

Synthesis and Reactions with Nucleophiles

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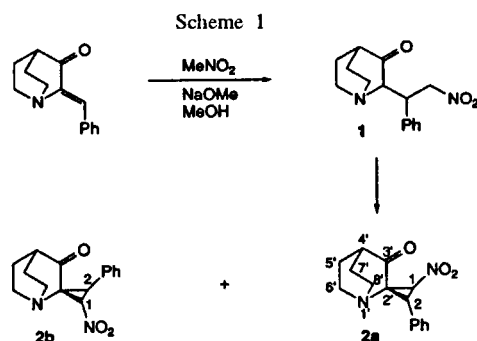
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3'-Keto-1-nitro-2-phenylspiro[cyclopropane-3,2'-quinuclidine] was synthesized by a two-step procedure from 2-benzylidenequinuclidin-3-one. Ring-opening reactions of the cyclopropane ring using a variety of *N*-, *O*-, and *C*-nucleophiles (amines, methoxide, nitromethane, cyanide anions, and lithium diphenylcopper) were studied, and a general mechanism for the transformations is proposed.

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The 2,3-disubstituted quinuclidine derivative CP 96,345 was the first potent and selective NK₁-receptor antagonist [1]. Structure-activity relationship (SAR) studies on CP 96,345 have mainly focused on variations in the C-3 positioned benzylamino moiety [2,3]. In the present study we have synthesized a number of novel quinuclidine derivatives with modifications in the C-2 position using the quinuclidine 2-spiro cyclopropane derivative **2a** (Scheme 1) as a key intermediate. Several of these derivatives may



be of interest as synthetic precursors to novel CP 96,345 analogues.

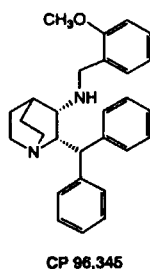
Synthetically useful reactions of electrophilic cyclopropanes are well documented; they may be converted by nucleophiles into 1,5-adducts or into larger rings [4,5]. Also the corresponding ring-opening reactions of nitrocyclopropanes have been studied [6-8]. Reports on the reactions of 1-acyl-2-nitro-cyclopropanes with alcoholate or diethyl malonate anions yielding methyl enol esters or α -

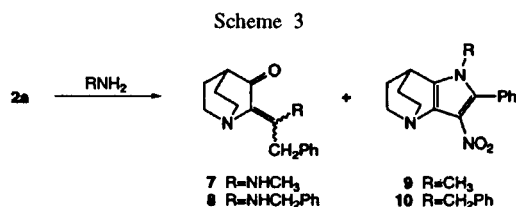
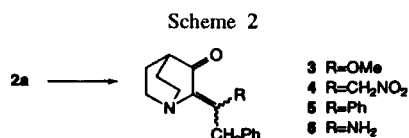
pyrrone esters, respectively, are particularly relevant to the present study [9-14] since the acidic proton α to the nitro group in the cyclopropane ring appears to be of importance for the reactivity of **2a** (see below).

Compound **2a** was synthesized according to the method of Smith and Engelhardt [9]: Michael addition of the anion of nitromethane to 2-benzylidenequinuclidin-3-one [15] gave 2-(2-nitro-1-phenylethyl)quinuclidin-3-one (**1**) as an equimolar mixture of two diastereomers. Bromination of **1** followed by dehydrobromination in the presence of base produced **2a** as the only stereoisomer in a moderate yield (Scheme 1). Alternatively, direct oxidation of **1** using potassium hexacyanoferrate produced an equimolar mixture of the isomers **2a** and **2b**. However, the lack of stereoselectivity, the lower yield and the low reproducibility in the latter reaction makes the former method preferable.

The assignment of the *trans*-stereochemistry in the cyclopropane ring of **2a** and **2b** is based on the relatively small coupling constants between H-1 and H-2 ($J = 6.3$ and 6.9 Hz respectively) observed in the ¹H nmr spectra. In the corresponding *cis*-isomers, this coupling constant is expected to be larger than 9 Hz (compare refs 16 and 17). In addition, no NOE interaction was observed between H-1 and H-2. The position of the nitro group relative to the carbonyl group in **2b** was suggested by the down-field shift of the H-1 signal (δ 5.42 in **2b** versus δ 4.83 in **2a**), which indicated that H-1 is deshielded by the carbonyl group.

