboxamide* **9**, *and* (5R*,6R*)-5-*Cyclohexyl*-1,4-*ethano*-2,3,5,6-*tetrahydro*-1H-1,4-*ethanobenzo*[f]*quinoline*-6-*carboxamide* **10** *by Catalytic Hydrogenation of Compound* **4a**.—A mixture of compound **4a** (1.0 g, 3.03 mmol) and PtO_2 hydrate (79–84% Pt content) (100 mg) in glacial acetic acid (50 cm^3) was hydrogenated at 60 psi in a Parr apparatus for 20 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was treated with 10% aq. Na_2CO_3 to pH 9–10 and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel with a gradient of 20–50% MeOH in $CHCl_3$ as eluent to give pure 5-phenyl compound **8** (0.37 g, 37%), 5-cyclohexyl compound **9** (0.18 g, 18%) and enamine **10** (0.09 g, 9%).

Compound **8**: m.p. 270 °C (decomp.); ν_{max}/cm^{-1} 1490 and 1610 (Ph), 1665 (C=O) and 3180 and 3300 (N–H); δ_H 1.36–1.82 (4 H, m, 2- and 12-H_2), 2.47–2.52 (1 H, m, 1-H), 2.52–3.06 (4 H, m, 3- and 11-H_2), 3.02 (1 H, app br d, 10b-H), 3.17 (1 H, dd, $J_1 = J_2 = 11.5$, 5-H), 3.60 (1 H, dd, $J_1 = J_2 = 11.5$, 4a-H), 3.64 (1 H, d, *J* 11.5, 6-H), 5.37 and 5.43 (2 H, 2 br s, NH_2) and 7.12–7.40 (9 H, m, ArH); δ_C 21.0, 25.7 and 27.7 (C-1, -2 and -12), 39.1, 40.9, 45.9, 49.9, 53.7 and 62.8 (C-3, -4a, -5, -6, -10b and -11), 126.0, 126.5, 126.9, 127.1, 127.3, 127.9, 128.6, 137.5 and 142.7 (ArC) and 174.6 (C=O); *m/z* 332 (M^+, 6%) and 205 (100) (Found: C, 77.2; H, 7.4; N, 7.8. $C_{22}H_{24}N_2O{\cdot}0.5$ H_2O requires C, 77.4; H, 7.3; N, 8.2%).

Compound **9**: m.p. 132–134 °C; ν_{max}/cm^{-1} 1655 (C=O) and 3400–3150 (NH); δ_H 1.15–1.90 (15 H, m, 2- and 11-H_2, cyclohexyl), 1.98 (1 H, app br t, 5-H), 2.38–2.45 (1 H, m, 1-H), 2.48–2.70 and 2.92–3.05 (4 H, m, 3- and 12-H_2), 2.74 (1 H, app br d, 10b-H), 3.17 (1 H, app t, 4a-H), 3.33 (1 H, d, *J* 11.2, 6-H),

5.72 (2 H, br s, NH_2) and 7.20–7.35 (4 H, m, ArH); δ_C 19.2, 20.5, 23.6, 23.8, 25.4, 25.9, 26.0, 26.3 and 27.1 (C-1, -2, -5, -12, and cyclohexyl), 38.2, 44.1, 47.2, 52.1 and 59.7 (C-3, -4a, -6, -10b and -11), 126.1, 127.9, 129.2, 130.4, 135.9 and 139.2 (ArC) and 172.8 (C=O); *m/z* 338 (M^+, 43%) and 205 (100). An analytical sample was obtained by conversion of the base into the *hydrochloride salt* by using ethereal HCl (Found: C, 68.9; H, 8.0; N, 6.9. $C_{22}H_{30}N_2O$·HCl·0.5 H_2O requires C, 68.8; H, 8.3; N, 7.3%).

