Synthesis of Perhydro-1,4-ethano-1,5-naphthyridine and Perhydro-4,7-ethanopyrrolo[3,2-*b*]pyridine Derivatives: Potential NK_1-receptor Antagonists. X-Ray Molecular Structures of (4a*R**,8*S**,8a*R**)-6-Oxo-8-phenylperhydro-1,4-ethano-1,5-naphthyridine and (4a*R**,7*R**,8*R**,8a*R**)-7,8-Diphenylperhydro-1,4-ethano-1,5-naphthyridine

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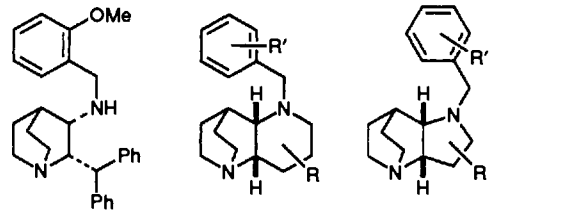
Derivatives of perhydro-1,4-ethano-1,5-naphthyridine and 4,7-ethanopyrrolo[3,2-*b*]pyridine were designed and synthesized as conformationally constrained analogues of the potent NK_1-receptor antagonist CP-96,345. 2-Benzylidenequinuclidin-3-one **1** was used as the common starting material: (i) heterocyclizations of compound **1** with *N*-(carbamoylmethyl)pyridinium chloride gave unsaturated pyridone derivatives which, after catalytic hydrogenation, afforded 1,5-naphthyridines, and (ii) functionalization of compound **1** by nucleophilic 1,4-addition reactions, followed by reductive cyclizations, gave quinuclidine derivatives with fused five- or six-membered rings. The cyclization reactions proceeded stereoselectively and the relative stereochemistries were determined by a combination of molecular mechanics calculations, X-ray crystallography, and NMR spectroscopy. The biological activities of the synthesized derivatives were evaluated by binding studies to human NK_1-receptors in UC11MG cells. The compounds had low to moderate affinity for the NK_1-receptor.

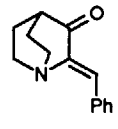
Substance P (SP) is a linear undecapeptide of the tachykinin family. It is known to be involved in several important physiological processes such as inflammation, pain transmission, and regulation of dopamine levels in the brain.[1] SP exerts its action through NK_1-receptor activation.[2] Recently, several selective non-peptide NK_1-receptor antagonists have been discovered;[3,4] *e.g.*, the quinuclidine derivative CP-96,345[3] (Fig. 1) exhibits high affinity and high selectivity for both central and peripheral NK_1-receptor binding sites. Thus, CP-96,345 represents a valuable pharmacological tool in studies of SP function.[5] Early structure–activity relationship studies of CP-96,345-analogues indicated that three structural elements were required for high affinity to the NK_1-receptor;[3c,3d] the substituted 3-benzylamino group, the quinuclidine nitrogen, and the benzhydryl group. More recently it was shown that substantial structural changes did not necessarily lead to a decreased potency; *e.g.*, the 2-(3-chlorophenyl) analogue of CP-96,345 was equipotent to the parent compound.[3j]

As part of an ongoing study on novel quinuclidine-based CP-96,345 analogues[6-8] we have produced compounds with the general structures shown in Fig. 1, in which the important substituents at C-2 and C-3 are incorporated in a fused ring. The new compounds, **7**, **8**, **10**, **22**, **23**, **24a**, **24b** and **29**, differ in the size of the fused ring, in the number of aryl groups, and in the relative stereochemistry. The biological activities were evaluated by binding studies to [^{3}H]-[Sar^9,Met(O$_2$)^{11}]SP-labelled human NK_1-receptors in UC11MG cells.



CP-96,345

Fig. 1 The potent NK_1-receptor antagonist CP-96,345 and the general structures of the compounds synthesized in this study



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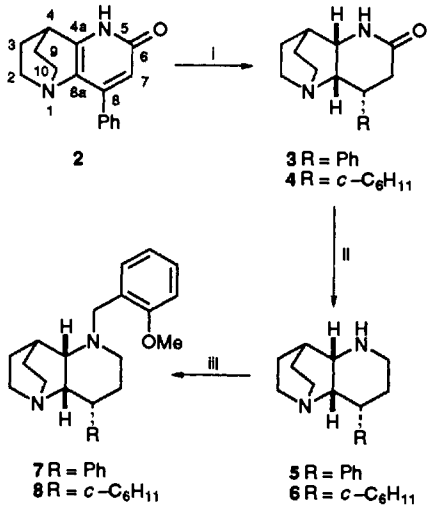
Results and Discussion

Synthesis.—2-Benzylidenequinuclidin-3-one **1**[9] was used as the key starting material in the syntheses. It contains a properly positioned phenyl substituent and exhibits a bifunctional reactivity at the electron-deficient C-3 and the vinylic β-carbon, which could be utilized in the construction of a new heterocyclic ring. Successful heterocyclizations using enone **1** or analogues thereof have been reported previously.[10-13] To promote heterocyclization of compound **1** we used *N*-(carbamoylmethyl)-pyridinium chloride†[14] which gave the desired naphthyridine derivative **2** (Scheme 1). The use of BuOH as the solvent and addition of piperidinium acetate made it possible to synthesize compound **2** in 82% yield. Compound **2** had to be reduced in order to give the desired saturated naphthyridine moiety. Since compound **2** was inert to reducing agents such as $LiAlH_4$ or Et_3SiH we attempted a catalytic hydrogenation as the first

† The activating group of this reagent (the pyridinium cation) is not transferred to the final product since it is an excellent leaving group. In contrast, reaction of compound **1** with 2-cyanothioacetamide produces a thiopyridone ring in which the cyano group is retained.[13]

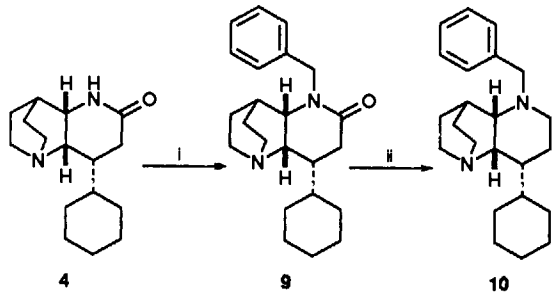
reduction step. Both palladium on charcoal and freshly prepared Raney nickel failed to catalyse the hydrogenation.[15] However, hydrogenation at 60 psi using the more active Adams catalyst (platinum oxide) in acetic acid (HOAc) efficiently reduced compound **2**. Unfortunately, these conditions affected not only the pyridone ring but also the 8-phenyl substituent, which was reduced to a cyclohexyl group. When the reaction time was long enough (2–3 days) the lactam group in substrate **2** was also reduced, to give perhydronaphthyridine **6** in up to 18–20% yield (Scheme 1). Compound **2** was not reduced



Scheme 1 *Reagents:* i, H_2, Pt; ii, $LiAlH_4$; iii, 2-methoxybenzyl chloride

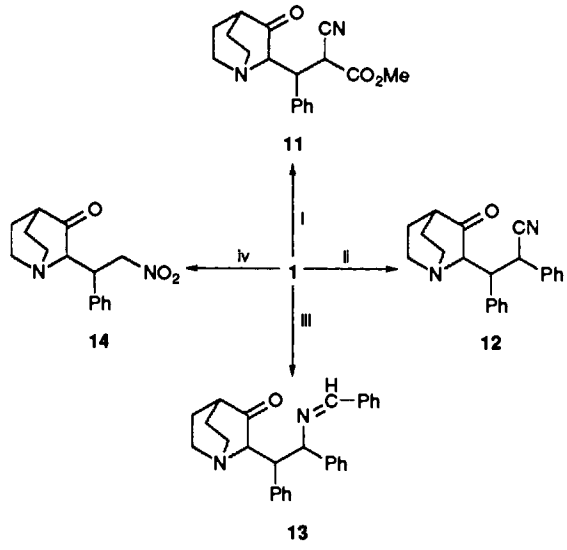
when dissolved in MeOH and the use of HOAc as solvent produced mainly the cyclohexyl product **4**.* However, the use of a MeOH–HOAc solvent mixture favoured the formation of the phenyl product **3** and gave a high yield of products **3** and **4** (85–90%). Mixtures of compounds **3** and **4** were separated by a combination of column chromatography and recrystallization but the isolated yield of pure compound **3** was never higher than 30%. Therefore we used the mixture in preparative experiments; reduction of compounds **3** and **4** with $LiAlH_4$ gave the amines **5** and **6**, and a subsequent benzylation afforded the perhydronaphthyridines **7** and **8**, respectively (Scheme 1). Compounds **7** and **8** were readily separated by column chromatography. The 8-cyclohexyl-substituted lactam derivative **4** was also benzylated to give compound **9**, which on reduction with $LiAlH_4$ afforded amine **10** (Scheme 2). All these derivatives had a *cis*-relation between 8-H and 8a-H according to NMR spectroscopy and X-ray crystallography (see below).

A different synthetic strategy was used for the syntheses of the fused quinuclidine derivatives with *trans*-positioned



Scheme 2 *Reagents:* i, $PhCH_2Cl$, NaOMe; ii, $LiAlH_4$

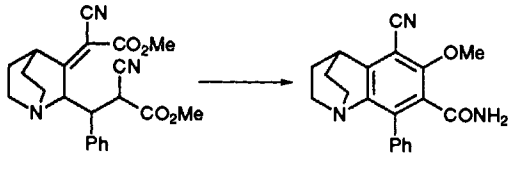
hydrogens on C-8 and C-8a. Starting materials were produced by Michael-type 1,4-addition reactions of enone **1** in alkaline media[16] (Scheme 3). The adducts **11**–**14** were produced in yields



Scheme 3 *Reagents:* i, $NCCH_2CO_2Me$, NaOMe; ii, $PhCH_2CN$, BuLi; iii, $PhCH_2N{=}CHPh$, NaOH; iv, $MeNO_2$, NaOMe

varying from 25% when using methyl cyanoacetate to 70% when using phenylacetonitrile (Scheme 3). Hence, the yields appear to increase with increasing nucleophilicity (basicity) of the attacking anion.