At room temperature **2a** and **2b** were found to be stable over a broad pH range (pH 2-9). However, more basic conditions in combination with elevated temperature caused opening of the cyclopropane ring leading to formation of α,β -unsaturated ketones substituted at the vinylic β -position by an incoming nucleophile (3-8, Schemes 2 and 3). Reaction of **2a** with methylamine gave the methylamino derivative **7** together with the pyrrole derivative **9**. Similarly, reaction of **2a** with benzylamine resulted in the formation of **8** and **10** (Scheme 3). Compound **8** was isolated as a mixture of *E* and *Z*-isomers



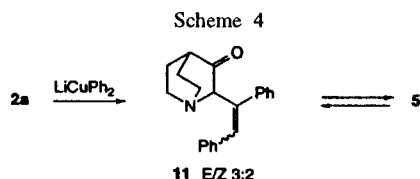


(7:1). The *E/Z* ratio was determined on the basis of the relative intensities of the benzyl methylene singlets in the ¹H nmr spectrum.

In the ¹H nmr spectra of 7 and 8 the α-protons of the *N*-substituent appeared as doublets (*J* = 5.0 and 6.8 Hz, respectively) due to coupling to the NH. The NH signals appeared at an unusually low field (δ 9.84 and 10.26, respectively) indicating the presence of an intramolecular hydrogen bond. This interpretation was corroborated by the ¹H nmr spectrum of the primary enamine 6 in which NH-signals appeared at δ 8.85 (bonded proton) and 4.56 (non-bonded).

The structural assignments of the pyrrole derivatives 9 and 10 are based on their strong uv absorption, the strong M⁺ peak in ms-spectra, ir-bands at 1355 and 1480 cm⁻¹ due to the presence of a nitro group together with the absence of a carbonyl absorption. In addition, the ¹H nmr spectra of 9 and 10 demonstrate a symmetric environment for the quinuclidine protons and a down-field shift of the signal due to H-4. The relative positions of the substituents in the pyrrole ring were established by the pronounced NOE interaction between the α-protons of the R-substituent and both the *ortho*-protons of the phenyl substituent and H-4.

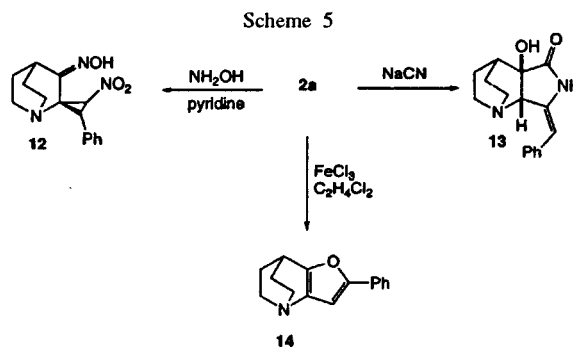
Addition of lithium diphenylcopper to 2a resulted in the formation of the regioisomers 5 and the major product 11



(Scheme 4). Compound 11 was probably formed *via* an enolate anion of 5 in the strongly alkaline medium of the reaction. This would require a shift of the carbon-carbon double bond to the β,γ position. However, isomerization of 11 to 5 occurred spontaneously in chloroform and was complete after about 20 hours.

A relatively high basicity of the reaction medium was necessary to promote ring cleavage in 2a. This is illustrat-

ed by the unsuccessful attempt to react 2a with primary amine hydrochlorides in pyridine even at 100°. Similarly, hydroxylamine hydrochloride in pyridine converted 2a to its oxime 12 without ring-opening (Scheme 5). However, reaction of 2a with sodium cyanide produced the fused pyrrolidone derivative 13 as the major product. The structure of 13 was indicated by the characteristic ir (1670, 3240 cm⁻¹) and nmr spectral properties. In particular, the nmr signals due to C-4a (δ 85.1) and C-5 (δ 171.5) but also the signals of the coupled pair of protons H-7a (broad singlet at δ 3.8) and CH-Ph (doublet at δ 7.54, *J* = 1.8 Hz) were useful in the structural assignment of 13. The *E* orientation of the double bond was confirmed by nmr experi-

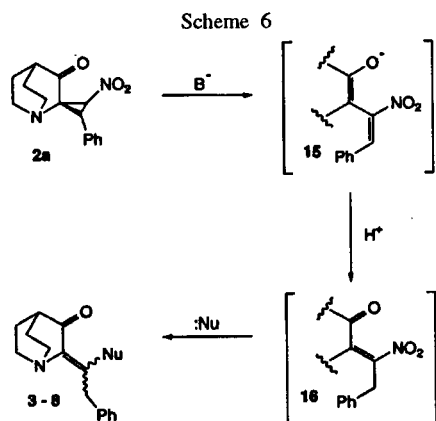


ments in which no NOE interaction was observed between H-7a and CH-Ph.