Compound **10**: m.p. 122–124 °C; δ_H 0.80–1.90 (15 H, m, 2- and 12-H_2 and cyclohexyl), 2.58–2.78 and 3.07–3.20 (4 H, m, 3- and 11-H_2), 2.92 (1 H, app br d, 5-H), 3.23–3.28 (1 H, m, 1-H), 3.63 (1 H, app br s, 6-H), 5.24 and 5.62 (2 H, 2 br s, NH_2) and 7.20–7.35 (4 H, m, ArH); δ_C 25.8, 26.3, 26.4, 26.7, 27.7, 28.4, 29.1, 30.9 and 40.8 (C-1, -2, -12, and cyclohexyl), 46.1, 48.2, 48.8 and 50.1 (C-3, -5, -6 and -11), 121.7, 127.3, 128.0, 129.3, 131.8, 132.5, 136.2 and 147.9 (ArC, C-4a and -10b) and 172.3 (C=O); *m/z* 336 (M^+, 6%) and 210 (100). An analytical sample was obtained by conversion of the base into the *hydrochloride salt* by using ethereal HCl; m.p. 186–187 °C (Found: C, 67.3; H, 7.7; N, 6.9. $C_{22}H_{28}N_2O$·HCl·H_2O requires C, 67.6; H, 7.9; N, 7.2%).

3,3-*Diphenylquinuclidine* **11**.—Quinuclidin-3-one hydrochloride (0.30 g, 1.86 mmol) was heated to reflux in benzene (3 cm^3) in the presence of anhydrous $AlCl_3$ (0.37 g, 2.8 mmol) for 3–5 h. The mixture was diluted with $CHCl_3$ (20 cm^3), quenched with water (3 cm^3), and 1 mol dm^{-3} NaOH was added (to pH 9–10). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on alumina with $CHCl_3$ as eluent to yield pure *compound* **11** (0.33 g, 68%); m.p. 135–136 °C; δ_H 1.50–1.76 (4 H, m, 5- and 7-H_2), 2.73–2.81 (4 H, m, 6- and 8-H_2), 2.82–2.88 (1 H, m, 4-H), 3.84 (2 H, s, 2-H_2) and 7.03–7.35 (10 H, m, Ph); δ_C 23.4 (C-5 and -7), 28.7 (C-4), 45.8 (C-3), 47.0 (C-6 and -8), 58.8 (C-2) and 125.2, 126.7, 128.2 and 148.6 (Ph); *m/z* 263 (M^+, 100%) (Found: C, 86.6; H, 8.2; N, 5.3. $C_{19}H_{21}N$ requires C, 86.7; H, 8.0; N, 5.3%).

(4aR*,5S*,6R*,10bR*)-6-*Aminomethyl*-5-*phenyl*-2,3,4a,5,6,10b-*hexahydro*-1H-1,4-*ethanobenzo*[f]*quinoline* **12**.—*Compound* **12** (0.12 g, 60%) was synthesized from amide **8** (0.20 g, 0.6 mmol) as described above for the synthesis of amine **6**; m.p. 287 °C (decomp.); δ_H 1.37–1.83 (4 H, m, 2- and 12-H_2), 1.51 (2 H, br s, NH_2), 2.50–2.54 (1 H, m, 1-H), 2.57–3.30 (8 H, m, 3- and 11-H_2, 5- and 6-H, and C$H_2$$NH_2$), 3.10 (1 H, app br d, 10b-H), 3.74 (1 H, app br t, $J_1 = J_2 = 11.0$, 4a-H) and 7.23–7.40 (9 H, m, ArH); δ_C 20.9, 25.2 and 27.6 (C-1, -2 and -12), 39.0, 39.1, 40.8, 44.0, 45.1, 49.8 and 64.6 (C-3, -4a, -5, -6, -10b, -11, and CH_2NH_2), and 124.6, 125.8, 126.1, 126.6, 127.4, 127.9, 128.6, 138.2, 139.8 and 143.7 (ArC); *m/z* 318 (M^+, 19%) and 82 (100) (Found: C, 82.8; H, 8.0; N, 8.4. $C_{22}H_{26}N_2$ requires C, 83.0; H, 8.2; N, 8.8%).

