Tetrahedron Vol. 40, No. 8, pp. 1419 to 1424, 1984
Printed in Great Britain

0040-4020/84 $3.00 + .00
Pergamon Press Ltd.

SYNTHETIC APPLICATIONS OF 2-CYANOPIPERIDINES. MODEL STUDIES IN THE SYNTHESIS OF BRIDGED INDOLE ALKALOIDS[1]

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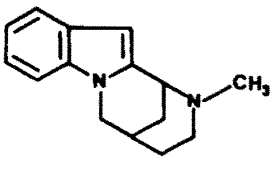
(*Received in UK 28 November* 1983)

Abstract – Acid cyclization of 4-(indol-1- and -3-ylmethyl)-2-cyanopiperidines 5 led to the bridged tetracyclic indole systems 1 and 2. The required 2-cyanopiperidines 5 were prepared by catalytic hydrogenation of 2-cyano-1,2,3,6-tetrahydropyridines 4 and by DIBAL reduction of lactams 7 followed by cyanide ion addition to the intermediate enamine.

2-Cyanopiperidines and 2-cyanotetrahydropyridines can be considered as latent forms of iminium salts due to their ability to lose a cyanide ion on acid treatment.[2-6] For this reason, these compounds have been frequently used as intermediates in alkaloid synthesis,[7] especially in that of indole alkaloids.[8-11] In this context, syntheses which imply an intramolecular cyclization upon the indole ring by electrophilic attack of an iminium salt generated from an appropriate 2-cyanopiperidine or 2-cyanotetrahydropyridine deserve especial attention.[12-15] However, there are few examples in which this property has been applied to the synthesis of bridged polycyclic systems condensed with the indole nucleus.[16]

In connection with our studies on the synthesis of bridged indole alkaloids and related structures[10,17-20] we wished to determine if the intramolecular cyclization of 2-cyano-4-(indol-1- and -3-ylmethyl)piperidines 5 was a suitable method for the synthesis of hexahydro-2,6-methano[1,4]diazocino[1,2-a]indole (1) and 1,5-methanoazocino[3,4-b]indole (2) systems. Compound 1 can be considered as the fundamental tetracyclic framework of the indole alkaloid vinoxine,[21] whereas 2 possesses four of the five rings of the indole alkaloids strictamine[22] and akuammiline.[23] The preparation of compounds 1 and 2 by mercuric acetate oxidation of the corresponding indolylmethylpiperidines 6 has been already described in a previous paper.[20,24]

Initially, we planned the preparation of the required 2-cyanopiperidines 5 by catalytic hydrogenation of the carbon-carbon double bond of 2-cyanotetrahydropyridines 4, since it is well known that 2-cyano-1,2,3,6-tetrahydropyridines are easi-



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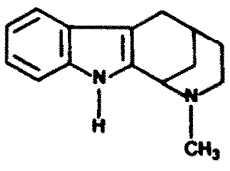

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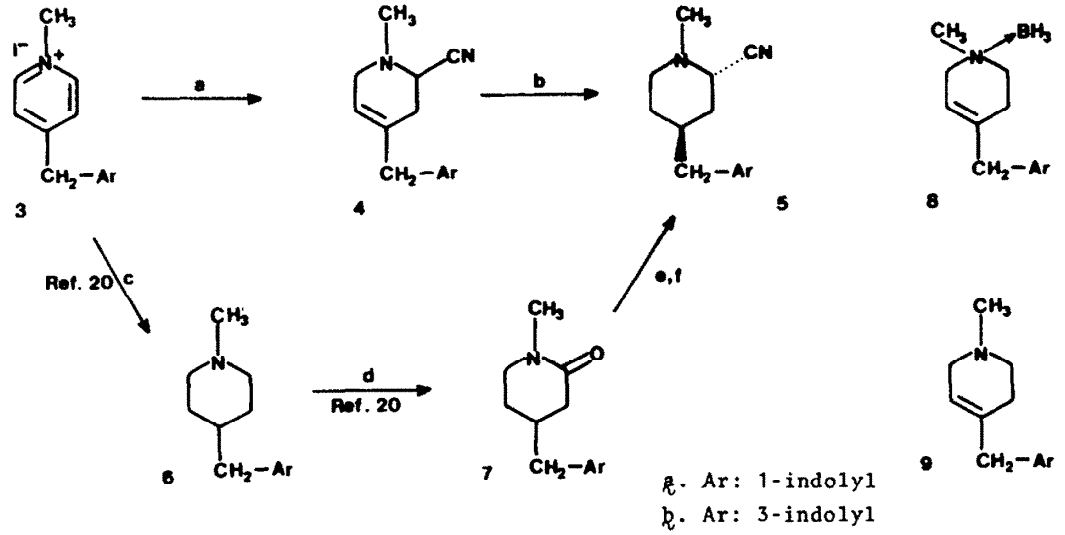
ly accessible by reductive cyanation of the corresponding pyridinium salts 3.[2] As expected, treatment of 3a[20] or 3b[20] with sodium borohydride in the presence of a large excess of cyanide ions afforded 2-cyanotetrahydropyridines 4a and 4b, respectively. The amine-borane complexes 8a and 8b were isolated as by-products and easily transformed into the corresponding tetrahydropyridines 9 by heating in ethanolic solution. 2-Cyanotetrahydropyridines 4a and 4b showed an ir absorption at 2220-2230 cm^{-1}, whereas the most characteristic signals in the nmr spectra were the doublet of doublets at δ3.4 and 3.7, respectively, due the C-2 methine proton.