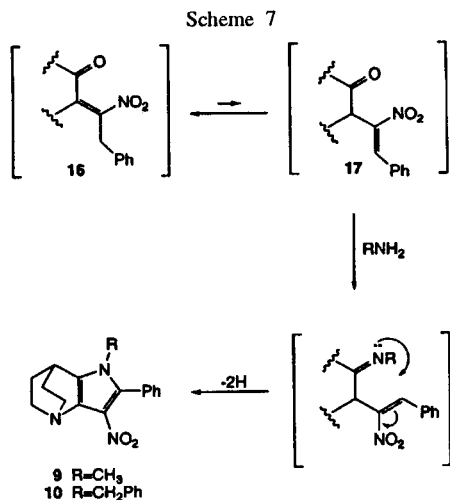
In the nucleophilic ring-opening reactions of cyclopropane 2a, only the bond between C-2 and C-3 was cleaved. In the majority of cases this resulted in the formation of a conjugated carbon-carbon double bond and substitution of the nitro group by the incoming nucleophile. These observations agree with results in previous studies of similar systems [9-12,14].

The synthetic transformations described herein were achieved only under basic conditions, indicating that deprotonation at C-1 is essential and since both the C-1 - C-2 and C-1 - C-3 bonds remained intact, α-deprotonation should lead to the electron-rich cyclopropane anion before the cyclopropane ring is opened. This is in contrast with both theoretical [18,19] and experimental data [6,8,13] which suggest a facile cleavage of the bonds adjacent to an electron withdrawing substituent in the cyclopropane ring.

To rationalize the present data, we suggest the tentative mechanism shown in Scheme 6. This mechanism involves a rearrangement of the initial α-anion of 2a to an intermediate 15 which is stabilized by conjugation. Protonation of 15 would lead to 16 which may be attacked by a nucleophile at the electrondeficient β-vinyl carbon atom, leading to substitution of the vinyl nitro group [20,21]. A similar mechanism would also explain the formation of



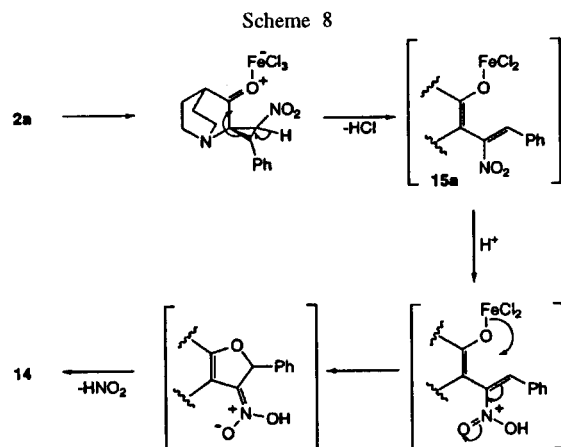
13; an intermolecular nucleophilic substitution of the nitro group by the nitrogen atom of a cyanohydrine intermediate would account for the observed product. The small amounts of nitropyrroles 9 and 10, which were produced in the amination reactions, appear to result from a Michael-type addition of the imine nitrogen to the less



thermodynamically favoured tautomer of intermediate 16 (*i.e.* 17) (Scheme 7).

The nitrocyclopropane 2a is fairly stable in acidic media. However, a strong Lewis acid like aluminum trichloride in dichloromethane reacted vigorously with 2a to give a complex mixture of products. In contrast, the less aggressive iron trichloride smoothly converted 2a into 14 in a moderate yield (Scheme 5). The position of the phenyl substituent in 14 is indicated by the ^{13}C nmr spectrum. This acid-catalyzed rearrangement may involve a similar intermediate 15a as the base-catalyzed reactions (Scheme 8). The cyclization which results in a final *cine*-substitution of the nitro group [20], could be promoted by protonation of the nitro group.

In conclusion, we have explored some new synthetic



applications of 1-acyl-2-nitrocyclopropanes. The high-yielding transformations of 2a to α,β -unsaturated ketones containing both a benzyl group and a broad variety of substituents at the β -vinylic atom (Schemes 2 and 3) offer interesting precursors to various analogues of CP 96,345. In addition, novel transformations of 2a produce fused pyrrolidone, pyrrole and furan derivatives.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The 1H nmr and ^{13}C nmr spectra were run in deuteriochloroform (unless otherwise stated) on a JEOL JNM-EX 270 NMR spectrometer and the chemical shifts were determined relative to internal tetramethylsilane. The NOE experiments were carried out to assign the structure of diastereoisomers and 1H - ^{13}C correlation experiments were performed to assign the ^{13}C signals. The ir spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. Mass spectral data together with GC were obtained with a combined Hewlett-Packard GC(5890)-MS(5791) unit. The reaction mixtures were monitored by tlc on aluminum sheets precoated with silica gel 60F₂₅₄ (E. Merck) in 0, 2, 5 or 10% methanol in dichloromethane. The elemental analyses were performed by MikroKemi AB, Uppsala, Sweden.

2-(2-Nitro-1-phenylethyl)quinuclidin-3-one (1).