(4aR*,5S*,6R*,10bR*)-5-*Phenyl*-2,3,4a,5,6,10b-*hexahydro*-1H-1,4-*ethanobenzo*[f]*quinolin*-6-*ol* **13**.—$LiAlH_4$ (68 mg, 1.8 mmol) was added to a solution of amide **8** (0.20 g, 0.6 mmol) in THF (10 cm^3). The mixture was refluxed and stirred for 4–5 h with an access of air. Ethanol (3 cm^3) was added carefully at 0 °C and the solution was filtered through Celite and concentrated under reduced pressure. The residue was partitioned between water and $CHCl_3$. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on alumina with $CHCl_3$ as eluent to give pure *alcohol* **13** (118 mg, 64%); m.p. 184–185 °C; ν_{max}/cm^{-1} 3620 (OH); δ_H 1.33–1.82 (4 H, m, 2- and 12-H_2), 1.84 (1 H, br s, OH), 2.48–2.54 (1 H, m, 1-H), 2.52–3.05 (5 H, m, 3- and 11-H_2 and 10b-H), 2.87 (1 H, dd, *J* 10.9 and 11.5, 5-H), 3.61 (1 H, dd, 4a-H), 4.70 (1 H, d, *J* 10.9, 6-H) and 7.25–7.73 (9 H, m, ArH); δ_C 21.0 (C-12), 25.4 (C-1), 27.6 (C-2), 38.7 (C-10b), 41.0 (C-11), 49.9 (C-3), 51.7 (C-5), 61.5 (C-4a), 71.2 (C-6) and 123.6, 125.9, 126.4, 126.9, 127.4, 128.4, 129.1, 135.8, 141.1 and 141.2 (ArC); *m/z* 305 (M^+, 55%) and 131 (100) (Found: C, 81.4; H, 7.7; N, 4.6. $C_{21}H_{23}NO$·0.25 H_2O requires C, 81.4; H, 7.6; N, 4.5%).

(4aR*,5S*,6R*,10bR*)-5-*Phenyl*-2,3,4a,5,6,10b-*hexahydro*-1H-1,4-*ethanobenzo*[f]*quinolin*-6-*yl Acetate* **14**.—Compound **13** (50 mg, 0.16 mmol) was treated with an excess of acetic anhydride (2 cm^3) in pyridine (2 cm^3) for 2 h at 20 °C. The mixture was quenched with water (10 cm^3) and concentrated under reduced pressure. The residue was partitioned between saturated aq. $NaHCO_3$ (pH 8–9) and $CHCl_3$. The organic phase was dried ($MgSO_4$), filtered, and concentrated to leave a residue, which was crystallized from diethyl ether–acetone (1 : 1) to yield *compound* **14** (44 mg, 78%); m.p. 158–160 °C; δ_H 1.32–1.86 (4 H, m, 2- and 12-H_2), 1.82 (3 H, s, Me), 2.48–2.54 (1 H, m, 1-H), 2.56–3.12 (6 H, m, 3- and 11-H_2, and 5-, 10b-H), 3.71 (1 H, dd, $J_1 = J_2 = 11.4$, 4a-H), 6.12 (1 H, d, *J* 11.2, 6-H) and 7.13–7.42 (9 H, m, ArH); δ_C 20.4 (Me), 21.0 (C-12), 25.4 (C-1), 27.6 (C-2), 38.7 (C-10b), 40.9 (C-11), 48.9 (C-3), 49.9 (C-5), 61.2 (C-4a), 73.0 (C-6), 123.0, 125.8, 126.9, 127.0, 127.3, 128.2, 128.3, 136.4, 138.3 and 140.9 (ArC) and 170.4 (C=O); *m/z* 347 (M^+, 28%) and 204 (100) (Found: C, 79.8; H, 6.9; N, 4.3. $C_{23}H_{25}NO_2$ requires C, 79.5; H, 7.2; N, 4.0%).

(4aR*,5S*,6R*,10bR*)-5-*Cyclohexyl*-2,3,4a,5,6,10b-*hexahydro*-1H-1,4-*ethanobenzo*[f]*quinolin*-6-*ol* **15a** *and* (4aR*,5S*,6S*,10bR*)-5-*Cyclohexyl*-2,3,4a,5,6,10b-*hexahydro*-1H-1,4-*ethanobenzo*[f]*quinolin*-6-*ol* **15b**.—Compound **15a** was synthesized from amide **9** (0.10 g, 0.3 mmol) as described above for the synthesis of alcohol **13**. Purification on alumina with 2% MeOH in $CHCl_3$ as eluent gave *title compound* **15a** (47 mg, 51%); m.p. 80–85 °C (decomp.); δ_H 1.20–1.82 (16 H, m, 2- and 12-H_2, OH, and cyclohexyl), 1.41 (1 H, app t, 5-H), 2.33–2.38 (1 H, m, 1-H), 2.42–2.61 and 2.83–2.98 (4 H, m, 3- and 11-H_2), 2.66 (1 H, app br d, 10b-H), 3.0 (1 H, dd, $J_1 = J_2 = 11.0$, 4a-H), 4.44 (1 H, dd, *J* 8.0 and 10.8, 6-H) and 7.12–7.60 (4 H, m, ArH); δ_C 21.3, 24.2, 27.3, 27.5, 27.6, 27.9, 28.2 and 33.9 (C-1, -2, -12, and cyclohexyl), 37.7 and 40.8 (C-5 and -10b), 47.9 and 49.8 (C-3 and -11), 58.3 (C-4a), 69.2 (C-6) and 122.8, 125.7, 126.1, 126.3, 126.6 and 137.0 (ArC); *m/z* 311 (M^+, 35%) and 228 (100) (Found: C, 80.9; H, 9.4; N, 4.4. $C_{21}H_{29}NO$ requires C, 81.0; H, 9.4; N, 4.5%).

