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2-CYANO Δ^3 PIPERIDINES VI[1] : A GENERAL METHOD FOR THE STEREOSELECTIVE SYNTHESIS OF *CIS* AND *TRANS* 2,6-DIALKYLPIPERIDINE ALKALOIDS

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Summary : The *cis* 2,6-dialkylpiperidine alkaloid (±) dihydro-pinidine 7b and the *trans* alkaloid (±) solenopsin A 5a were synthesized from a common α-aminonitrile synthon 1. The key step in this synthesis was the stereoselective reductive decyanation of the 1-benzyl-2-cyano-2',6-dialkylpiperidines 3a and 3b.

2,6-dialkylpiperidine alkaloids are a widely distributed class of compounds exhibiting diverse biological activities. They have been isolated from both animal (eg. histrionicotoxin[2], solenopsin A 5a[3]) and plant species (eg sedinine[4], pinidine[5a], carpaine[6]). The synthesis of many of these alkaloids has been achieved by catalytic or sodium/alcohol reduction of the corresponding pyridine derivatives[3]. Other methods used have included :

a) catalytic or hydride reduction of substituted imines[5a-c],

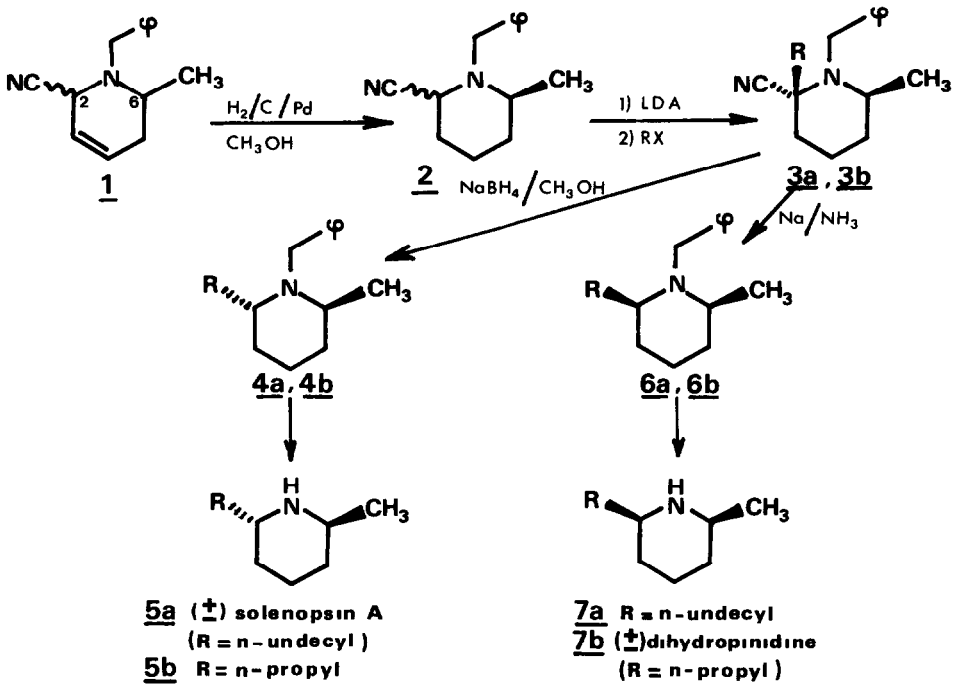
b) intramolecular amination of olefins in the presence of mercuric ion[7] or C_6H_5SeCl[8], and

c) cyclization of aminoketones[9]. Whereas a number of these methods are amenable to the stereoselective synthesis of *cis*-2,6 disubstituted alkaloids none of these methods is efficient for the preparation of the *trans*-2,6 system. *Trans* 2,6-dialkylpiperidines have always been isolated as minor components from product mixtures containing both isomers[10].

In this paper we wish to report the development of a new, general synthetic route for the preparation of *cis*, and in particular *trans* 2,6-dialkylpiperidine alkaloids starting from a common synthon. The key step in this strategy is the efficient reductive decyanation of intermediate 2,6-dialkyl-2'-cyanopiperidines to either the *cis* or *trans* alkaloid systems through a proper choice of reaction conditions.