Nitromethane (2.55 ml, 47 mmol) was added to a solution of 2-benzylidenequinuclidin-3-one [15] (5 g, 23.5 mmol) and sodium methoxide (1.3 g, 25.0 mmol) in methanol (100 ml). After being stirred for 3 hours at 55–60°, the mixture was allowed to reach room temperature. Water was added and the methanol was evaporated *in vacuo*. The remaining water solution was extracted with chloroform (3 x 50 ml). The organic extract was dried (magnesium sulfate) and concentrated to give an oil which was triturated with 2-propanol for 20 hours at 0°. The resulting crystals were filtered off and washed with cold 2-propanol to afford 1 as an equimolar mixture of two diastereomers (4.18 g, 65%), mp 84–86°; ir: ν 1725 (CO), 1460, 1380 (NO_2) cm^{-1} ; 1H nmr: δ 1.90–2.10 (m, 4H, 5-H's, 7-H's), 2.38–2.47

(m, 1H, 4-H), 2.60-3.10 (m, 4H, 6-H's, 8-H's), 3.36, 3.46 (d, 1H, $J = 10.1$, 10.7 Hz, 2-H), 3.77-3.84 (m, 1H, *CHPh*), 4.62, 4.67 (m, 1H, *CH₂NO₂*), 5.00, 5.40 (dd, 1H, $J_1 = 4.9$, 5.4 Hz, $J_2 = 12.8$, 13.2 Hz, *CH₂NO₂*), 7.20-7.40 (m, 5H, Ph); ms (two isomers): m/z 246, 246 ($M^+ - CO$).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.7; H, 6.6; N, 10.2. Found: C, 65.6; H, 6.7; N, 10.3.

(1*S**, 2*S**, 2'*S*')-3'-Keto-1-nitro-2-phenylspiro[cyclopropane-3,2'-quinuclidine] (**2a**).

Bromine (0.46 ml, 8.8 mmol) was added dropwise to a cooled (-20°) solution of **1** (2.0 g, 7.2 mmol) and sodium methoxide (870 mg, 16 mmol) in methanol (20 ml). The mixture was stirred at -20° for 1 hour and water (50 ml) was added. The methanol was evaporated and the residue was extracted with chloroform (2 x 50 ml). The organic extract, containing at least four diastereomeric monobromides according to tlc, was dried (magnesium sulfate) and concentrated *in vacuo*. The residue was dissolved in methanol (50 ml) and heated at 50° while stirring for 30 minutes in the presence of anhydrous sodium acetate (1.64 g, 20 mmol). The cooled mixture was filtered and concentrated *in vacuo*. The residue was partitioned between chloroform and water (pH 7-8) and purified on a silica gel column using 20% ethyl acetate in hexane as eluent to afford **2a** (1.25 g, 63%) as a yellowish oil which slowly solidified, mp $122-124^\circ$; 1H nmr: 1.95-2.17 (m, 4H, 5'-H's, 7'-H's), 2.30-3.42 (m, 4H, 6'-H's, 8'-H's), 2.66-2.70 (m, 1H, 4'-H), 3.96 (d, 1H, $J = 6.9$ Hz, 2-H), 4.83 (d, 1H, 1-H), 7.28-7.37 (m, 5H, Ph); ^{13}C nmr: δ 25.2, 26.7 (C-5', C-7'), 39.0 (C-2), 41.0 (C-4'), 44.9, 46.9 (C-6', C-8'), 61.2 (C-2'), 71.6 (C-1), 127.9, 128.2, 128.4, 131.0 (Ph), 212.3 (C-3'); ms: m/z 272 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.2; H, 5.9; N, 10.3. Found: C, 66.2; H, 6.3; N, 10.2.

Direct Oxidation of **1** to a Diastereomeric Mixture of (1*S**, 2*S**, 2'*S*')-**2a** and (1*S**, 2*S**, 2'*R*')-**2b**.

A solution of **1** (500 mg, 1.82 mmol) in 50% aqueous acetone (10 ml) was stirred at ambient temperature in the presence of potassium hexacyanoferrate (3.3 g, 10 mmol) for 48 hours. Water (50 ml) was added and the mixture was extracted twice with chloroform. The organic layer was dried (magnesium sulfate) and concentrated. Column chromatography on silica using a gradient of 10-30% ethyl acetate in hexane as eluent afforded epimers **2a** (lower R_f , 55 mg, 11%) (see above) and **2b** (50 mg, 10%) as an oil; 1H nmr: δ 2.00-2.18 (m, 4H, 5'-H's, 7'-H's), 2.54-2.58 (m, 1H, 4'-H), 2.78-3.50 (m, 4H, 6'-H's, 8'-H's), 4.02 (d, 1H, $J = 6.3$ Hz, 2-H), 5.42 (d, 1H, 1-H), 7.17-7.38 (m, 5H, Ph); ^{13}C nmr: δ 23.7, 27.7 (C-5', C-7'), 40.5 (C-4'), 41.3 (C-2), 46.7, 47.2 (C-6', C-8'), 61.4 (C-2'), 69.5 (C-1), 128.1, 128.3, 128.6, 129.8 (Ph), 210.4 (C-3'); ms: m/z 272 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_3 \cdot 0.5 H_2O$: C, 64.1; H, 6.0; N, 10.0. Found: C, 64.1; H, 6.1; N, 9.8.