Our first attempts on the reduction of the carbon-carbon double bond of 2-cyanotetrahydropyridines 4 were unsuccessful[18,25] owing to the easy hydrogenolysis of the cyano group. The corresponding tetrahydropyridines 9 and piperidines 6 were the only isolable products. On the other hand, the reduction appeared to be very dependent on the experimental conditions. However, when the hydrogenation was carried out at atmospheric pressure in methanolic solution in the presence of a 35% by weight of 10% palladium on charcoal according to the conditions described by Husson for the reduction of several 2-cyano-1,2,5,6-tetrahydropyridines,[4,7,27-29] 2-cyanopiperidines 5 were obtained in good yields.

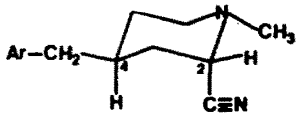
An alternative synthetic route to the required 2-cyanopiperidines 5 was based on the controlled reduction, followed by cyanation,[30] of 2-piperidones 7, whose preparation in excellent yield by mercuric acetate-EDTA oxidation under alkaline conditions of piperidines 6 we described in a previous work.[20] Thus, reduction of 7a with diisobutylaluminium hydride[31,34] followed by addition of potassium cyanide to the resulting enamine-iminium salt afforded 2-cyanopiperidine 5a in 61% yield. Similarly, 2-piperidone 7b was converted to 2-cyanopiperidine 5b in 45% yield.

2-Cyanopiperidines 5 showed a characteristic ir absorption due to the cyano group as well as nmr spectra (200 MHz) consistent with the proposed structures. However, it is worth commenting that only the *trans* diastereomer was detected in both series regardless of the method of preparation. Thus, the signals for the C-2 methine proton of 5a and 5b appeared at δ3.8 as apparent triplets with J=4 Hz, clearly indicating the equatorial orientation of this proton and, therefore, that the cyano group was positioned axially. Since the multiplicity of the axial C-3 and C-5 protons confirmed that the bulky indolylmethyl substituent at C-4 was, as



Reagents: (a) $NaBH_4$, NaCN; (b) H_2, Pd/C, CH_3OH; (c) H_2, PtO_2; (d) $Hg(AcO)_2$, EDTA, H_2O; (e) DIBAL, -70°C; (f) KCN, NH_4Cl

expected, equatorially oriented, the *trans* stereochemistry of 5a and 5b is well established. The axial preference of a cyano group, as well as the facile equatorial-axial epimerization of this group in 2-cyanopiperidines, has been previously observed.[28,29] On the other hand, the cyanide ion addition to 4-substituted 3,4,5,6-tetrahydropyridinium salts has been reported to occur in a stereospecific manner to give the *trans* diastereomers in which the cyano group is also in an axial orientation.[15,16,35]



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a. Ar: 1-indolyl
b. Ar: 3-indolyl

It was expected that treatment of cyanopiperidines 5 with acid would generate an iminium salt by elimination of the cyano group, thus allowing cyclization upon indole to occur. Indeed, heating a solution of 5a in aqueous acetic acid afforded the fundamental tetracyclic framework of vinoxine 1 in 70% yield, much higher than that obtained[20] by mercuric acetate oxidation of the corresponding piperidine 6a. Similarly, 2-cyanopiperidine 5b was converted on acid treatment into the tetracyclic ring system 2 in 85% yield. The presence of an unsubstituted indole C-3 position can probably account for the lower yield in the first case.