A sample (30 mg) was heated in acetone at 40–50 °C for 5–10 min and the precipitated crystals were filtered off to give *compound* **15b** (22 mg); m.p. 142 °C (decomp.); δ_H 0.95–2.21 (16 H, m, 2- and 12-H_2, OH, and cyclohexyl), 2.54–2.62 (2 H, m, 1- and 5-H), 2.90–3.05, 3.28–3.58 and 4.33–4.48 (5 H, m, 3- and 11-H_2, and 4a-H), 3.72 (1 H, app br d, 10b-H), 4.78 (1 H, d, *J* 1.8, 6-H) and 7.16–7.50 (4 H, m, ArH); δ_C 18.7, 24.1, 25.8, 26.2, 26.3, 27.9, 30.2 and 31.1 (C-1, -2, -12, cyclohexyl), 37.3 and 42.9 (C-5 and -10b), 47.4 and 50.0 (C-3 and -11), 60.8 (C-4a), 67.2 (C-6) and 127.2, 127.4, 128.3, 130.2, 133.8 and 136.9 (ArC); *m/z* 311 (M^+, 17%) and 82 (100) (Found: C, 80.4; H, 9.3; N, 4.4%).

X-Ray Analysis.—Crystals of compound **14** ($C_{23}H_{25}NO_2$, M_w 347.456) were grown from a diethyl ether–acetone (1 : 1) solution. The diffraction data were collected on an STOE/AED2 diffractometer with graphite-monochromized Mo-Kα radiation (λ 0.710 69 Å, θ_{max} 45°) at room temperature. The intensities of 4920 reflections were measured and corrected for background, Lorentz and polarization effects. The selected single crystal, approximately 0.42 × 0.38 × 0.40 mm, showed triclinic ($P\bar{1}$) symmetry, with unit-cell dimensions a = 9.790(2), b = 11.006(3), c = 19.030(4) Å, α = 80.26(1), β = 81.87(1), γ = 68.62(1)° and V_c = 1874.7(7) Å^3. In the least-squares refinement of the cell parameters the 2θ-values of 48 reflections

with $16 < 2\theta < 22°$ were used. The unit cell contains two crystallographically independent molecules [$Z = 4$, $D_c = 1.2310(5)$ g cm^{-3}, $F(000) = 744$ and $\mu = 0.726$ cm^{-1}].

Structure analysis and refinement. The preliminary structure model was derived by application of direct methods (SHELXS)[21] and refined by full-matrix least-squares methods based on $|F|$ (SHELX).[22] The hydrogen atoms were assumed to be in idealized positions with C–H 1.00 Å, which were recalculated after each refinement cycle using geometric evidence. The methyl groups were treated as rigid. The non-hydrogen-atom positions were refined together with their anisotropic displacement parameters, and four collective isotropic vibrational parameters (one for the methyl- and one for the other H-atoms in each molecule) were refined for the hydrogens. Accordingly, refinement of 479 variables against 2831 reflections with $I > 3\sigma(I)$ converged to R [$= \Sigma|\Delta F|/\Sigma|F_0|$] $= 0.037$ and wR [$= \Sigma w|\Delta F|^2/\Sigma w|F_0|^2)^{1/2}$] $= 0.049$. Refinement of the final model using all the 4288 unique, non-zero reflections yielded a wR_{tot}-value of 0.053. The weights of the structure factors were assumed[22] as $w = [\sigma^2(F) + 0.000\,65F^2]^{-1}$.

Supplementary data. Lists of the refined fractional atomic coordinates and of bond distances and angles involving non-hydrogen atoms have been deposited as supplementary data at the Cambridge Crystallographic Data Centre (see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, Issue 1). Lists of the anisotropic displacement parameters of the non-hydrogen atoms and the observed and calculated structure factors are available directly from the authors (I. C.).

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