(*Z*)-2-(1-Methoxy-2-phenylethylidene)quinuclidin-3-one (**3**).

A solution of sodium methoxide (38 mg, 0.7 mmol) in methanol (3 ml) was added to a solution of **2a** (136 mg, 0.5 mmol) in methanol (3 ml) at ambient temperature. The mixture was stirred at $45-50^\circ$ for 10-15 minutes. The red solution was partitioned between water and chloroform (2 x 30 ml). The organic layer was dried (magnesium sulfate), concentrated and purified on a short silica gel column using 2% methanol in chloroform as eluent to give **3** (95 mg, 74%) as a yellowish powder,

mp 127° (from ether); 1H nmr: δ 1.85-2.08 (m, 4H, 5-H's, 7-H's), 2.55-2.59 (m, 1H, 4-H), 2.87-3.17 (m, 4H, 6-H's, 8-H's), 3.82 (s, 3H, *CH₃*), 4.37 (s, 2H, *CH₂Ph*), 7.18-7.34 (m, 5H, Ph); ^{13}C nmr: δ 26.1 (C-5, C-7), 34.1 (*CH₂Ph*), 41.8 (C-4), 48.8 (C-6, C-8), 57.0 (Me), 126.5, 128.0, 128.2, 128.7, 136.6 (Ph, C-2), 160.6 (olefinic), 205.4 (C-3); ms: m/z 257 (M^+).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.7; H, 7.4; N, 5.4. Found: C, 75.0; H, 7.5; N, 5.2.

(*E*)- and (*Z*)-2-(1-Nitromethyl-2-phenylethylidene)quinuclidin-3-one (**4**).

A solution of nitromethane (0.11 ml, 2 mmol) and sodium methoxide (65 mg, 1.2 mmol) in methanol (5 ml) was added to a solution of **2a** (272 mg, 1 mmol) in methanol (5 ml). The mixture was refluxed for 5 hours. Analyses (tlc) indicated the presence of starting material, a major product with a higher R_f value and several minor products with lower R_f values. Water (30 ml) was added and the solution was extracted with chloroform (2 x 30 ml). The organic extract was dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on a silica gel column using a gradient of 10-20% ethyl acetate in hexane as eluent to give **4** (114 mg, 40%) as a yellow oil consisting of a 1:1 mixture of the *E* and *Z* isomers; 1H nmr: δ 1.90-2.10 (m, 4H, 5-H's, 7-H's), 2.60-2.69 (m, 1H, 4-H), 2.85-3.23 (m, 4H, 6-H's, 8-H's), 3.84, 4.16 (2 s, 2H, *CH₂Ph*), 5.27, 5.54 (2 s, 2H, *CH₂NO₂*), 7.10-7.35 (m, 5H, Ph); ^{13}C nmr: δ 25.4 (C-5, C-7), 34.8, 36.2 (*CH₂Ph*), 42.0, 42.3 (C-4), 47.8, 47.9 (C-6, C-8), 73.8, 74.9 (*CH₂NO₂*), 127.0, 128.8, 128.9, 129.2, 129.3, 136.9, 137.1 (Ph), 132.4, 133.7 (olefinic), 145.8, 146.3 (C-2), 206.1 (C-3).

Anal. Calcd. for $C_{16}H_{18}N_2O_3 \cdot 0.5 H_2O$: C, 65.1; H, 6.4; N, 9.5. Found: C, 64.9; H, 6.6; N, 9.4.

General Procedure for the Amination of **2a**.

Compound **2a** (272 mg, 1 mmol) was treated with an excess of a concentrated solution of the appropriate amine in a tightly closed flask at $90-100^\circ$ for 4-5 hours. The mixture was concentrated *in vacuo* and the remaining volatiles were coevaporated with acetonitrile. The products were separated by column chromatography on silica gel, using 2% methanol in chloroform as eluent.

2-(1-Amino-2-phenylethylidene)quinuclidin-3-one (**6**).

Reaction of **2a** with 25% aqueous ammonia (5 ml) afforded **6** (198 mg, 82%) as white crystals, mp $101-102^\circ$ (from ether); 1H nmr: δ 1.75-1.90 (m, 4H, 5-H's, 7-H's), 2.48-2.51 (m, 1H, 4-H), 2.66-3.07 (m, 4H, 6-H's, 8-H's), 3.80 (s, 2H, *CH₂Ph*), 4.56, 8.85 (2 bs, 2H, *NH₂*), 7.17-7.32 (m, 5H, Ph); ^{13}C nmr: δ 26.7 (C-5, C-7), 36.4 (*CH₂Ph*), 41.1 (C-4), 50.2 (C-6, C-8), 118.2 (C-2), 127.3, 128.7, 129.1, 136.9 (Ph), 155.6 (olefinic), 203.7 (C-3); ms: m/z 242 (M^+).