To illustrate this approach we have synthesized the *trans* alkaloid (±) solenopsin A 5a, and the *cis* alkaloid (±) dihydropinidine 7b (and their epimers 5b and 7a) from the 2-cyano Δ^3 piperidine 1

Aminonitrile 1 (obtained as an inseparable mixture of epimers)[11] was prepared from 2-picoline according to our procedure[12] (Y = 53%). The double bond of 1 was selectively hydrogenated in the presence of Pd/C affording 2[13] (Y = 95 %). Alkylation of the anion derived from 2 respectively with propyl and undecyl bromides resulted in the formation of the 2,6-disubstituted products 3a[14] (Y = 77%) and 3b[14] (Y = 60%) only[15] Reductive decyanation of 3b with sodium in liquid ammonia /THF at -78° [16] gave 6b[17] in nearly quantitative yield.



The *cis* relationship between the C-2 and C-6 alkyl substituents was inferred from the singlet resonance (δ = 3.7 ppm) observed for the benzyl methylene protons in the ^{1}H NMR spectrum of 6b [18], and by the subsequent debenzylation of 6b to (±) dihydropinidine 7b [5a] (Y = 95 %). The detection (NMR, GC assay) of the *cis* 2-6-dialkyl isomer only from this reaction was in keeping with previous observations which showed that decyanation of α-aminonitriles with solvated electrons occurs with retention of configuration [16]

In contrast, reductive decyanation of 3b with $NaBH_4$ in MeOH [19] led to predominant formation of the *trans* isomer 4b [20] (80 : 20 mixture with the *cis* isomer 6b, Y = 85 %) As above, the formation of the *trans* disubstituted system was inferred from the ^{1}H NMR signal for the benzyl methylene protons [18] (δ = 3.5 and 3.8ppm, 2d, J_{AB} = 14 Hz), and by subsequent debenzylation of 4b to product 5b [21] [22] It is noteworthy that this reaction which probably proceeded *via* an iminium intermediate gave a ratio of isomers 4b/6b which is opposite to that obtained through $NaBH_4$ reduction of the corresponding imine [5a]

This same route was followed for the preparation of the *trans* 2,6-dialkylpiperidine alkaloid (±) solenopsin A 5a, a constituent of the fire ant venom. The reaction of 3a with $NaBH_4$ afforded the decyano product 4a [23] in 80 % yield. Compound 4a was then debenzylated to solenopsin A 5a [23] (52 % overall yield from 1 in four steps) The stereoselective (8 2) formation of the *trans* isomer by this sequence of reactions contrasts markedly with previously reported syntheses of solenopsin A 5a [3,5a,8,24] where predominant formation of

the undesired *cis* isomer was observed.

To complete the study the *cis* product epi-solenopsin A 7a was in turn prepared by treatment of 3a with sodium in liquid ammonia at -78°. Product 6a [25] (Y = 80 %) formed stereospecifically in this step was subsequently debenzylated giving 7a in 98 % yield

In conclusion the alkylation products of 1-benzyl-2-cyano-6-methyl-piperidine 2 could be transformed stereospecifically into the *cis* isomer or stereoselectively (> 80 %) into the *trans* isomer depending upon the reduction method employed. The extension of this work to include piperidine alkaloids having also a $\Delta^{3,4}$ double bond[4] or a 3-hydroxyl group[6] will be described in a forthcoming communication

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10 - During the course of the writing of this paper Yamamoto et al. (Tetrahedron Letters, 1982, 23, 1929) have published a highly stereoselective synthesis of solenopsin A.

11 - 1 : Oil ; MS m/e (relative intensity) 212 (M^+ , 25) 197 (38), 91 (100) ; IR (neat) 2210, 1630, 1600cm^{-1} , ^1H NMR ($CDCl_3$, 400 MHz, TMS δ = 0) ; 1 20 and 1 27 (d, J = 6 Hz, $\underline{H_3}C-C-H$), 3.4 and 4 23 (2d, J_{AB}= 14 Hz, N-$\underline{CH_2}\phi$), 3.89 (broad s, N-$\underline{CH_2}$-ϕ), 3.86 and 4.03 (m, NC-C-$\underline{H}$)

12 - D.S. Grierson, M. Harris and H.-P. Husson, J. Am. Chem. Soc., 1980, 102, 1064.

13 - 2 : oil ; MS m/e (relative intensity) : 214 ($M^{+\cdot}$, 30), 199 (100), 188 (41), 173 (46), 123 (80), 91 (100) ; IR (neat) 2200, 1600cm^{-1} ; ^{1}H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 1.18 (d, 6 Hz, $\underline{H}_3C$-C-H), 3.18 and 4.20 (2d, J_{AB}= 14 Hz, N-$\underline{CH}_2\phi$), 3.59 (m, NC-C-$\underline{H}$) ; ^{13}C NMR revealed a 9/1 mixture of epimers, facile epimerization of the cyano group of 1 (6/4) on the catalyst during hydrogenation to give 2 (9/1) is likely.