Compound **1** was not completely converted into the desired products even if an excess of the nucleophile was used in the 1,4-addition reactions. The moderate yields may be due to the relatively low reactivity at the electropositive benzylidene atom of substrate **1**[17] and competing 1,2-addition reactions. This is exemplified by the formation of diester **15** as a by-product in the reaction of enone **1** with methyl cyanoacetate (Scheme 4) and

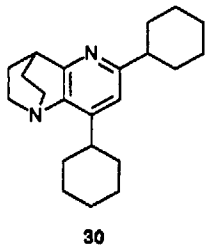


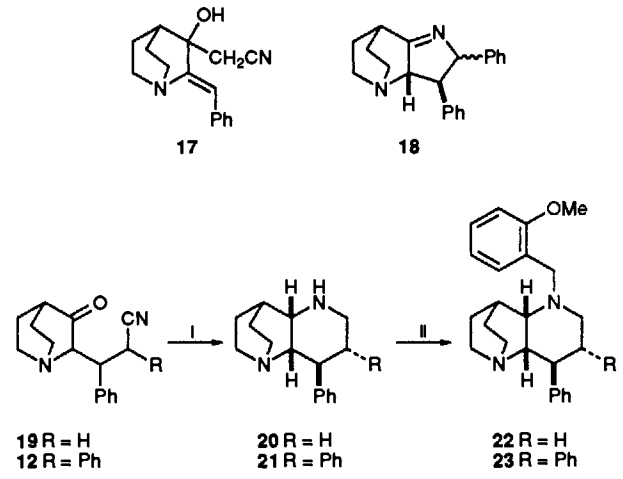
Scheme 4 *Reagent:* HCl

in the smooth conversion of enone **1** into the 3-(cyanomethyl)quinuclidin-3-ol derivative **17** on reaction with the anion of acetonitrile. Compound **15** was conveniently cyclized by treatment with acid to the polysubstituted benzene derivative **16** (Scheme 4).

The reaction of enone **1** with benzylidenebenzylamine was

* The same reaction conditions (PtO_2/HOAc) applied to 6,8-diphenyl-3,4-dihydro-2*H*-1,4-ethano-1,5-naphthyridine[10] resulted in formation of 6,8-dicyclohexyl-3,4-dihydro-2*H*-1,4-ethano-1,5-naphthyridine **30** as the main product (see the Experimental section).

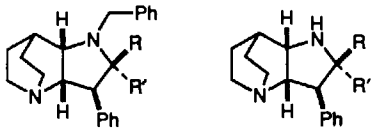




Scheme 5 *Reagents:* i, H_2/Ni(Ra); ii, 2-methoxybenzyl chloride

accomplished using phase-transfer conditions which prevent solvolysis of the reagent.[18] However, some hydrolytic cleavage of the imino group occurred in the adduct **13**. This was verified by the isolation of the by-product **18**, which is formed by an intramolecular amination of C-3.

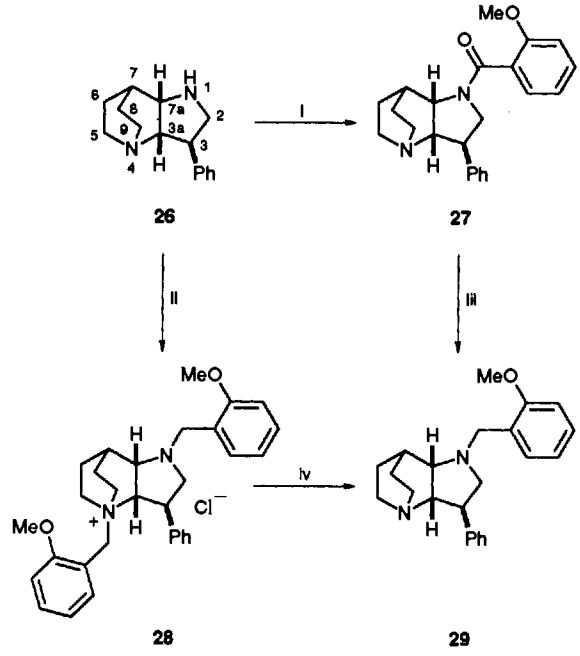
All the Michael adducts derived from enone **1** gave mixtures of diastereoisomers. Typically, a 1 : 1 ratio of two isomers was observed. In contrast, all four isomers of cyanoacetate adduct **11** were observed by GLC, but these formed two diastereoisomers after chromatography on silica gel. After work-up of nitrile **12** two diastereoisomers were observed but equilibration in methanolic sodium methoxide afforded only the thermodynamically more stable isomer. The epimeric mixtures of adducts **12–14**, and **19** (Scheme 5; obtained by hydrolysis and decarboxylation of cyano ester **11** in refluxing 0.5% hydrochloric acid) were used directly in subsequent reductive cyclizations.



24a R = H, R' = Ph
24b R = Ph, R' = H
25a R = H, R' = Ph
25b R = Ph, R' = H

γ-Cyano ketones have been converted into piperidine derivatives by using catalytic hydrogenation on Pd,[19] Pt,[20] Raney Co[21] or Ni,[22] or $LiAlH_4$ in glyme.[23] Also, a nitro group has been selectively reduced in the presence of a carbonyl group by titanium(II) reagents.[24] However, in our hands, the best selectivities and yields in the cyclization of compounds **12**, **14** and **19** were achieved using freshly prepared Raney nickel in propan-2-ol (Scheme 5).[25] The diastereoisomeric mixtures of **12**, **14** and **19** surprisingly gave only one diastereoisomer of the cyclized products (**21**, **26** and **20**, respectively). Compound **13** reacted slowly under the above reaction conditions but cyclized smoothly in the presence of sodium cyanoboranuide ($NaCNBH_3$)[26] to a mixture of two isomers, **24a** and **24b**, in a total yield of 84%. These isomers were separated by column chromatography. Compound **18** was similarly reduced with $NaCNBH_3$ to a 1 : 1 mixture of the two C-2 isomers **25a** and **25b**.

Benzylation of N-5 in the perhydronaphthyridines **5**, **6** (Scheme 1), **20** and **21** (Scheme 5), proceeded smoothly using an excess of 2-methoxybenzyl chloride in dichloromethane at ambient temperature. The addition of triethylamine increased the rate and the yield of the reaction. It is noteworthy that the highly basic quinuclidine nitrogen was not benzylated.* This is probably due to steric hindrance by the C-8 substituent. In contrast, the fused pyrrolidine derivative **26** was benzylated at both nitrogens, to yield the salt **28**, even when less than 1 mole equivalent of 2-methoxybenzyl chloride was used (Scheme 6). A comparison of energy-minimized (MM2)† low-energy conformers of compounds **26** and **5**, **6**, **20** and **21** revealed less steric shielding of the quinuclidine nitrogen by the substituent in the fused five-membered ring than in the corresponding six-membered ring analogues. The more labile N^4–benzyl bond in the salt **28** could be selectively cleaved by treatment with piperidine at elevated temperature or catalytically (H_2/Pd) to yield compound **29**. Alternatively, compound **29** was synthesized *via* benzoylation of substrate **26**, to afford the amide **27**, which was subsequently reduced to amine **29** (Scheme 6).



Scheme 6 *Reagents:* i, 2-methoxybenzoyl chloride; ii, 2-methoxybenzyl chloride; iii, $LiAlH_4$; iv, H_2/Pd or piperidine

Stereochemical Assignments.—The relative stereochemistries of the final products were determined by a combination of molecular mechanics calculations, X-ray data, and NMR data using a modified Karplus equation.[27]

The cyclizations involving a reductive amination were performed using diastereoisomeric mixtures as starting materials. However, the reactions produced only one diastereoisomer. Protons 4a-H and 8a-H (3a-H and 7a-H) were *cis*-related in all products regardless of whether a six- or five-membered ring was formed. This was demonstrated by NMR experiments showing nuclear Overhauser effects (NOEs) between 4a-H and 8a-H (3a-H and 7a-H). Further, molecular mechanics calculations (MM2) gave a higher relative steric energy for the *trans*- as compared with the *cis*-derivatives (ΔE_s > 10 kJ mol^{-1} in the perhydronaphthyridine series and ΔE_s > 60 kJ mol^{-1} for the perhydropyrrolopyridines).

* Derivatives of CP-96,345 alkylated on the quinuclidine nitrogen have been synthesized, but prolonged reaction times in refluxing ethanol and an excess of the alkylating agent were needed.[3k]

† The conformational analyses were performed using the MM2 force field as included in the MacMimic program (v. 1.0.3). The MacMimic program can be obtained from InStar Software, IDEON Research Park, S-223 70 Lund, Sweden.

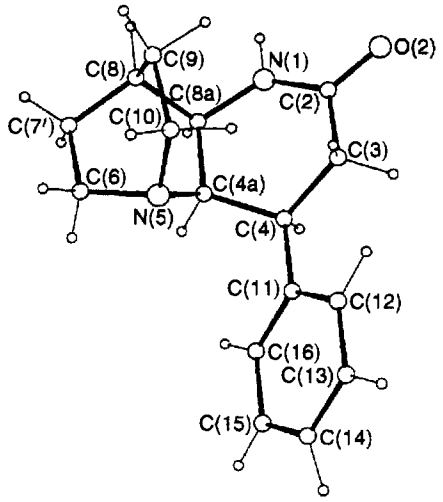


Fig. 2 Perspective view of compound **3** with the crystallographic labelling of the atoms

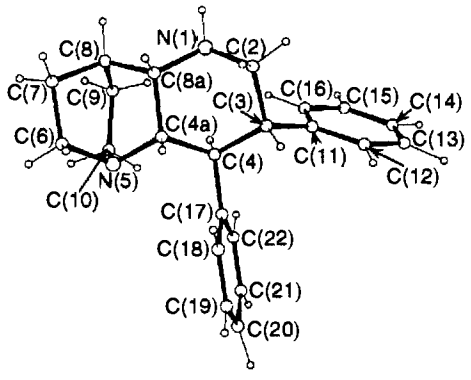


Fig. 3 Perspective view of compound **21** with the crystallographic labelling of the atoms

Table 1 Effects of compounds **23** and **29** upon the specific binding of [^{3}H]-[Sar^9,Met(O$_2$)^{11}]SP to the NK$_1$-receptor in intact human UC11MG astrocytoma cells[a]

Compound	Specific binding (% of control) at 0.01 μmol dm^{-3}	0.1 μmol dm^{-3}	1 μmol dm^{-3}
23·2HCl (N = 3)[b]	98 ± 1	70 ± 8	14 ± 8
29·HCl (N = 4)	104 ± 6	84 ± 2	42 ± 3

[a] Data are means ± S.E.M; each compound was tested using a ligand concentration between 0.62–1.19 nmol dm^{-3}. (±)-CP-96,345 was used as a positive control in each experiment (N = 7), and gave specific binding values (% of control) of 49 ± 6 and 24 ± 3% at 1 and 3 nmol dm^{-3}, respectively. [b] N = number of experiments.