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.4; H, 7.4; N, 11.6. Found: C, 74.2; H, 7.0; N, 11.3.

(*E*)-2-(1-Methylamino-2-phenylethylidene)quinuclidin-3-one (**7**) and 1,4-Ethano-5-methyl-7-nitro-6-phenyl-1,2,3,4-tetrahydropyrrolo[3,2-*b*]pyridine (**9**).

Reaction of **2a** with 40% methanolic methylamine (3 ml in 3 ml water) gave **7** (194 mg, 76%) as white crystals and **9** (17 mg, 6%) as yellow crystals; **7**, mp $127-128^\circ$ (from ether); 1H nmr: δ 1.70-1.85 (m, 4H, 5-H's, 7-H's), 2.44-2.48 (m, 1H, 4-H), 2.6-2.96 (m, 4H, 6-H's, 8-H's), 2.72 (d, 3H, $J = 5.0$ Hz, *CH₃*), 3.92 (s, 2H, *CH₂Ph*), 7.06-7.26 (m, 5H, Ph), 9.84 (app bs, 1H, *NH*);

^{13}C nmr: δ 26.8 (C-5, C-7), 29.7 (Me), 31.6 (CH_2Ph), 40.5 (C-4), 50.5, 50.7 (C-6, C-8), 118.0 (C-2), 126.2, 128.0, 128.6, 136.6 (Ph), 159.0 (olefinic), 201.4 (C-3); ms: m/z 256 (M^+).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$: C, 75.0; H, 7.8; N, 10.9. Found: C, 75.1; H, 7.7; N, 10.9.

Compound **9** had mp 258–259° dec (from 10% aqueous ethanol); ^1H nmr: δ 1.50–1.96 (m, 4H, 3-H's, 8-H's), 2.70–3.34 (m, 4H, 2-H's, 9-H's), 3.36–3.39 (m, 1H, 4-H), 3.40 (s, 3H, CH_3), 7.34–7.48 (m, 5H, Ph); ^{13}C nmr: δ 25.8 (C-4), 29.3 (C-3, C-8), 31.8 (Me), 50.7 (C-2, C-9), 127.9, 128.1, 128.7, 129.7, 135.4, 128.4, 129.0, 130.7 (C-4a, C-6, C-7, C-7a, Ph); ms: m/z 283 (M^+).

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_2 \cdot 0.5\text{H}_2\text{O}$: C, 65.8; H, 6.2; N, 14.4. Found: C, 65.7; H, 6.2; N, 14.4.

(*E*)- and (*Z*)-2-(1-Benzylamino-2-phenylethylidene)quinuclidin-3-one (**8**) and 5-Benzyl-1,4-ethano-7-nitro-6-phenyl-1,2,3,4-tetrahydropyrrolo[3,2-*b*]pyridine (**10**).

Reaction of **2a** with benzylamine (1 ml in 50% aqueous methanol, 5 ml) afforded **8** (235 mg, 71%) as an isomeric mixture (*E/Z* 7 : 1) and **10** (18 mg, 5%) as yellow crystals.

Compound (*E*)-**8** was obtained as a yellowish oil; ^1H nmr: δ 1.70–1.86 (m, 4H, 5-H's, 7-H's), 2.50–2.54 (m, 1H, 4-H), 2.58–2.97 (m, 4H, 6-H's, 8-H's), 3.94 (s, 2H, CH_2Ph), 4.20 (d, 2H, J = 6.8 Hz, NCH_2Ph), 7.00–7.28 (m, 10H, Ph), 10.26 (1H, NH); ^{13}C nmr: δ 26.8 (C-5, C-7), 32.0 (CH_2Ph), 40.8 (C-4), 47.1 (NCH_2Ph), 50.7 (C-6, C-8), 118.4 (C-2), 126.8, 127.0, 127.3, 127.8, 128.8, 128.9, 136.7, 137.9 (Ph), 157.6 (olefinic), 202.6 (C-3); ms: m/z 332 (M^+).

Anal. Calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}$: C, 79.5; H, 7.2; N, 8.4. Found: C, 79.2; H, 6.9; N, 8.2.

Compound **10** had mp 211–212° dec (from 10% aqueous ethanol); ^1H nmr: δ 1.25–1.74 (m, 4H, 3-H's, 8-H's), 2.62–3.23 (m, 4H, 2-H's, 9-H's), 3.01–3.05 (m, 1H, 4-H), 4.87 (s, 2H, CH_2Ph), 6.80–7.38 (m, 10H, Ph); ^{13}C nmr: δ 26.2 (C-4), 29.3 (C-3, C-8), 48.4 (CH_2Ph), 50.8 (C-2, C-9), 126.1, 126.9, 127.8, 128.2, 128.5, 128.9, 129.0, 129.3, 129.6, 135.5, 136.9, 130.8 (C-4a, C-6, C-7, C-7a, Ph); ms: m/z 359 (M^+).