The results here reported make evident the usefulness of 2-cyanopiperidines as latent forms of iminium salts as well as their application to the synthesis of structures related with bridged indole alkaloids.

EXPERIMENTAL

General. PMR spectra were recorded in $CDCl_3$ with TMS as internal standard (60 MHz: Perkin-Elmer R-24B; 200 MHz: Varian XL-200). Chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were taken with a Perkin-Elmer 577 Spectrophotometer, and only noteworthy absorptions (reciprocal centimeters) are listed. Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. Column and thin-layer chromatography were done by using silica gel 60 (Merck). Iodoplatinate reagent was used to locate the reaction components. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed by the Instituto de Química Bio-Orgánica, Barcelona.

4-(1-Indolylmethyl)-1-methyl-1,2,3,6-tetrahydropyridine-2-carbonitrile (4a). Hydrochloric acid (6N, 3.8 ml) was added dropwise to a stirred solution of sodium cyanide (2.75 g, 56 mmol) in water (70 ml), keeping the temperature below 15°C. To the resulting solution were added 125 ml of ether, 5 g (14.2 mmol) of the pyridinium iodide 3a,[20] and then 0.7 g (18.4 mmol) of sodium borohydride. The mixture was stirred at room temperature for 4 h, the ether was decanted, and the aqueous layer was extracted with ether. The combined ethereal solutions were extracted with 5% hydrochloric acid, dried, and evaporated to give 1 g of *4-(1-indolylmethyl)-1-methyl-1,2,3,6-tetrahydropyridine-borane* (8a); NMR 2.2 (s,3H,NCH_3), 4.4 (s,2H, $ArCH_2$), 5.2 (br,1H,=CH), 6.35 (d,J=4Hz,1H,indole H-3), 6.9 (d,J=4Hz,1H,indole H-2), 6.7-7.3 (m,3H,indole), 7.5-7.8 (m,1H,indole H-7); IR ($CHCl_3$) 2380-2280 (BH). The aqueous acidic extracts were basified with sodium carbonate and extracted with ether to give cyanotetrahydropyridine 4a (2.4 g, 67%). A sample recrystallized from absolute ethanol melted at 55-56°C; NMR 2.2 (s,3H,NCH_3), 3.4 (dd,1H,NCH), 4.4 (s,2H,$ArCH_2$), 5.3 (br,1H,=CH), 6.3 (d,J=4Hz,1H,indole H-3), 6.7 (d,J=4Hz,1H,indole H-2) 6.8-7.1 (m,3H,indole), 7.2-7.5 (m,1H,indole H-7); IR (KBr) 2220 (cyano). (Found: C,76.18; H,6.83; N,16.55. Calcd. for $C_{16}H_{17}N_3$: C,76.46; H,6.81; N,16.72).

4-(3-Indolylmethyl)-1-methyl-1,2,3,6-tetrahydropyridine-2-carbonitrile (4b). Pyridinium salt 3b[20] (13 g, 37 mmol) was allowed to react as above with sodium cyanide (6.65 g, 0.13 mol) and sodium borohydride (1.75 g, 46 mmol). Evaporation of the initial ethereal extracts gave 0.2 g of *4-(3-indolylmethyl)-1-methyl-1,2,3,6-tetrahydropyridine-borane* (8b). A sample recrystallized from ether melted at 117-118°C; NMR 2.5 (s,3H,NCH_3), 3.45 (s,4H,$ArCH_2$ and NCH_2), 5.4 (br,1H,=CH), 6.9-7.8 (m,5H,indole), 8.05 (br,1H,indole NH); IR (KBr) 2500-2240 (BH). (Found: C,71.90; H,8.86; N,11.36. Calcd. for $C_{15}H_{21}BN_2 \cdot 1/2H_2O$: C,72.31; H,8.90; N,11.24). Evapora-

tion of the aminated ethereal extracts gave 2-cyanotetrahydropyridine **4b** (7 g, 75%). A sample recrystallized from ether melted at 122-124°C; NMR 2.35 (s,3H,NCH_3), 3.4 (s,2H,$ArCH_2$), 3.7 (dd,1H,NCH), 5.5 (br,1H,=CH), 6.9-7.4 (m,4H,indole), 7.4-7.6 (m,1H,indole H-7), 8.2 (br,1H,indole NH); IR (KBr) 2230 (cyano). (Found: C,76.77; H,6.99; N,16.96.Calcd. for $C_{16}H_{17}N_3$: C,76.46; H,6.81; N,16.72).