The relative configurations at C-8 and C-8a in the piperidine moiety in compound **3** and at C-7, C-8 and C-8a in compound **21** were determined by X-ray crystallographic analysis (Figs. 2 and 3). This was especially important in compound **21** since it was impossible to assign the structure solely from coupling constants in ^{1}H NMR spectra because several signals overlapped. In contrast, NOE experiments on lactam **3** showed that 4a-H, 8-H and 8a-H were positioned on the same face of the piperidone ring. In the X-ray analyses the observed bond distances and bond angles generally conformed to expected values. The piperidone ring of compound **3** adopts a flattened half-boat conformation with the phenyl group equatorially positioned. In compound **21**, the piperidine ring adopts a strongly distorted half-chair conformation with the two phenyl groups pseudo equatorially positioned.

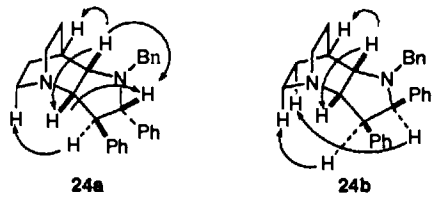


Fig. 4 Observed NOE correlations used in the determination of the relative stereochemistries of epimers **24a** and **24b**

A product structurally related to compound **5** was expected to be formed in the cyclization of nitrile **19** (Scheme 5). Since the product **20** gave (i) the same molecular ion as compound **5**, (ii) similar, yet distinctly different, NMR spectra as compared with compound **5**, and (iii) different physicochemical properties, it was formulated as a diastereoisomer in which 8-H and 8a-H adopt a *trans*-relationship.

The *trans*-stereochemistry of 3-H and 3a-H in the ring homologue **26** was evident since no NOE was observed between these two protons.

A complete assignment of the relative stereochemistries in the derivatives **24a** and **24b** was performed by a detailed investigation of NOEs throughout the molecules (Fig. 4). The studies indicated a stereochemical difference only at C-2.

Factors influencing the Observed Stereoselectivities.—Catalytic hydrogenation of the highly substituted double bonds in naphthyridone **2** may be hampered by the presence of the C-8 phenyl group and the sterically rigid quinuclidine fragment. The *cis*-stereoselectivity observed in the reduction of the pyridone moiety is not unexpected since a heteroaromatic ring is believed to remain adsorbed on the catalyst surface until complete hydrogenation has occurred.[28] Thus, a mixture of products **3** and **4** was obtained with the phenyl or cyclohexyl substituents assuming *endo*-positions.

The use of diastereoisomeric mixtures as starting materials in the Raney nickel-catalysed cyclizations of substrates **12**, **14** and **19** resulted in only one diastereoisomer of the product. The relatively high acidity of 2-H in compounds **12**, **14** and **19** might be responsible for a rapid epimerization on the alkaline surface of the catalyst. The corresponding proton exchange is not expected to be equally efficient in the intermediate cyclic imines due to the weaker electron-accepting ability of the imino group and the increased rigidity of the cyclic systems. Therefore, we suppose that the cyclization step in the stereospecific reactions affording products **20**, **21** and **26** is kinetically controlled, favouring the epimer giving a cyclic product with the substituents at C-8 and C-8a (C-3 and C-3a) in a *trans*-orientation. Reduction of the imines resulted in a *cis*-relationship between 4a-H and 8a-H (3a-H and 7a-H) probably due to steric interactions between the catalyst and the quinuclidine nucleus.* The weaker electron-accepting ability of imines is also apparent in the cyclization of ketone **13** with $NaCNBH_3$ since it produced a C-2 diastereoisomeric mixture of products (**24a** and **24b**).

Test Results.—The affinities for the human NK$_1$-receptor were assessed by determining the effects of the compounds on the specific binding of [^{3}H]-[Sar^9,Met(O$_2$)^{11}]SP to intact human UC11MG astrocytoma cells, which have been shown

* It is noteworthy that the related reductive cyclization of 2-(α-cyanobenzyl)cyclohexanone gives the cyclic perhydroindole with a *trans*-relationship between the corresponding hydrogens.[25]

previously to express high densities of NK_1-receptors coupled to the phosphoinositide signal transduction system.[29-32] As a positive control, the potent antagonist (±)-CP-96,345[5] was included.

The majority of the compounds tested had a low affinity for the NK_1-receptor at the concentrations tested (< 20% inhibition at 1 μmol dm^{-3}). The only active compounds, **23** and **29**, appeared to be moderately potent NK_1-receptor antagonists, producing 86 and 58% inhibition at 1 μmol dm^{-3}, respectively (Table 1). However, these derivatives were considerably less active than (±)-CP-96,345, which produced 51 and 76% inhibition at 1 and 3 nmol dm^{-3}, respectively, a finding in agreement with previous studies using this cell line.[31,32]

Conclusions.—We have synthesized conformationally constrained analogues of CP-96,345 by efficient and stereoselective reactions. Although the new compounds did not show high NK_1-receptor affinities, the synthetic methods presented herein should be useful in the development of other derivatives of potential interest as NK_1-receptor antagonists.

Experimental

Chemistry.—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 NMR spectrometer for solutions in $CDCl_3$ (if not otherwise stated) and the chemical shifts were determined relative to tetramethylsilane. *J*-Values are given in Hz. The numbering of the atoms of the naphthyridine derivatives is given in Scheme 1 and that of the pyrrolopyridines in Scheme 6. The IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer (KBr tablets). Mass spectral data together with GLC data were obtained with a combined Hewlett-Packard GC(5890)-MS(5791) unit. The reaction mixtures were monitored by TLC on aluminium sheets precoated with silica gel ($60F_{254}$, E. Merck) or with alumina, using 10% or 2% MeOH in CH_2Cl_2 as eluent, respectively. Elemental analyses were performed by MikroKemi AB, Uppsala, Sweden. Compound **1** was obtained from Astra Pain Control AB and 6,8-diphenyl-1,2,3,4-tetrahydro-1,4-ethano-1,5-naphthyridine was synthesized from compound **1** according to the method of Madhav.[10] Extracts were dried over $MgSO_4$. pH Values were measured with litmus paper.

Receptor-binding Tests.—Methods and materials. UC11MG cells were obtained from Dr. Carl Johnson, University of Cincinnati, and were used between passage numbers 7 and 10 after arrival at Astra (each time the cells are split into a new growth medium is called one passage). [^{3}H]-[Sar^9, Met$(O_2)^{11}$]SP (specific activity 42 Ci $mmol^{-1}$) was obtained from NEN (Du Pont Scandinavia AB, Biotechnology Systems Division, Stockholm, Sweden). Physalaemin was obtained from Peninsula Laboratories Europe Ltd., St. Helens, UK, and was dissolved in 10 mmol dm^{-3} acetic acid to a stock solution of 1 mmol dm^{-3}. (±)-CP-96,345 [(±)-*cis*-2-diphenylmethyl-3-(2-methoxybenzylamine)quinuclidine dihydrochloride][3a] was synthesized at Astra Pain Control AB and was dissolved in distilled water to give a stock solution of 1 mmol dm^{-3}. RPMI 1640 cell culture media, together with foetal calf serum and glutamine were obtained from Gibco, Paisley, UK. Penicillin G and streptomycin were obtained from Astra and the Sigma Chemical Co., respectively. The test compounds were dissolved in dimethyl sulfoxide at a stock solution of 10 mmol dm^{-3}.

[^{3}H]-[*Sar*^{9},*Met*$(O_2)^{11}$]*SP-binding assay.* The binding of [^{3}H]-[Sar^9,Met$(O_2)^{11}$]SP to intact UC11MG cells was undertaken as described previously.[31,32] Briefly, UC11MG cells were cultured in 75 cm^2 flasks in RPMI 1640 medium supplemented with 10% foetal calf serum, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid HEPES (10 mmol dm^{-3}, pH 7.35), penicillin G (50 U cm^{-3}) and streptomycin (50 μg cm^{-3}). The cells were plated out onto 24-well culture plates 2–4 days before assay at a cell density of 34 000–50 000 cells/well. Upon assay, the wells were rinsed with 0.5 cm^3 ice-cold assay buffer (phosphate-buffered saline, 10 mg cm^{-3} bovine serum albumin, 1.8 mmol dm^{-3} $CaCl_2$ + 0.81 mmol dm^{-3} $MgSO_4$). Test compounds and radioligand (both dissolved in the assay buffer) were added to the wells and incubated at 4 °C for 2 h. The assay volume was 0.5 cm^3. Physalaemin (1 μmol dm^{-3}) was used to define non-specific binding. After incubation, the wells were washed three times with 0.5 cm^3 of ice-cold assay buffer. Bound [^{3}H]-[Sar^9,Met$(O_2)^{11}$]SP was removed by addition of 0.2 mol dm^{-3} NaOH (0.5 cm^3) and incubation at 65–75 °C for 15 min. Aliquots were then counted (d.p.m.) by liquid scintillation spectroscopy.

General Procedure for Reductive Cyclization with Raney Nickel.—Freshly prepared Raney nickel (3–5-fold molar excess) was added to a solution of the substrate (**12**, **14** or **19**) in propan-2-ol. The mixture was hydrogenated in a Parr apparatus at 60 psi for 48 h. The catalyst was removed by filtration and the solution was concentrated under reduced pressure. The residue was purified on silica gel, using a gradient of 20–50% MeOH in $CHCl_3$ as eluent, or on alumina, using a gradient of 0–5% MeOH in EtOAc as eluent. Analytical samples were obtained by conversion of the oily bases into crystalline hydrochloride salts by addition of ethereal HCl.

General Procedure for Benzylation with Benzyl Chloride and 2-Methoxybenzyl Chloride.—The quinuclidine derivative (**5**, **6**, **20**, **21** or **26**) (0.5 mmol), benzyl chloride (or 2-methoxybenzyl chloride) (1.0 mmol) and triethylamine (0.07 cm^3, 0.5 mmol) were mixed in CH_2Cl_2 (15 cm^3) and kept at ambient temperature for 8–10 h. The clear solution was washed successively with 0.5 mol dm^{-3} NaOH (10 cm^3) and water (15 cm^3) and the organic phase was dried, filtered, and concentrated. The residue was purified by column chromatography on either silica gel, using a gradient of 5–10% MeOH in $CHCl_3$ as eluent, or on alumina, using a gradient of 30–60% EtOAc in hexane as eluent, to give the desired products as oily bases or crystalline hydrochlorides.