Anal. Calcd. for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2 \cdot 0.5\text{H}_2\text{O}$: C, 71.7; H, 6.0; N, 11.4. Found: C, 71.6; H, 6.2; N, 11.5.

(*E*)- and (*Z*)-2-(1,2-Diphenylethylidene)quinuclidin-3-one (**5**) and (*E*)- and (*Z*)-2-(1,2-Diphenylvinyl)quinuclidin-3-one (**11**).

A solution of lithium diphenylcopper was prepared by dropwise addition of phenyllithium (2*M* solution in hexane, 1.25 ml, 2.5 mmoles) to a suspension of cuprous bromide (dried by coevaporation with tetrahydrofuran, 200 mg, 1.4 mmoles) in tetrahydrofuran (5 ml) at 0°. The resulting mixture was stirred at ambient temperature for 20–30 minutes. A solution of **2a** (272 mg, 1 mmole) in tetrahydrofuran (3 ml) was added dropwise at 0°. After stirring for 1 hour at 0° the mixture was quenched with water (20 ml), extracted with chloroform (2 x 30 ml) and quickly purified on a silica gel column using a gradient of 30–50% of ethyl acetate in hexane as eluent to give **5** (57 mg, 19%, high R_f , see below) and an oily product consisting mostly (around 90%) of **11** (166 mg, 55%, lower R_f) as an isomeric mixture (*E/Z* 3:2) according to the tlc and nmr spectra; ^1H nmr: δ 1.50–2.10 (m, 4H, 5-H's, 7-H's), 2.48–2.63 (m, 1H, 4-H), 2.60–3.40 (m, 4H, 6-H's, 8-H's), 4.14, 4.52 (app bs, 1H, 2-H), 6.47, 6.81 (2 app bs, 1H, olefinic), 6.80–7.40 (m, 10H, Ph); ^{13}C nmr: δ 23.8, 25.0, 25.7, 27.5 (C-5, C-7), 40.8, 41.0, 41.1, 43.4, 48.4, 49.0 (C-4, C-

6, C-8), 71.2, 76.6 (C-2), 127.4, 127.7, 128.2, 128.3, 128.4, 128.5; 128.6, 129.0, 129.4, 130.1, 136.2, 136.8, 137.0, 137.4, 140.0, 140.6, 143.1 (Ph, olefinic), 219.6, 220.0 (C-3).

Upon standing at room temperature from several hours to a couple of days **11** was spontaneously isomerizing to a 3:1 mixture of (*Z*)- and (*E*)-**5**. The mixture was purified on a silica gel column using 20% ethyl acetate in hexane as eluent; (*Z*)-**5**, mp 110–112°; ^1H nmr: δ 1.87–2.14 (m, 4H, 5-H's, 7-H's), 2.63 (ddd, 1H, J = 2.8 Hz, 4-H), 2.80–3.04 (m, 4H, 6-H's, 8-H's), 4.38 (s, 2H, CH_2Ph), 7.00–7.30 (m, 10H, Ph); ^{13}C nmr: δ 25.8 (C-5, C-7) 38.7 (C-4), 42.6 (CH_2Ph), 48.1 (C-6, C-8), 127.3, 127.8, 127.9, 128.2, 128.9, 138.5, 140.0, 140.8 (vinyl, Ph); ms: m/z 303 (M^+).

Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{NO}$: C, 83.2; H, 6.9; N, 4.6. Found: C, 82.9; H, 6.6; N, 4.4.

Compound (*E*)-**5** had ^1H nmr: δ 1.90–2.10 (m, 4H, 5-H's, 7-H's), 2.46 (ddd, 1H, J = 2.8 Hz, 4-H), 3.00–3.27 (m, 4H, 6-H's, 8-H's), 4.00 (s, 2H, CH_2Ph), 6.93–7.32 (m, 10H, Ph); ^{13}C nmr: δ 25.7 (C-5, C-7), 40.7 (C-4), 42.0 (CH_2Ph), 48.4 (C-6, C-8), 126.1, 127.3, 127.5, 127.8, 128.1, 128.3, 128.9, 129.0, 138.1; 139.2 (vinyl, Ph); ms: m/z 303 (M^+).

Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{NO}$: C, 83.2; H, 6.9; N, 4.6. Found: C, 83.0; H, 6.6; N, 4.5.

(*1S**,*2S**,*2'S**)-1-Nitro-2-phenylspiro[cyclopropane-3,2'-quinuclidin]-3'-oxime (**12**).