1-[1-Methyl-1,2,3,6-tetrahydro-4-pyridylmethyl]indole (**9a**). The amine-borane complex **8a** (1 g, 4.16 mmol) was refluxed in ethanol (200 ml) for 24 h. The residue after evaporation was dissolved in water and extracted with ether to afford tetrahydropyridine **9a** (0.6 g, 62%); NMR 2.2 (s,3H,NCH_3), 4.4 (s,2H, $ArCH_2$), 5.3 (br,1H, =CH), 6.3 (d,J=4Hz,1H,indole H-3), 6.9 (d,J=4Hz,1H,indole H-2), 7.0-7.3 (m,3H,indole), 7.3-7.8 (m,1H,indole H-7). The picrate melted at 180-182°C (absolute ethanol). (Found: C,55.68; H,4.90; N,15.53. Calcd. for $C_{21}H_{21}N_5O_7$: C,55.38; H,4.62; N,15.38). The same tetrahydropyridine **9a** was obtained in 61% yield, after the usual workup, by treatment of the pyridinium salt **3a** (2 g, 5.7 mmol) with sodium borohydride (0.5 g, 13 mmol) in ethanol (50 ml) and 0.1N sodium hydroxide (15 ml) at room temperature for 4 h.

3-[1-Methyl-1,2,3,6-tetrahydro-4-pyridylmethyl]indole (**9b**). Operating as above, the amine-borane complex **8b** was transformed into the tetrahydropyridine **9b**. A sample recrystallized from ether-ethanol melted at 152-153°C; NMR 2.3 (s,3H,NCH_3), 3.45 (s,2H,$ArCH_2$), 5.5 (br,1H,=CH), 6.85-7.45 (m,4H,indole), 7.45-7.75 (m,1H, indole H-7), 8.6 (br,1H,indole NH). (Found: C,79.45; H,8.27; N,12.43. Calcd. for $C_{15}H_{18}N_2$: C,79.61; H,8.01; N,12.37). The same tetrahydropyridine **9b** was obtained in 94% yield, after the usual workup, by treatment of the pyridinium salt **3b** (1 g, 2.8 mmol) with sodium borohydride (0.25 g, 65 mmol) in ethanol (10 ml) and 0.1 N sodium hydroxide (10 ml) at reflux for 4 h.

4-[1-Indolylmethyl]-1-methylpiperidine-2-carbonitrile (**5a**).

Method A. A solution of cyanotetrahydropyridine **4a** (0.5 g, 1.99 mmol) in 15 ml of methanol was hydrogenated at room temperature and atmospheric pressure over 175 mg of 10% palladium on charcoal (Merck). When the volume corresponding to one equivalent of hydrogen was absorbed, the catalyst was filtered off, and the filtrate was evaporated to give an oil which was purified by column chromatography. Elution with 6:4 benzene-chloroform afforded cyanopiperidine **5a** (0.25 g, 50%); NMR 1.35 (qd,J=4.2Hz,12Hz,1H,H-5ax), 1.62 (td,J=4.2,12Hz,1H,H-3ax), 1.74-2.07 (m,2H, H-3eq and H-5eq), 2.16 (m,1H,H-4ax), 2.20 (td,J=2.8,12.8Hz,1H,H-6ax), 2.34 (s,3H, NCH_3), 2.70 (dt,J=3.6,12Hz,1H,H-6eq), 3.78 (apparent t,J=4Hz,1H,H-2eq), 3.96 and 4.02 (2dd,1H each,J=7.0,16.8Hz,$ArCH_2$), 6.48 (d,J=3.6Hz,1H,indole H-3), 7.00 (d, J=3.6Hz,1H,indole H-2), 7.00-7.32 (m,3H,indole), 7.59 (d,J=7.2Hz,1H,indole H-7); IR (NaCl) 2220 (cyano). (Found: C,75.54; H,7.75; N,16.18. Calcd. for $C_{16}H_{19}N_3$: C, 75.85; H,7.55; N,16.58). On elution with 95:5 chloroform-methanol, a 1:1 mixture (80 mg) of piperidine **6a** and tetrahydropyridine **9a** was obtained.