6-*Oxo*-8-*phenyl*-3,4,5,6-*tetrahydro*-2H-1,4-*ethano*-1,5-*naphthyridine* **2**.—A stirred mixture of 2-benzylidenequinuclidin-3-one **1** (3.0 g, 14.1 mmol) and *N*-(carbamoylmethyl)pyridinium chloride (7.3 g, 42.3 mmol) in butan-1-ol (100 cm^3) containing piperidine (5 cm^3) and HOAc (3 cm^3) was heated at 115–120 °C for 18 h. After cooling, the solution was concentrated under reduced pressure and the residue was partitioned between 5% MeOH in $CHCl_3$ (2 × 150 cm^3) and water. The organic phase was concentrated to leave a crystalline residue, which was recrystallized from MeOH to give *title compound* **2** (2.91 g, 82%); m.p. 285–287 °C; ν_{max}/cm^{-1} 3000–2300 (NH) and 1640 (C=O); δ_H 1.55–2.2 (5 H, m, 3- and 9-H_2, NH), 2.45–3.5 (5 H, m, 2- and 10-H_2 and 8-H), 6.47 (1 H, s, 7-H) and 7.38–7.6 (5 H, m, Ph); δ_C 22.9, 29.3 (C-3, -4, -9), 53.8 (C-2 and -10), 116.2, 122.1, 127.8, 130.2, 130.4 and 132.2 (C-7 and -8, and Ph), 148.6 and 151.5 (C-4a, -8a) and 162.8 (C-6). An analytical sample was obtained by conversion of the base into the *hydrochloride salt* using ethereal HCl (m.p. 241 °C) (Found: C, 66.3; H, 6.0; N, 9.7. $C_{16}H_{16}N_2O \cdot HCl$ requires C, 66.6; H, 5.9; N, 9.7%).

(4aR*,8S*,8aR*)-6-*Oxo*-8-*phenylperhydro*-1,4-*ethano*-1,5-*naphthyridine* **3**.—A mixture of compound **2** (0.10 g, 4.0 mmol) and platinum dioxide hydrate (79–84% Pt content) (70 mg) in

3% HOAc in MeOH (50 cm^3) was hydrogenated in a Parr apparatus at 60 psi for 20 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. GLC of the reaction mixture showed the presence of compounds **3** and **4** in a 2:1 ratio. Column chromatography using a gradient of 5–10% MeOH in $CHCl_3$ as eluent afforded compounds **3** (0.18 g, 18%), **4** (0.11 g, 11%) and a mixed fraction (0.46 g, 45%). Since compound **3** showed less solubility in diethyl ether compared with compound **4** the mixed solid from the fraction was triturated several times with hot diethyl ether to give an additional amount of pure *compound* **3** (0.11 g, 11%); m.p. 227–228 °C; δ_H 1.30–1.90 (4 H, m, 3- and 9-H_2), 2.00–2.04 (1 H, m, 4-H), 2.61–2.80 (4 H, m, 2- and 10-H_2), 2.92–3.11 (2 H, m, 7-H_2), 3.23 (1 H, dd, J_1 6.1, J_2 8.8, 8a-H), 3.4 (1 H, m, 8-H), 3.81 (1 H, dd, J_1 4.4, J_2 8.8, 4a-H), 7.04 (1 H, br s, NH) and 7.21–7.42 (5 H, m, Ph); δ_C 19.3, 24.5 (C-3, -9), 28.6 (C-4), 33.6 (C-7), 41.2 (C-8), 44.8 and 51.5 (C-2, -10), 53.3 (C-4a), 55.6 (C-8a), 126.7, 127.7, 128.3 and 140.5 (Ph) and 172.6 (C-6); *m/z* 256 (M^+, 100%) (Found: C, 73.0; H, 7.8; N, 10.5. $C_{16}H_{20}N_2O \cdot \frac{1}{2}H_2O$ requires C, 72.5; H, 7.9; N, 10.6%).

(4aR*,8S*,8aR*)-8-*Cyclohexyl*-6-*oxoperhydro*-1,4-*ethano*-1,5-*naphthyridine* **4**.—Compound **4** was synthesized from compound **2** as described for compound **3** except that glacial HOAc (50 cm^3) was used as solvent and the reaction time was 8 h. Purification on silica gel gave pure *title compound* **4** (0.78 g, 75%); m.p. 201–202 °C; ν_{max}/cm^{-1} 3200 (NH) and 1650 (C=O); δ_H 0.80–2.00 (17 H, m, 3- and 9-H_2, 4- and 8-H, and cyclohexyl), 2.26 (1 H, dd, J_1 13.5, J −18.2, 7-H^a), 2.56 (1 H, dd, J_1 6.0, J_2 −18.2, 7-H^b), 2.70–2.90 (4 H, m, 2- and 10-H_2), 3.11 (1 H, dd, J_1 5.9, J_2 8.3, 8a-H), 3.66 (1 H, dd, J_1 4.7, J_2 8.3, 4a-H) and 6.75 (1 H, br s, NH); δ_C($CDCl_3$) 19.4, 24.6, 25.9, 26.0, 26.5, 28.4, 30.5, 30.8, 32.5 and 37.9 (C-3, -4, -8, -9 and cyclohexyl), 40.6, 44.9, 50.9, 51.1 and 52.9 (C-2, -4a, -7, -8a and -10) and 172.9 (C-6); *m/z* 262 (M^+, 29%) and 82 (100) (Found: C, 72.7; H, 9.9; N, 10.4. $C_{16}H_{26}N_2O$ requires C, 73.2; H, 10.0; N, 10.7%).

(4aR*,8S*,8aR*)-8-*Phenylperhydro*-1,4-*ethano*-1,5-*naphthyridine* **5**.—Compound **3** (0.20 g, 0.78 mmol) was added in portions to a stirred solution of $LiAlH_4$ (74 mg, 1.95 mmol) in tetrahydrofuran (THF) (20 cm^3), kept under N_2. The mixture was refluxed for 5 h. Water (20 cm^{-3}) was carefully added at 5 °C, and the layers were separated. The aqueous phase was extracted with diethyl ether (20 cm^3) and the combined organic phases were dried, filtered, and concentrated under reduced pressure. Purification on alumina, using a gradient of 0–4% MeOH in EtOAc as eluent, gave pure *amine* **5** as an oil (0.14 g, 75%); δ_H 1.20–2.20 (8 H, m, 3-, 7- and 9-H_2, 4-H and NH), 2.50–3.30 (9 H, m, 2-, 6- and 10-H_2 and 4a- 8- and 8a-H) and 7.15–7.38 (5 H, m, Ph); δ_C 20.8, 25.5, 28.7 and 29.3 (C-3, -4, -7 and -9), 45.2, 45.4, 45.8, 50.9, 54.4 and 57.3 (C-2, -4a, -6, -7, -8 and -8a) and 125.7, 127.1, 127.6, 127.8 and 129.2 (Ph); *m/z* 242 (M^+, 54%) and 97 (100) (Found: C, 55.9; H, 7.7; N, 8.3. $C_{16}H_{22}N_2 \cdot 2\,HCl \cdot 1.5\,H_2O$ requires C, 56.1; H, 7.9; N, 8.2%).

(4aR*,8S*,8aR*)-8-*Cyclohexylperhydro*-1,4-*ethano*-1,5-*naphthyridine* **6**.—Compound **6** was synthesized from lactam **4** (0.20 g, 0.76 mmol) as described above for the synthesis of amine **5**. After chromatographic purification the product was recrystallized from water–ethanol (5:1) to give pure *title compound* **6** (0.14 g, 72%); m.p. 91–92 °C; δ_H 0.80–1.90 (20 H, m, 3-, 7- and 9-H_2, 4- and 8-H, NH and cyclohexyl) and 2.51–3.22 (8 H, m, 2-, 6- and 10-H_2, and 4a- and 8a-H); δ_C 21.1, 25.6, 26.0, 26.2, 26.8, 27.7, 28.4, 30.6, 31.3, 37.9 and 44.8 (C-3, -4, -7, -8, -9 and cyclohexyl) and 45.5, 45.6, 50.4, 53.5 and 54.4 (C-2, -4a, -6, -8a and -10); *m/z* 248 (M^+, 45%) and 82 (100) (Found: C, 77.1; H, 11.6; N, 11.1. $C_{16}H_{28}N_2$ requires C, 77.4; H, 11.3; N, 11.3%).

(4aR*,8S*,8aR*)-5-(2-*Methoxybenzyl*)-8-*phenylperhydro*-1,4-*ethano*-1,5-*naphthyridine* **7**.—Compound **7** was synthesized from compound **5** (0.12 mg, 0.5 mmol) according to the general procedure in 72% yield (0.13 g); m.p. 145–148 °C (monohydrochloride); δ_H(10% C_6D_6 in $CDCl_3$) 1.10–1.25 and 1.52–1.71 (4 H, m, 3- and 9-H_2), 1.95–2.08 (2 H, m, 6- and 7-H^a), 2.13–2.27 (2 H, m, 4-H and 7-H^b), 2.50–2.61 (3 H, m, 4a-H and 10-H_2), 2.62–2.73 (1 H, m, 2-H^a), 2.79–2.84 (1 H, m, 8-H), 2.96 (1 H, dd, J_1 6.7, J_2 7.1, 8a-H), 3.06 (1 H, m, 6-H^b), 3.34 and 3.9 (2 H, 2 d, J −14.5, CH_2Ph), 3.35–3.41 (1 H, m, 2-H^b), 3.7 (3 H, s, OMe) and 6.81–7.48 (9 H, m , ArH); δ_C 21.0, 24.7, 26.8 and 28.2 (C-3, -4, -7 and C-9), 46.0, 46.1, 51.0, 51.7, 52.5, 54.9, 58.5 and 60.7 (C-2, -4a, -6, -8, -8a and -10, OMe and CH_2Ph) and 110.1, 120.4, 125.8, 127.3, 127.4, 127.7, 127.8, 127.9, 128.1, 129.2, 144.2 and 157.7 (ArC); *m/z* 362 (M^+, 63%) and 241 (100) (Found: C, 69.0; H, 8.1; N, 6.8. $C_{24}H_{30}NO \cdot HCl \cdot H_2O$ requires C, 69.1; H, 7.9; N, 6.7%).