A mixture of **2a** (0.2 g, 0.74 mmole) and hydroxylamine hydrochloride (103 mg, 1.48 mmoles) was heated in 10 ml of dry pyridine at 80–90° for 20 minutes. The solvent was removed *in vacuo*, and the residue was quickly partitioned between water (pH 7) and chloroform. The dried (magnesium sulfate) organic solution was concentrated and coevaporation with toluene produced a coloured oil, containing a new compound with lower R_f value (**12**). Compound **12** undergoes complete degradation to a dark blue tar on storage for several hours. The degradation occurred immediately at pH >9; ^1H nmr: δ 1.65–1.82 (m, 4H, 5'-H's, 7'-H's), 2.30–3.39 (m, 4H, 6'-H's, 8'-H's), 3.62–3.66 (m, 1H, 4'-H), 3.87 (d, 1H, J = 6.4 Hz, 2-H), 4.86 (d, 1H, 1-H), 7.25–7.35 (m, 5H, Ph), 10.7 (1H, OH); ^{13}C nmr: δ 24.1, 24.2, 25.8 (C-5', C-7', C-4'), 37.9 (C-2), 44.7, 46.8 (C-6', C-8'), 56.2 (C-2'), 71.6 (C-1), 127.4, 128.1, 128.3, 132.7 (Ph), 158.2 (C-3').

(4a*R**,7a*S**)-7-[(*E*)-Benzylidene]-1,4-ethano-4a-hydroxyperhydropyrrolo[4,3-*b*]pyridin-5-one (**13**).

A mixture containing **2a** (272 mg, 1 mmole) and sodium cyanide (73.5 mg, 1.5 mmoles) in 50% aqueous ethanol (7 ml) was stirred at 50° for 1 hour and was then kept at 0° for 5 hours. The precipitated crystals were collected, dried *in vacuo* and then recrystallized from chloroform. The mother liquor was concentrated to leave a residue which was filtered through a short silica gel column using 10% methanol in chloroform as eluent. The eluent was evaporated *in vacuo* and the residue was titrated with chloroform to afford an additional amount of pure **13** giving a total yield of 62% (167 mg) as white crystals; mp 228–230° dec; ^1H nmr: δ 1.45–2.12 (m, 4H, 3-H's, 8-H's), 1.70 (bs, 1H, OH), 2.08–2.12 (m, 1H, 4-H), 2.56–3.22 (m, 4H, 2-H's, 9-H's), 3.8 (app bs, 1H, 7a-H), 6.83 (bs, 1H, NH), 7.28–7.81 (m, 5H, Ph), 7.54 (d, 1H, J = 1.8 Hz, CH-Ph); ^{13}C nmr (20% deuterio-methanol in deuteriochloroform): δ 22.2, 23.6 (C-3, C-8), 32.0 (C-4), 41.3, 47.4 (C-2, C-9), 66.9 (C-7a), 85.1 (C-4a), 128.0, 129.2, 130.7, 131.8, 134.5, 138.2 (benzylidene), 171.7 (C-5); ms: m/z 252 ($\text{M}^+ - \text{H}_2\text{O}$).

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.1; H, 6.7; N, 10.4. Found: C, 70.8; H, 6.7; N, 10.1.

1,4-Ethano-6-phenyl-1,2,3,4-tetrahydrofurano[3,2-*b*]pyridine (**14**).

A stirred mixture of **2a** (272 mg, 1 mmole) and anhydrous iron trichloride (162 mg, 1 mmole) in dichloroethane (10 ml) was refluxed under nitrogen for 24 hours. The cooled mixture was diluted with chloroform, triturated with 10% aqueous sodium carbonate, filtered through *Celite* and concentrated *in vacuo*. The residue was purified on a silica gel column using a gradient of 0-3% methanol in ethyl acetate as eluent to afford **14** as an oil (115 mg, 51%); 1H nmr: δ 1.55-1.94 (m, 4H, 3-H's, 8-H's), 2.58-3.18 (m, 4H, 2-H's, 9-H's), 3.40-3.44 (m, 1H, 4-H), 6.58 (s, 1H, 7-H), 7.17-7.66 (m, 5H, Ph); ^{13}C nmr: δ 28.0 (C-4), 29.9 (C-3, C-8), 51.1 (C-2, C-9), 101.9 (C-7), 123.0, 126.6, 128.6, 131.4, 134.6 (Ph, C-7a), 150.7, 157.1 (C-4a, C-6); ms: m/z 225 (M^+). An analytical sample was obtained by conversion of the base into the hydrochloride salt using ethereal hydrogen chloride, mp, 114-117° dec.

Anal. Calcd. for $C_{15}H_{15}NO \cdot HCl$: C, 68.8; H, 6.1; N, 5.4. Found: C, 68.7; H, 6.2; N, 5.2.

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