Method B. Diisobutylaluminium hydride (DIBAL) in toluene (1.2M, 4.78 ml, 5.74 mmol) was added dropwise (30 minutes) under nitrogen to a cooled (-70°C) solution of piperidone **7a**[20] (1 g, 4.1 mmol) in 10 ml of anhydrous tetrahydrofuran. The mixture was stirred at -70°C for 1 h and then allowed to rise to 0°C. Methanol (10 ml) and 1N NaOH (20 ml) were added to the reaction mixture, and the resulting solution was stirred for 20 minutes and then extracted with methylene chloride. Evaporation of the extracts left a residue which was dissolved in a solution of potassium cyanide (3 g, 46.1 mmol) and ammonium chloride (2.4 g, 44.8 mmol) in 100 ml of ethanol-water (4:1). After the mixture was stirred at room temperature for 10 h, the solvent was removed, the residue was dissolved in methanol (20 ml), and the resulting solution was refluxed for 1 h. The methanol was evaporated, and the oily residue was distributed between water and methylene chloride. The organic layer was separated, the aqueous one was extracted with methylene chloride, and the combined organic extracts were dried and evaporated to give an oil (0.9 g) which was chromatographed. On elution with 6:4 benzene-chloroform, cyanopiperidine **5a** (0.65 g, 61%) was obtained, whereas on elution with chloroform, the starting piperidone **7a** (0.15 g) was recovered. When this reaction was effected at higher temperature or for longer reaction time, the corresponding piperidine **6a** was also isolated.

4-[3-Indolylmethyl]-1-methylpiperidine-2-carbonitrile (**5b**).

Method A. Operating as in the above method A, 2-cyanotetrahydropyridine **4b** (0.4 g, 1.59 mmol) was hydrogenated over 10% palladium on charcoal (140 mg) to give essentially pure **5b** (0.35 g, 84%). An analytical sample was obtained by column chromatography (chloroform as eluent); NMR 1.29 (qd,J=4.2,12Hz,1H,H-5ax), 1.58 (td,J= 4.2,14.4Hz,1H,H-3ax), 1.72 (dt,J=3.0, 12 Hz,1H,H-3eq), 1.98 (dt,J=3.0,14.4Hz,1H, H-5eq), 1.89-2.07 (masked,1H,H-4ax), 2.32 (td,J=3,12Hz,1H,H-6ax), 2.34 (s,3H,NCH_3), 2.55-2.77 (masked,1H,H-6eq), 2.70 (d,J=7.2 Hz,2H,$ArCH_2$), 3.79 (apparent t,J=3.6Hz, 1H,H-2eq), 6.93 (d,J=3.6Hz,1H,indole H-2),7.05-7.38 (m,3H,indole), 7.56 (d,J=7.2 Hz,1H,indole H-7), 8.1 (br,1H,indole NH); IR (NaCl) 2220 (cyano). The picrate melted at 220-222°C (absolute ethanol). (Found: C,54.20; H,4.50; N,16.90. Calcd. for: $C_{22}H_{22}N_6O_7.1/2H_2O$: C,53.92; H,4.72; N,17.13.

Method B. Operating as in the above method B, piperidone **7b**[20] (0.4 g, 1.65 mmol) was reduced with 1.2M DIBAL (1.78 ml, 2.14 mmol) in toluene, and then treated with potassium cyanide (1.5 g, 23 mmol) and ammonium chloride (1.2 g, 22.4 mmol). After the usual workup, an oil was obtained (0.34 g), which was chromatographed. On elution with chloroform, cyanopiperidine **5b** (0.19 g, 45.5%) was obtained, whereas on

elution with 99:1 chloroform-ethanol 0.1 g of the starting piperidone 7b was recovered.

5-Methyl-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-a]indole (1). A stirred solution of cyanopiperidine 5a (0.13 g, 0.5 mmol) in 80% acetic acid (10 ml) was heated under nitrogen at 70-80°C over a 10 h period. The resulting solution was cooled, basified with 1N NaOH, and extracted with methylene chloride. Drying and evaporation of the organic extracts gave an oil (110 mg) which by NMR was found to be a 6:1 mixture of the cyclized product 1 and the starting nitrile 5a. Pure 1^{20} (78 mg, 70%) was obtained by column chromatography using chloroform as eluent. When cyclization was effected at lower temperature and/or for shorter reaction time, increasing amounts of 2-cyanopiperidine 5a were recovered.

2-Methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-b]indole (2). Operating as above from cyanopiperidine 5b (0.12 g, 0.47 mmol) and 50% acetic acid (10 ml) at 60°C for 1 h 45 minutes, essentially pure 2^{29} (90 mg, 85%) was obtained.

Acknowledgements- This work was supported by the Comisión Asesora de Investigación Científica y Técnica, Spain.

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