(4aR*,8S*,8aR*)-8-*Cyclohexyl*-5-(2-*methoxybenzyl*)*perhydro*-1,4-*ethano*-1,5-*naphthyridine* **8**.—*Compound* **8** was synthesized from substrate **6** (0.12 g, 0.50 mmol) according to the general procedure, in 68% yield (0.12 g); m.p. 223–225 °C (monohydrochloride); δ_H(10% C_6D_6 in $CDCl_3$) 0.75–2.20 (18 H, m, 3-, 7- and 9-H_2, 8-H and cyclohexyl), 2.27–2.34 (1 H, m, 4-H), 2.35–2.42 (1 H, dd, $J_1 = J_2 = 5.6$, 4a-H), 2.83–2.92 (1 H, m, 6-H^a), 3.03 (1 H, dd, $J_1 = J_2 = 5.6$, 8a-H), 3.08–3.22 (2 H, m, 6-H^b and 2-H^a), 3.18 and 3.71 (2 H, d, CH_2Ar), 3.42–3.57 (3 H, m, 2-H^b and 10-H_2), 3.61 (3 H, s, OMe), 6.80–7.35 (4 H, m, Ph) and 10.3 (1 H, br s, NH); δ_C(10% C_6D_6 in $CDCl_3$) 18.3, 21.3, 24.9, 25.0, 25.5, 25.8, 26.2, 30.9, 31.9 (C-3, -4, -7, -8, -9 and cyclohexyl), 36.0, 44.3, 46.7, 50.9, 52.6, 55.1 and 58.3 (C-2, -4a, -6, -8a, -10, OMe and CH_2Ar) and 110.5, 120.5, 125.0, 128.5, 129.9 and 157.7 (ArC); *m/z* 368 (M^+, 66%) and 247 (100) (Found: C, 69.8; H, 9.1; N, 6.8. $C_{24}H_{36}N_2O \cdot HCl \cdot \frac{1}{2}H_2O$ requires C, 69.6; H, 9.3; N, 6.8%).

(4aR*,8S*,8aR*)-5-*Benzyl*-8-*cyclohexyl*-6-*oxoperhydro*-1,4-*ethano*-1,5-*naphthyridine* **9**.—A mixture of lactam **4** (0.20 g, 0.76 mmol), benzyl chloride (0.23 cm^3, 1.91 mmol) and sodium methoxide (82 mg, 1.52 mmol) in dry DMF (10 cm^3) was stirred for 48 h at ambient temperature. Water (20 cm^3) was added, and the solution was concentrated. The residue was partitioned between dichloromethane (2 × 30 cm^3) and water (30 cm^3). The organic layer was dried and filtered. After concentration under reduced pressure the residue was purified on silica gel, with a gradient of 30–50% EtOAc in hexane as eluent, to afford *title compound* **9** (0.11 g, 42%); m.p. 133–134 °C; ν_{max}/cm^{-1} 1640 (C=O); δ_H 0.81–1.91 (16 H, m, 3- and 9-H_2, 8-H and cyclohexyl), 2.10–2.17 (1 H, m, 4-H), 2.38 (1 H, dd, J_1 13.5, J_2 −17.7, 7-H^a), 2.70–2.82 (4 H, m, 2- and 10-H_2), 2.87–3.03 (1 H, m, 7-H^b), 3.08 (1 H, m, J_1 5.1, J_2 9.2, 4a-H), 3.38 (1 H, ddd, J_1 1.1, J_2 7.1, J_3 9.2, 8a-H), 3.81 and 5.60 (2 H, 2 d, CH_2Ph) and 7.20–7.40 (5 H, m, Ph); δ_C 19.1, 24.8, 24.9, 26.0, 26.1, 26.5, 30.6, 30.8 and 33.5 (C-3, -7, -9 and cyclohexyl), 37.7 and 40.6 (C-4 and -8), 45.2 and 46.3 (C-2 and -10), 51.4 (CH_2Ph), 52.6 and 56.3 (C-4a and -8a), 127.3, 128.0, 128.6 and 137.1 (Ph) and 171.1 (C-6); *m/z* 352 (M^+, 40%) and 91 (100) (Found: C, 78.3; H, 9.5; N, 8.2. $C_{23}H_{32}N_2O$ requires C, 78.4; H, 9.2; N, 8.0%).

(4aR*,8S*,8aR*)-5-*Benzyl*-4-*cyclohexylperhydro*-1,4-*ethano*-1,5-*naphthyridine* **10**.—*Compound* **10** was synthesized from lactam **9** (0.18 g, 0.5 mmol) as described above for the synthesis of compound **5**, in 59% yield (0.10 g); δ_H 0.8–1.9 (18 H, m, 3-, 7- and 9-H_2, 8-H and cyclohexyl), 2.0–2.11 (1 H, m, 6-H^a), 2.22–2.28 (1 H, m, 4-H), 2.36–2.42 (1 H, m, 4a-H), 2.68–2.93 (5 H, m, 8a-H and 2-and 10-H_2), 3.00 and 4.08 (2 H, 2 d, CH_2Ph), 3.25–3.35 (1 H, m, 6-H^b) and 7.20–7.40 (5 H, m, Ph); δ_C 21.2, 25.0, 26.1, 26.2, 26.4, 26.7, 26.8, 30.7, 31.4 and 37.7 (C-3, -4, -7, -9 and

cyclohexyl), 45.3 (C-8), 46.2, 50.7, 51.6 and 59.0 (C-2, -6, -10 and CH_2Ph), 54.6 and 61.7 (C-4a and -8a) and 126.5, 128.1, 128.5 and 132.9 (Ph); *m/z* 338 (M^+, 55%) and 247 (100) (Found: C, 80.4; H, 10.3; N, 8.0. $C_{23}H_{34}N_2 \cdot \frac{1}{4}H_2O$ requires C, 80.6; H, 10.1; N, 8.2%).

Methyl 2-Cyano-3-(3-oxoquinuclidin-2-yl)-3-phenylpropanoate **11** *and Methyl 2-Cyano-3-{3-[cyano(methoxycarbonyl)methylene]quinuclidin-2-yl}-3-phenylpropanoate* **15**.—Methyl cyanoacetate (0.83 cm^3, 9.4 mmol) was added to a solution of enone **1** (1.00 g, 4.7 mmol) and sodium methoxide (0.25 g, 4.7 mmol) in MeOH (20 cm^3). The mixture was stirred for 3 h at 55–60 °C and then cooled to room temperature, an equal volume of water was added, and the methanol was evaporated off under reduced pressure. The aqueous solution (50 cm^3; pH 7–8) was extracted with $CHCl_3$ (3 × 50 cm^3). The extract was dried and concentrated to give an oil, which was triturated with propan-2-ol for 20 h at 0 °C. Concentration under reduced pressure and purification on silica gel, with a gradient of 2–4% MeOH in $CHCl_3$ as eluent, yielded keto ester **11** as a yellow oil (0.37 g, 25%), contaminated with 4% of impurities according to GLC; ν_{max}/cm^{-1} 2240 and 2200 (CN) and 1745–1725 (C=O); *m/z* 284 and 284 (M^+ − CO, 100%) and 225 (68); δ_H 1.85–2.05 (4 H, m, quin 5- and 8-H_2), 2.26–2.31 and 2.41–2.46 (1 H, m, quin 4-H), 2.50–3.05 (5 H, m, 3-H and quin 6- and 7-H_2), 3.48 and 3.50 (3 H, 2 s, OMe), 4.05 and 4.37 (1 H, d, quin 2-H), 4.95 and 4.98 (1 H, 2 d, 2-H) and 7.20–7.35 (5 H, m, Ph). The crude solution was used without further purification.

Continued elution of the column with a gradient of 10–15% MeOH in $CHCl_3$ gave diester **15** (10–15%) as a powder, consisting of mostly one epimer according to NMR analysis; δ_H 1.3–1.8 (4 H, m, quin 5- and 8-H_2), 2.28–2.33 (1 H, m, quin 4-H), 2.6–3.15 (4 H, m, quin 6- and 7-H_2), 3.13 (1 H, m, 3-H), 3.16 and 3.54 (6 H, 2 s, OMe), 4.07 (1 H, d, *J* 0.8, quin 2-H), 6.35 (1 H, app br s, 2-H) and 7.1–7.27 (5 H, m, Ph).

3-(3-Oxoquinuclidin-2-yl)-1,2-diphenylpropanonitrile **12**.—Compound **1** (2.13 g, 10 mmol) was added in portions to a stirred solution of α-lithiophenylacetonitrile [prepared from BuLi in hexane (1.6 mol dm^{-3}; 7.5 cm^3, 12 mmol) and phenylacetonitrile (1.5 cm^3, 13 mmol) at −78 °C] in dry THF (100 cm^3) at −40 °C under nitrogen. The mixture was allowed to warm slowly to 0 °C and was maintained at 0 °C for 2 h. After addition of an equal volume of water the organic layer was separated. The aqueous phase was extracted with $CHCl_3$ and the combined extract was dried ($MgSO_4$) and concentrated to give *nitrile* **12** (2.31 g, 70%); m.p. 160–162 °C (from MeOH); ν_{max}/cm^{-1} 2242 (CN), 1733 (C=O), and 1605 and 1500 (Ph); δ_H 1.9–2.1 (4 H, m, quin 5- and 8-H_2), 2.35–2.40, 2.43–2.65 (2 H, m, quin 4-H and 7-H^a), 2.9–3.04 and 3.15–3.3 (4 H, m, 3-H, and quin 6-H_2 and 7-H^b), 3.73 and 3.83 (1 H, 2 d, *J* 10.7, quin 2-H), 4.79 and 5.30 (1 H, 2 d, *J* 4.9, 2-H) and 6.90–7.30 (10 H, m, Ph); *m/z* 302 and 302 (M^+ − CO, 58%) and 186 (100) (Found: C, 79.9; H, 6.7; N, 8.3. $C_{22}H_{22}N_2O$ requires C, 80.0; H, 6.7; N, 8.5%).

