2-Cyano-Δ^3-piperideines.† 12. Stereochemistry of Formation of *N*-Benzyl-2-cyano-Δ^3-piperideines and Facile Isomerization on Alumina to 2-Cyano-Δ^4-piperideines. A Potentially General Route to the Synthesis of 2,6-Disubstituted Piperidine Alkaloids

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Received September 13, 1983

The reaction of the piperideine *N*-oxides **1a–f** with trifluoroacetic anhydride in CH_2Cl_2 at 0 °C (Polonovski–Potier reaction) led to the formation of the *N*-benzyl-2-cyano-Δ^3-piperideines **3a–f**. Epimeric mixtures were obtained for the amino nitriles **3b,c,f** bearing an alkyl substituent at C-6. On examination of the ^1H and ^{13}C NMR spectra for these mixtures, it was found that both the *trans*-**A** and *cis*-**B** epimers preferred conformations wherein the cyano group was axial. On stirring a slurry of alumina and amino nitriles **3a–d** in CH_2Cl_2 an isomerization to the corresponding 2-cyano-Δ^4-piperideines **15a–d** occurred. Optimum rates and yields (90%) were obtained for this reaction when a substituent was present at C-6 of **3**. No isomerization was observed when the 3-ethyl amino nitrile **3e** was treated with alumina and the 4-cyano-Δ^2-piperideine **19f** was produced from **3f**. The stereoselective conversion of amino nitriles **3b** to the *trans*-2-propyl-6-methyl-Δ^3-piperideine **21** was achieved in two steps: (i) LDA, PrBr, −30 °C, THF; (ii) $NaBH_4$, EtOH (86/14, *t*/*c*). Conversely the cis epimer **22** was obtained directly from **3b** on reaction with PrMgBr (83/17, *c*/*t*). By isomerization of **3b** to **15b** on alumina and repeating the above sequence of reactions it was possible to prepare the corresponding *trans*- and *cis*-2-propyl-6-methyl-Δ^4-piperideines **24** and **25** (54/46, *t*/*c* and 92/8, *c*/*t*). In this way both 2,6-substituted epimers of the Δ^3- and Δ^4-piperideine system were prepared from a common starting material **3b**.

Introduction

The reaction of tetrahydropyridine *N*-oxides **1** with trifluoroacetic anhydride (Polonovski–Potier reaction[1]) provides an efficient method for the formation of 5,6-dihydropyridinium salts **2** (Scheme I). These compounds are potentially powerful synthons for the preparation of functionalized piperidines as one can envisage successive control over three of the ring carbon centers (C-2,3,4). However, the chemistry of this system has received little attention due for the most part to its inherent instability.

In a recent report[2] we described a method for the stabilization of the conjugated iminium system of **2** through formation of the corresponding 2-cyano-Δ^3-piperideines **3**. These stable cyanide addition adducts react as 5,6-dihydropyridinium "equivalents" since under appropriate reaction conditions (H^+,[3] Lewis acids,[4] or complexation with metal ions[5]) the carbon-nitrile bond is cleaved, regenerating **2** in a controlled manner. This "potential" reactivity has since been exploited in a number of syntheses, primarily in the indole alkaloid area.[3,5]

In this paper we describe in detail the stereochemistry of the formation of the *N*-benzyl-2-cyano-Δ^3-piperideines **3a-f** (Scheme I) and present our results on the facile isomerization of these molecules on contact with alumina to the corresponding 2-cyano-Δ^4-piperideines **15**. A mild method for the conversion of 5,6-dihydropyridinium synthons **3** to the stable, synthetically useful, "equivalents" of the 1,2-dihydropyridines has thus been achieved.[6,7]

Finally we wish to describe the preliminary results on a program aimed at a potentially general approach from a common starting material to the synthesis of piperidine alkaloids possessing in addition to the substituents at the 2- and 6-positions either an endocyclic double bond ($\Delta^{3(5)}$) or a hydroxyl group (C-3(5)). An evergrowing array of such compounds now exist, displaying both 2,6-cis and trans configurations. Representative examples are sederine (**4**),[8] prosopinine (**5**),[9] carpamic acid (**6**),[10] sedacryptine (**7**),[8] and palustrine (**8**)[11] (Chart I).

Our present objective was to demonstrate that a propyl group could be introduced regio- and stereoselectively at the C-2 position of 2-cyano-6-methyl-Δ^3-piperideine **3b**, and to correctly orient the endocyclic double bond (also a latent OH group)[12] with respect to this side chain using the above mentioned isomerization method (Scheme V). The four piperideines **21**, **22**, **24**, and **25** were prepared by this route.

Results and Discussion

The *N*-benzyl-2-cyano-Δ^3-piperideines **3a–f** were prepared from the corresponding tetrahydropyridine *N*-oxides **1a–f** according to our procedure,[2] i.e., reaction of **1a–f** with

† For part 11 in this series see: Grierson, D. S.; Urrea, M.; Husson, H.-P. *J. Chem. Soc., Chem. Commun.* **1983**, 891–893.

(1) Ahond, A.; Cavé, A.; Kan-Fan, C.; Husson, H.-P.; De Rostolan, J.; Potier, P. *J. Am. Chem. Soc.* **1968**, *90*, 5622–5623.