14 - 3a : oil ; MS m/e (relative intentity) : 368 ($M^{+\cdot}$, 3), 353 (8), 342 (25), 213 (81), 198 (100), 187 (16), 91 (97). IR (neat) 2210cm^{-1} ; ^{1}H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 0.88 (d, 6 Hz, $\underline{H}_3C$-CH), 3.55 and 3.95 (2d, J_{AB}= 16 Hz, N-$\underline{CH}_2$-ϕ) ; ^{13}C NMR ($CDCl_3$, 22.63 MHz, TMS δ= 0) 14.2 (q), 22.8(2t), 24.1 (t), 29.4 (t), 29.4-29.6 (5 t), 32 (t), 34.8 (t), 35 (t), 39.5 (t), 55.2 (d), 57 (t), 64.3 (s), 120.2 (s), 126.3 (d), 126 7 (2 d) 127.9 (2 d), 128.1 (d), 142.2 (s).

3b : oil ; MS m/e (relative intensity) 256 ($M^{+\cdot}$, 1), 241 (5) 229 (50) ; IR (neat) 2200cm^{-1} ^{1}H NMR ($CDCl_3$, 400 MHz, TMS δ = 0) : 0.95 (d, 6 Hz, $\underline{H}_3C$-C-H), 3.6 and 4.1 (2d, J_{AB}= 16 Hz, N-$\underline{CH}_2\phi$) ^{13}C NMR ($CDCl_3$, 22.63 MHz, TMS δ = 0) ; 14 (q), 17.5 (t), 21.2 (q) 22.7 (t), 34.7 (t), 35.1 (t), 41.4 (t), 55.2 (s), 57.0 (d), 64.1 (t), 120.3 (s), 126.2 (d), 126.7 (2 d), 128 1 (d), 128.3 (d), 142.2 (s).

15 - The configuration at C-2 of 3a and 3b (ie. CN axial) follows from stereoelectronic arguments and from observations (publication in preparation) that the cyano group in N-benzyl -2-cyanopiperidines is labile. The equatorial → axial isomerization of this group occurs very readily on chromatographic purification of crude reaction mixtures.

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17 - 6b : oil ; MS (relative intensity) 231 ($M^{+\cdot}$, 1), 216 (1), 188 (50), 91 (30) ; ^{1}H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 1 (d, 6 Hz, $\underline{H}_3C$-C-H), 3 7 (s, N-$\underline{CH}_2$-ϕ)

18 - R.K. Hill and T.H. Chan, Tetrahedron, 1965, 21, 2015.

19 - S.I. Yamada and H. Akimoto, Tetrahedron Letters, 1969, 3105.

20 - 4b . oil ; MS m/e (relative intensity) : 231 ($M^{+\cdot}$, 13), 216 (18), 188 (100), 91 (100) ; ^{1}H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 0.95 (t, J = 5 Hz, $\underline{CH}_3$-CH_2), 1 (d, J = 6 Hz, $\underline{CH}_3$-CH), 3.5 and 3.8 (2d, J_{AB}= 14 Hz) N-$\underline{CH}_2$-ϕ).

21 - S. Yamada, K. Tomioko and K. Koja, Tetrahedron Letters, 1976, 61.

22 - 5b . epi-dihydropinidine HCl m.p. 134-135°c (ether-methanol), microanalysis $C_9H_{19}N$, HCl. Base, MS m/e (relative intensity) : 141 ($M^{+\cdot}$, 5), 126 (15), 98 (100), 70 (10).

23 - 4a : oil , MS m/e (relative intensity) : 343 ($M^{+\cdot}$, 97), 328 (99), 188 (99), 91 (100) ; ^{1}H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 0.82 (t, $\underline{CH}_3$-CH_2), 1 (d, J = 6 Hz, $\underline{CH}_3$-CH), 3.4 and 3.7 (2d, J_{AB}= 14 Hz, N-$\underline{CH}_2$-ϕ).

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25 - 6a : oil : MS m/e (relative intensity) : 343 ($M^{+\cdot}$, 2) 328 (18), 188 (100), 91 (63) ; ^{1}H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 0.88 (t, $\underline{CH}_3$-CH_2), 1 (d, 6 Hz, $\underline{CH}_3$-CH), 3.72 (s, N-$\underline{CH}_2$-ϕ).

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