2-(2′-Benzylideneamino-1′,2′-diphenylethyl)quinuclidin-3-one **13** *and (2RS,3R*,3aS*)-2,3-Diphenyl-2,3,3a,5,6,7-hexahydro-4,7-ethanopyrrolo[3,2-b]pyridine* **18**.—Compound **1** (1.28 g, 6.0 mmol) benzylidenebenzylamine (1.29 g, 6.6 mmol) and triethylbenzylammonium chloride (0.14 g, 0.6 mmol) were mixed in benzene (6 cm^3), and 50% aq. NaOH (4.8 g, 60 mmol) was added. The heterogeneous mixture was stirred vigorously at room temperature for 5 h. Water (100 cm^3) was added and the mixture was extracted with CH_2Cl_2 (100 cm^3). The organic phase was dried, filtered, and concentrated under reduced pressure. The residue was purified on silica gel with $CHCl_3$ as eluent to give imine **13** (1.34 g, 55%) as a mixture of two diastereoisomers in the ratio 2:1 and tricycle **18** (0.18 g, 10%) as a mixture of two diastereoisomers in the ratio 1.7:1.

Compound **13**: δ_H 1.30–2.25 (4 H, m, quin 5- and 8-H_2), 2.32–2.37 (1 H, m, quin 4-H), 2.40–2.80, 3.00–3.30 and 3.50–3.60 (4 H, m, quin 6- and 7-H_2), 3.61 and 3.82 (1 H, 2 d, *J* 10.0 and 8.8, quin 2-H), 4.31 and 5.03 (1 H, 2 d, 1′-H), 4.67, 4.8 (1 H, 2 app br s, 2′-H) and 7.05–7.65 (16 H, m, Ph and CH=N).

Compound **18**: δ_H 1.80–2.10 (4 H, m, 6- and 8-H_2), 2.70–2.85 and 3.00–3.2 (4 H, m, 5- and 9-H_2), 2.93–2.96 and 3.02–3.05 (1 H, m, 7-H), 3.30–3.42 and 3.90–4.05 (2 H, m, 3- and 3a-H), 5.01 and 5.42 (1 H, dd, J_1 1.8, J_2 7.8 and 10.3, 2-H) and 6.70–7.30 (10 H, m, Ph); δ_C 188.0 and 190.6 (C=N); *m/z* 302 (M^+, 100%).

2-(2′-Nitro-1′-phenylethyl)quinuclidin-3-one **14**.—Compound **14** was synthesized from enone **1** (5.0 g, 23.5 mmol) nitromethane (2.55 cm^3, 47 mmol) and sodium methoxide (1.30 g, 25.0 mmol) in MeOH (100 cm^3) according to the procedure described for the synthesis of cyano ester **11**. After trituration the resulting crystals were filtered off, and washed with cold propan-2-ol to give *title product* **14** consisting of an equimolar mixture of two diastereoisomers (4.18 g, 65%); m.p. 84–86 °C; ν_{max}/cm^{-1} 1725 (C=O) and 1460 and 1380 (NO_2); δ_H 1.9–2.1 (4 H, m, quin 5- and 8-H_2), 2.38–2.41 and 2.44–2.47 (1 H, m, quin 4-H), 2.6–3.1 (4 H, quin 6- and 7-H_2), 3.36 and 3.46 (1 H, 2 d, *J* 10.1 and 10.7, quin 2-H), 3.77–3.84 (1 H, m, 1′-H), 4.62 and 4.67 (1 H, m, 2′-H^a), 5.0 and 5.4 (1 H, 2 dd, J_1 4.9 and 5.4; J_2 −12.8 and −13.2, 2′-H^b) and 7.2–7.4 (5 H, m, Ph); *m/z* 246 and 246 (M^+ − CO, 100%) and 200 (100) (Found: C, 65.6; H, 6.7; N, 10.3. $C_{15}H_{18}N_2O_3$ requires C, 65.7; H, 6.6; N, 10.2%).

5-Cyano-6-methoxy-8-phenyl-3,4-dihydro-2H-1,4-ethanoquinoline-7-carboxamide **16**.—A solution of diester **15** (0.10 g, 0.25 mmol) in 0.5% HCl in 80% HOAc (10 cm^3) was heated at 90–100 °C for 4 h. After cooling, the solution was concentrated under reduced pressure and the residue was partitioned between $CHCl_3$ (2 × 50 cm^3) and an aqueous alkaline solution (pH 9–10). The organic layer was dried and concentrated to leave an oil residue, which was purified on silica gel with a gradient of 50–75% EtOAc in hexane as eluent to afford title compound **16** (35 mg, 42%); m.p. 219–221 °C (from acetone); δ_H 1.5–1.65 and 1.85–1.97 (4 H, m, 3- and 9-H_2), 2.45–2.60 and 2.97–3.12 (4 H, m, 2- and 10-H_2), 3.32 (3 H, s, OMe), 3.46–3.51 (1 H, m, 4-H), 5.65 (2 H, br s, NH_2) and 7.13–7.42 (5 H, m, Ph); δ_C 27.5 (C-3 and -9), 30.7 (C-4), 49.1 (C-2 and -10), 51.6 (OMe), 93.7 (CN), 113.4, 115.7, 127.4, 127.5, 128.3, 137.9, 138.3, 142.6, 147.9 and 152.9 (ArC) and 168.9 (C=O); *m/z* 333 (M^+, 100%) (Found: C, 72.2; H, 6.0; N, 12.9. $C_{20}H_{19}N_3O_2$ requires C, 72.1; H, 5.7; N, 12.6%).

(2-Benzylidene-3-hydroxyquinuclidin-3-yl)acetonitrile **17**.—Compound **17** was synthesized from enone **1** (0.43 g, 2.0 mmol), cyanomethyllithium [prepared from BuLi in hexane (1.6 mol dm^{-3}; 1.38 cm^3, 2.2 mmol) and acetonitrile (0.12 cm^3, 13 mmol) at −78 °C] in dry THF (20 cm^3) as described above for the synthesis of compound **12** to afford the *cyanohydrin* **19** (0.32 g, 62%); m.p. 143–145 °C (from diethyl ether); ν_{max}/cm^{-1} 3496 (OH) and 2245 (CN); δ_H 1.50–1.62, 1.64–1.85 and 1.90–2.08 (4 H, m, 5- and 8-H_2), 2.23–2.28 (1 H, m, 4-H), 2.5 (1 H, br s, OH), 2.65–2.80 and 2.95–3.15 (4 H, m, 6- and 7-H_2), 3.01 (2 H, app br s, CH_2CN), 6.39 (1 H, s, C*H*Ph), 7.40–7.55 (3 H, m, Ph) and 7.94–8.03 (2 H, m, Ph); δ_C 21.3, 23.8, 29.7 and 33.6 (C-4, -5, -8 and CH_2CN), 45.9 and 47.4 (C-6 and -7), 71.6 (C-3), 117.3, 122.1, 127.6, 128.1, 129.7 and 134.9 (CHPh) and 152.2 (C-2) (Found: C, 75.9; H, 7.4; N, 11.4. $C_{16}H_{18}N_2O$ requires C, 75.6; H, 7.1; N, 11.0%).

3-(3-Oxoquinuclidin-2-yl)-3-phenylpropanonitrile **19**.—Compound **11** (0.50 g, 1.6 mmol) was converted into the title product

19 according to the procedure described above for the synthesis of amide **16**. Compound **19** was isolated as a viscous oil containing two diastereoisomers (0.22 g, 54%); ν_{max}/cm^{-1} 2225 (CN) and 1740 (C=O); δ_H 1.92–2.08 (4 H, m, quin 5- and 8-H_2), 2.36 and 2.49 (1 H, 2 app q, quin 4-H), 2.55–3.35 (7 H, m, 1-H_2, 2-H, and quin 6- and 7-H_2), 3.46 and 3.53 (1 H, 2 d, *J* 10.2, quin 2-H) and 7.2–7.4 (5 H, m, Ph); δ_C 23.9, 24.0, 24.9, 25.7, 26.0 and 26.9 (quin C-4, -5 and -8), 40.4, 40.8, 41.2, 41.6, 41.7, 41.8, 49.0 and 49.1 (quin C-6 and -7, and C-1, -2), 70.0 and 70.6 (quin C-2), 118.3 and 118.5 (CN), 127.6, 127.7, 127.8, 127.9, 139.4 and 139.7 (Ph) and 218.0 and 221.0 (C=O); *m/z* 226 and 226 ($M^+ - CO$, 100%).

(4aR*,8R*,8aR*)-8-*Phenylperhydro*-1,4-*ethano*-1,5-*naphthyridine* **20**.—*Compound* **20** was synthesized from nitrile **19** (0.50 g, 1.97 mmol) according to the general procedure, in 70% yield (0.32 g); δ_H 1.40–2.40 (8 H, m, 3-, 7- and 9-H_2, 4-H, and NH), 2.70–3.80 (9 H, m, 2-, 6- and 10-H_2, 4a-H, 8- and 8a-H) and 7.10–7.35 (5 H, m, Ph); δ_C 19.1, 24.5, 25.4 and 26.5 (C-3, -4, -7 and -9), 36.0, 39.8, 40.9, 49.1, 55.0 and 61.0 (C-2, -4, -4a, -6, -8, -8a and -10) and 127.0, 127.2, 128.7 and 141.9 (Ph); *m/z* 242 (M^+, 65%) and 97 (100) (Found: C, 67.1; H, 7.9; N, 10.0. $C_{16}H_{22}N_2 \cdot HCl \cdot \frac{1}{2}H_2O$ requires C, 66.8; H, 8.4; N, 9.7%).

(4aR*,7R*,8R*,8aR*)-7,8-*Diphenylperhydro*-1,4-*ethano*-1,5-*naphthyridine* **21**.—*Compound* **21** was synthesized from nitrile **12** (0.50 g, 1.52 mmol) according to the general procedure in 65% yield (0.31 g); m.p. 157–159 °C; δ_H 1.3–1.45, 1.53–1.75 and 1.92–2.04 (5 H, m, 3- and 9-H_2, NH), 1.77–1.82 (1 H, m, 4-H), 2.55–3.43 (10 H, m, 2-, 6- and 10-H_2, 4a-, 7-, 8- and 8a-H) and 6.9-7.13 (10 H, m, Ph); δ_C 20.2 and 26.5 (C-3 and -9), 27.4 (C-4), 41.3, 49.7 and 51.7 (C-2, -6 and -10), 44.6 and 47.3 (C-7 and -8), 55.9 and 63.4 (C-4a and -8a) and 125.7, 125.8, 127.8, 127.9, 128.0, 128.2, 142.7 and 145.4 (Ph); *m/z* 318 (M^+, 100%) (Found: C, 80.8; H, 8.2; N, 8.5. $C_{22}H_{26}N_2 \cdot \frac{1}{2}H_2O$ requires C, 80.7; H, 8.3; N, 8.6%).

(4aR*,8R*,8aR*)-5-(2-*Methoxybenzyl*)-8-*phenylperhydro*-1,4-*ethano*-1,5-*naphthyridine* **22**.—Compound **22** was synthesized from compound **20** (0.12 g, 0.5 mmol) according to the general procedure (98 mg, 54%); δ_H 1.22–2.20 (7 H, m, 3-, 7- and 9-H_2, and 4-H), 2.50–3.42 (9 H, m, 2-, 6- and 10-H_2, 4a-, 8a- and 8-H), 3.12 and 3.92 (2 H, 2 d, *J* ~ 14.2, CH_2Ph), 3.80 (3 H, s, OMe) and 6.81–7.55 (9 H, m, ArH); δ_C 21.0, 24.4, 26.1 and 29.8 (C-3, -4, -7 and -9), 37.4, 41.6, 49.1, 49.9, 51.7, 55.2, 62.2 and 63.3 (C-2, -4a, -6, -8, -8a, -10, OMe, CH_2Ph) and 110.2, 120.3, 126.0, 127,4, 127.5, 127.7, 128.4, 129.5, 145.8 and 157.6 (ArC); *m/z* 362 (M^+, 87%) and 241 (100) (Found: C, 79.2; H, 8.5; N, 7.7. $C_{24}H_{30}N_2O$ requires C, 79.5; H, 8.3; N, 7.7%).

(4aR*,7R*,8R*,8aR*)-5-(2-*Methoxybenzyl*)-7,8-*diphenylperhydro*-1,4-*ethano*-1,5-*naphthyridine* **23**.—*Compound* **23** was synthesized from compound **21** (0.16 g, 0.5 mmol), according to the general procedure, in 65% yield (0.14 g); δ_H 1.75–2.65 (4 H, m, 3- and 9-H_2), 2.63–2.90 and 3.02–3.50 (9 H, m, 2-, 6- and 10-H_2, 4-, 7- and 8-H), 2.97 (1 H, br d, 4a-H), 3.21 and 4.04 (2 H, 2 d, CH_2Ph), 3.85 (3 H, s, OMe), 4.06 (1 H, m, 8a-H) and 6.67–6.72, 6.87–7.0 and 7.12–7.3 (14 H, m, ArH); δ_C 17.9 (C-9), 22.1 (C-3), 23.6 (C-4), 41.8 and 49.9 (C-2 and -10), 46.1 (C-7), 46.3 (C-8), 52.1 (CH_2Ph), 55.3 (OMe), 56.4 (C-6), 61.1 (C-4a), 62.8 (C-8a) and 110.4, 120.3, 125.2, 126.2, 127.1, 127.9, 128.1, 128.4, 131.2, 137.1, 144.6 and 157.8 (ArC); *m/z* 438 (M^+, 56%) and 317 (100) (Found: C, 75.5; H, 7.6; N, 5.8. $C_{30}H_{34}N_2O \cdot HCl$ requires C, 75.9; H, 7.4; N, 5.9%).

(2R*,3S*,3aR*,7aR*)-1-*Benzyl*-2,3-*diphenylperhydro*-4,7-*ethanopyrrolo*[3,2-b]*pyridine* **24a** *and* (2R*,3R*,3aS*,7aS*)-1-*Benzyl*-2,3-*diphenylperhydro*-4,7-*ethanopyrrolo*[3,2-b]*pyridine* **24b**.—Compound **13** (0.50 g, 1.22 mmol) was dissolved in MeOH (10 cm^3) and acidified with HOAc to pH 3.5–4.5. Sodium cyanoboranuide (0.31 g, 4.9 mmol) was added in portions during 10 min at room temperature and the mixture was stirred for 6–8 h. Water (20 cm^3) was added, and methanol was removed under reduced pressure. The aqueous phase was extracted with $CHCl_3$ (2 × 30 cm^3) and the extract was dried, filtered, and concentrated. The residue was separated on silica gel with 5% MeOH in $CHCl_3$ as eluent to give the pure epimers **24a** (higher R_f, 0.24 g) and **24b** (0.17 g) in 84% total yield.

Isomer **24a**: m.p. 143–145 °C; δ_H 1.2–1.6 and 2.10–2.25 (4 H, m, 6- and 8-H_2), 1.50–1.54 (1 H, m, 7-H), 2.65–2.75, 2.9–3.05, 3.35–3.55 (4 H, m, 5- and 9-H_2), 2.78 (1 H, dd, J_1 3.2, J_2 8.8, 7a-H), 3.27 (1 H, dd, $J_1 = J_2 = 8.8$, 3-H), 3.37 (1 H, dd, $J_1 = J_2 = 8.8$, 3a-H), 3.67 (1 H, d, *J* 9.5, 2-H), 3.42 and 3.91 (2 H, 2 d, *J* ~ 13.2, CH_2Ph) and 7.03–7.42 (15 H, m, Ph); δ_C 20.3 and 24.1 (C-6 and -8), 25.2 (C-7), 41.8 and 49.5 (C-5 and -9), 55.9 (C-3), 56.5 (CH_2Ph), 64.1 (C-7a), 67.7 (C-3a), 74.7 (C-2) and 126.3, 126.8, 127.2, 127.7, 127.8, 128.2, 128.3, 129.4, 137.9, 140.8 and 141.4 (Ph); *m/z* 394 (M^+, 75%) and 303 (100) (Found: C, 85.1; H, 7.3; N, 7.0. $C_{28}H_{30}N_2$ requires C, 85.3; H, 7.6; N, 7.1%).

Isomer **24b**: m.p. 201–203 °C; δ_H 1.20–1.95 (4 H, m, 6- and 8-H_2), 2.00–2.04 (1 H, m, 7-H), 2.35–2.5, 2.65–2.8 and 2.9–3.05 (4 H, m, 5- and 9-H_2), 3.42 (1 H, m, 7a-H), 3.75–3.90 (4 H, m, 3- and 3a-H, and CH_2Ph), 4.88 (1 H, app dt, *J* 6.5 and 8.7, 2-H) and 7.05–7.65 (15 H, m, Ph); δ_C 21.2 and 25.1 (C-6 and -8), 24.1 (C-7), 42.4 and 49.9 (C-5 and -9), 50.6 (CH_2Ph), 55.6 (C-3), 58.4 (C-7a), 63.1 (C-3a), 68.9 (C-2) and 125.8, 126.5, 127.5, 127.8, 127.9, 128.0, 128.4, 128.6, 138.4, 139.8 and 142.7 (Ph); *m/z* 394 (M^+, 68%) and 303 (100) (Found: C, 85.4; H, 7.5; N, 7.0%).

(2R*,3S*,3aR*,7aR*)-2,3-*Diphenylperhydro*-4,7-*ethanopyrrolo*[3,2-b]*pyridine* **25a** *and* (2R*,3R*,3aS*,7aS*)-2,3-*Diphenylperhydro*-4,7-*ethanopyrrolo*[3,2-b]*pyridine* **25b**.—A mixture of two diastereoisomers of imine **18** (0.15 g, 0.5 mmol) was treated with sodium cyanoboranuide as described for the synthesis of compounds **24** to give the pure epimers **25a** (higher R_f, 62 mg) and **25b** (69 mg) in 87% total yield.

Isomer **25a**: m.p. 123–125 °C; δ_H 1.36–1.58, 1.67–1.8 and 2.22–2.40 (4 H, m, 6- and 8-H_2), 1.95–1.99 (1 H, m, 7-H), 2.70–2.87, 2.98–3.12 and 3.35–3.52 (4 H, m, 5- and 9-H_2), 3.17 (1 H, dd, J_1 7.1, J_2 9.8, 3-H), 3.38–3.45 (2 H, m, 3a- and 7a-H), 4.23 (1 H, d, 2-H) and 7.10–7.35 (10 H, m, Ph); δ_C 19.9 and 24.3 (C-6 and -8), 27.0 (C-7), 41.9 and 49.5 (C-5 and -9), 55.6 (C-3), 57.1 (C-7a), 68.1 (C-3a), 69.5 (C-2) and 126.5, 126.8, 127.2, 128.1, 128.3, 128.4, 140.8 and 142.2 (Ph); *m/z* 304 (M^+, 100%) (Found: C, 82.1; H, 7.6; N, 9.1. $C_{21}H_{24}N_2 \cdot \frac{1}{2}H_2O$ requires C, 81.8; H, 7.9; N, 9.1%).

Isomer **25b**: m.p. 125–126 °C; δ_H 1.40–1.52, 1.56–1.67, 1.68–1.82 and 2.05–2.20 (4 H, m, 6- and 8-H_2), 1.93–1.97 (1 H, m, 7-H), 2.72–2.93, 3.0–3.13 and 3.28–3.43 (4 H, m, 5- and 9-H_2), 3.65 (1 H, dd, J_1 6.0, J_2 9.2, 3a-H), 3.70 (1 H, br s, NH), 3.75 (1 H, dd, *J* 3.0 and 10.1, 7a-H), 3.91 (1 H, dd, $J_1 = J_2 = 7.2$, 3-H), 4.90 (1 H, d, 2-H) and 6.82–6.95 and 7.00–7.10 (10 H, m, Ph); δ_C 19.5 and 24.7 (C-6 and -8), 28.2 (C-7), 42.4 and 49.8 (C-5 and -9), 52.1 (C-3), 58.0 (C-7a), 66.2 (C-3a and -2) and 126.2, 126.6, 127.2, 127.8, 127.9, 128.6, 139.9 and 142.2 (Ph); *m/z* 304 (M^+, 100%) (Found: C, 82.5; H, 8.1; N, 9.0. $C_{21}H_{24}N_2$ requires C, 82.9; H, 7.9; N, 9.2%).

(3R*,3aS*,7aS*)-3-*Phenylperhydro*-4,7-*ethanopyrrolo*[3,2-b]-pyridine **26**.—*Compound* **26** was synthesized from compound **14** (0.50 g, 1.82 mmol) according to the general procedure, and was obtained as an oil (295 mg, 71%); δ_H 1.13–1.54, 1.62–1.74 and 1.87–2.0 (6 H, m, 6- and 8-H_2, 7-H, and NH), 2.65–2.82, 2.86–3.08 and 3.10–3.58 (9 H, m, 2-, 5- and 9-H_2, 3-, 3a- and 7a-H) and 7.15–7.30 (5 H, m, Ph); δ_C 19.4 and 24.7 (C-6 and -8), 26.1 (C-7), 41.4 (C-2), 46.6 (C-3), 49.4 and 52.5 (C-5 and -9),

58.7 and 68.7 (C-3a and -7a) and 126.3, 127.3, 128.4 and 142.0 (Ph); *m/z* 228 (M^+, 100%) (Found: C, 64.6; H, 7.7; N, 9.8. $C_{15}H_{20}N_2 \cdot HCl \cdot \frac{3}{4}H_2O$ requires C, 64.7; H, 8.1; N, 10.1%).

(3R*,3aS*,7aS*)-1-(2-*Methoxybenzoyl*)-3-*phenylperhydro*-4,7-*ethanopyrrolo*[3,2-b]*pyridine* **27**.—2-Methoxybenzoyl chloride (0.30 g, 1.76 mmol) was added to a solution of amine **26** (0.20 g, 0.88 mmol) in pyridine (10 cm^3) at 5 °C. After 24 h at ambient temperature the mixture was quenched with water (20 cm^3) and concentrated under reduced pressure. The residue was partitioned between 10% aq. Na_2CO_3 (20 cm^3) and $CHCl_3$ (2 × 20 cm^3). The combined organic phase was dried, filtered, and concentrated under reduced pressure. The residue was purified on silica gel with a gradient of 5–10% MeOH in $CHCl_3$ as eluent to afford *title amide* **27** (0.27 g, 86%); m.p. 122–123 °C; δ_H(mixture of rotamers) 1.02–1.95 (4 H, m, 6- and 8-H_2), 2.36–2.46 (1 H, m, 7-H), 2.65–3.20, 3.35–3.61, 3.90–4.15 and 4.30–4.45 (9 H, m, 2-, 5- and 9-H_2 and 3-, 3a- and 7a-H), 3.80 and 3.91 (3 H, 2 s, OMe) and 7.08–7.40 (9 H, m, ArH) (Found: C, 76.6; H, 7.1; N, 7.7. $C_{23}H_{26}N_2O_2$ requires C, 76.2; H, 7.2; N, 7.7%).

(3R*,3aS*,7aS*)-1,4-*Bis*(2-*methoxybenzyl*)-3-*phenylperhydro*-4,7-*ethanopyrrolo*[3,2-b]*pyridinium Chloride* **28**.—Compound **28** was synthesized from free amine **26** (0.11 g, 0.5 mmol) according to the general procedure. After the reaction had finished (TLC) the mixture was washed with water. The aqueous layer was extracted twice with $CHCl_3$ (50 cm^3). The combined extract was dried, filtered, and concentrated, to give a residue, which was purified on silica gel to afford the *salt* **28** (0.21 g, 83%); m.p. 140 °C (decomp.); δ_H 1.50–2.62 (5 H, m, 6- and 8-H_2, and 7-H), 2.80–2.96 (1 H, m, 5-H^a), 3.05–3.20 (1 H, m, 2-H^a), 3.30–3.50 (2 H, m , 5-H^b and 7a-H), 3.43 and 3.90 (2 H, 2 d, CH_2Ar), 3.75–3.97 (3 H, m, 3-H and 9-H_2), 3.82 and 3.85 (6 H, 2 s, OMe), 4.06 and 4.41 (2 H, 2 d, $CH_2C_6H_4$OMe), 4.44–4.58 (1 H, m, 2-H^b), 5.2 (1 H, dd, $J_1 = J_2$ = 8.3, 3a-H) and 6.85–7.0, 7.15–7.43 and 7.56–7.68 (13 H, m, ArH); δ_C 18.6, 22.2 and 23.3 (C-6, -7 and -8), 45.3, 47.7, 51.0, 54.9, 55.2, 55.7, 59.2, 61.2, 64.1 and 74.3 (C-2, -3, -3a, -5, -7a, -9, OMe and CH_2Ph) and 110.4, 111.1, 115.0, 120.2, 121.2, 125.3, 127.6, 128.1, 128.8, 129.2, 130.8, 132.3, 135.7, 138.3, 157.6 and 158.3 (ArC) (Found: C, 71.7; H, 7.5; N, 5.3. $C_{31}H_{37}ClN_2O_2 \cdot \frac{3}{4}H_2O$ requires C, 71.9; H, 7.4; N, 5.4%).

(3R*,3aS*,7aS*)-1-(2-*Methoxybenzyl*)-3-*phenylperhydro*-4,7-*ethanopyrrolo*[3,2-b]*pyridine* **29**.—Compound **28** (200 mg, 0.40 mmol) was dissolved in toluene (10 cm^3) containing butan-1-ol) (1 cm^3) and piperidine (0.5 cm3). The solution was refluxed for 4–5 h, and was then cooled to room temperature. The residue obtained after concentration under reduced pressure was purified on alumina to give pure *title product* **29** (86 mg, 62%); m.p. 233–235 °C (dihydrochloride); δ_H 1.40–1.90 (3 H, m, 6-H^a and 8-H_2), 1.95–2.02 (1 H, m, 7-H), 2.04–2.18 (1 H, m, 6-H^b), 2.3 (1 H, dd, J_1 8.9, J_2 10.9, 2-H^a), 2.51 (1 H, dd, J_1 4.0, J_2 9.1, 7a-H), 2.63–2.76 (2 H, m, 5-H_2), 2.94–3.08 (1 H, m, 9-H^a), 3.21 (1 H, dd, $J_1 = J_2$ = 9.1, 3a-H), 3.28–3.37 (2 H, m, 2- and 9-H^b), 3.40–3.52 (1 H, m, 3-H), 3.48 and 3.91 (2 H, 2 d, CH_2Ar), 3.8 (3 H, s, OMe) and 6.85–6.97 and 7.15–7.40 (9 H, m, ArH); δ_C 17.4, 21.6 and 22.6 (C-6, -7 and -8), 41.3, 42.8, 47.6, 51.4, 55.8, 59.1, 62.4, 64.2 and 64.4 (C-2, -3, -3a, -5, -7a, -9, OMe and CH_2Ar) and 111.0, 116.4, 121.5, 128.2, 128.8, 128.9, 132.4, 133.5, 134.1 and 158.1 (ArC); *m/z* 348 (M^+, 44%) and 227 (100) (Found: C, 63.2; H, 7.2; N, 6.5. $C_{23}H_{28}N_2O \cdot 2\ HCl \cdot H_2O$ requires C, 62.9; H, 7.3; N, 6.4).

Compound **28** was also debenzylated by catalytic hydrogenation [Pd(C)/MeOH] in a Parr apparatus at 45–50 psi for 3 h. After the catalyst had been filtered off, purification as described above gave compound **29** in 35% yield.

Reduction of amide **27** with $LiAlH_4$ as described above for the synthesis of compound **5** produced amine **29** in 62% yield.

6,8-*Dicyclohexyl*-3,4-*dihydro*-2H-1,4-*ethano*-1,5-*naphthyridine* **30**.—Hydrogenation of 6,8-diphenyl-3,4-dihydro-2*H*-1,4-ethano-1,5-naphthyridine[10] (0.20 g, 0.64 mmol) as described above for the synthesis of lactam **3** afforded *title compound* **30** (93 mg, 45%); δ_H 1.20–2.05 (24 H, m, 3- and 9-H^a, and cyclohexyl), 2.51–2.75 (3 H, m, 2-H^a and 3- and 9-H^b), 3.05–3.25 (3 H, m, 2-H^b and 10-H_2), 3.25–3.31 (1 H, m, 4-H) and 6.90 (1 H, s, 7-H); *m/z* 324 (M^+, 27%) and 269 (100) (Found: C, 81.7; H, 10.3; N, 8.6. $C_{22}H_{32}N_2$ requires C, 81.5; H, 9.9; N, 8.6%).

Crystal-structure Determination.—Data collection and processing. The intensities of 2434 and 3399 reflections were collected at room temperature from the selected single crystals of compounds **3** (0.09 × 0.190 × 0.38 mm) and **21** (0.26 × 0.38 × 0.07 mm), respectively, using Cu-Kα radiation (λ = 1.541 83 Å, θ_{max} = 70°). Data reductions included corrections for background, decay, Lorentz and polarization effects, but the rather low absorption effects [μ = 5.89 (**3**) and 5.06 cm^{-1} (**21**)] were ignored. The number of unique, non-zero observations was 2233 for **3** and 2704 for **21**. The unit-cell parameters were refined against θ-values of 58 (30 < 2θ < 50°) (**3**) and 56 (23 < 2θ < 47°) reflections (**21**).

Structural analysis and refinements. The structures were solved by application of direct methods (SHELXS)[33] and refined by full-matrix least-squares method based on |*F*| (SHELX).[34] The non-hydrogen atoms were treated anisotropically, whereas isotropic displacement parameters were refined for the hydrogens, either located from difference electron density ($\Delta\rho$) maps and held riding on their parent atoms during the subsequent calculations, or assumed in idealized positions with C–H = 1.00 Å, which were recalculated after each refinement cycle using geometric evidence. Final refinements of 192 and 245 variables for compounds **3** and **21**, respectively, yielded the final *R*-values listed below. In the last refinement calculation for structure **3**, four strong low-θ reflections with considerably lower F_{obs} than F_{calc}, probably due to extinction effects, were omitted. In case of structure **21**, an empirical isotropic extinction parameter χ [$F' = (1 - 0.0001\chi \cdot F^2/\sin\theta)$][34] was also included in the final refinement calculation; its value converged to χ = 0.353. The weights of the structure factors were assumed[34] as $w = [\sigma^2(F) + |g| \cdot F^2]^{-1}$ with g = 0.000 25 and 0.000 50 for structures **3** and **21**, respectively.*

Crystal data. Compound **3**: $C_{16}H_{20}N_2O$, M_w = 256.347, triclinic ($P\bar{1}$), a = 6.591(1), b = 10.731(1), c = 10.972(2) Å, α = 107.126(7), β = 105.591(7), γ = 103.081(7)°, V_c = 673.8(2) Å^3, Z = 2, D_c = 1.2634(4) g cm^{-3}, $F(000)$ = 276. Final R = 0.047 and wR = 0.066 for 1573 reflections with $I > 3\sigma(I)$.

Compound **21**: $C_{22}H_{26}N_2$, M_w = 318.461, triclinic ($P\bar{1}$), a = 6.102(1), b = 10.552(1), c = 13.982(1) Å, α = 79.906(8), β = 83.393(8), γ = 80.366(9)°, V_c = 870.4(2) Å^3, Z = 2, D_c = 1.2151(3) g cm^{-3}, $F(000)$ = 344. Final R = 0.040 and wR = 0.050 for 1821 reflections with $I/\sigma(I) > 2.5$.

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

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