(2) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064–1082.

(3) (a) Harris, M.; Grierson, D. S.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1980**, *21*, 1957–1960. (b) Harris, M.; Besselièvre, R.; Grierson, D. S.; Husson, H.-P. *Ibid.* **1981**, *22*, 331–334. (c) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683–3694.

(4) Guibé, F.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 5055–5058.

(5) Grierson, D. S.; Vuilhorgne, M.; Lemoine, G.; Husson, H.-P. *J. Org. Chem.* **1982**, *47*, 4439–4452.

(6) The direct equilibration of dihydropyridinium salts to the corresponding 1,2-dihydropyridines can not in general be realized due to a rapid dimerization of the two species by a process analogous to that discussed by Beeken, P.; Fowler, F. W. *J. Org. Chem.* **1980**, *45*, 1336–1338. For a synthetically interesting case where dimerization is not observed, see ref 7.

(7) (a) Fry, E. M. *J. Org. Chem.* **1963**, *28*, 1869–1874. (b) Fry, E. M. *Ibid.* **1964**, *29*, 1647–1650. (c) Jacobson, A. E.; May, E. L. *J. Med. Chem.* **1964**, *7*, 409–412. (d) Ashcroft, W. R.; Joule, J. A. *Tetrahedron Lett.* **1980**, *21*, 2341–2344. (e) Felix, M.; Bosch, J.; Mauléon, D.; Amat, M.; Domingo, A. *J. Org. Chem.* **1982**, *47*, 2435–2440 and references therein.

(8) Colau, B.; Hootelé, C. *Can. J. Chem.* 1983, *61*, 470–472.

(9) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488–492.

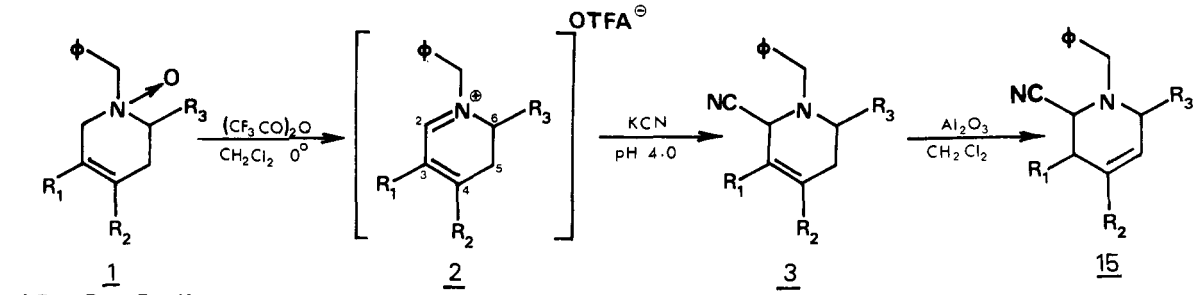
(10) Barger, J. *J. Chem. Soc.* **1910**, *97*, 466.

(11) Wälchi, P.; Eugster, C. H. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 160–161.

(12) Methods available for the conversion of the piperideine double bond to an OH group include (i) epoxidation followed by reductive ring opening, (ii) hydroboration or oxymercuration, and (iii) allylic oxidation and hydrogenation.

0022-3263/84/1949-2392$01.50/0

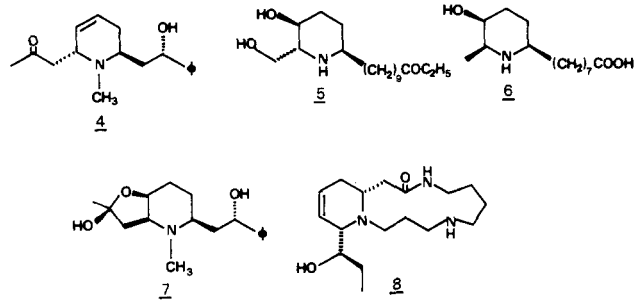
Scheme I



1 2 3 15

a) $R_1 = R_2 = R_3 = H$
b) $R_1 = R_2 = H$, $R_3 = CH_3$
c) $R_1 = R_2 = H$, $R_3 = C_3H_7$
d) $R_1 = H$, $R_2 = CH_3$, $R_3 = H$
e) $R_1 = C_2H_5$, $R_2 = R_3 = H$
f) $R_1 = C_2H_5$, $R_2 = H$, $R_3 = CH_3$

Chart I



4 5 6 7 8

trifluoroacetic anhydride in CH_2Cl_2 at 0 °C for 1 h, followed by reaction of the intermediate dihydropyridinium salts **2a–f** with KCN in a two-phase system (CH_2Cl_2–H_2O, KCN, pH 4.0) (Scheme I). Yields of the order of 60–65% were generally obtained for these reactions.

The ^1H and ^{13}C NMR spectra of amino nitriles **3a,d,e** all having one asymmetric center (C-2) were straightforward. The carbon-2 absorptions occurred in the region δ 51–54 in the ^{13}C spectra and characteristic broadened singlet absorptions were observed at δ 3.9 in the ^1H spectra for the hydrogens at position-2.

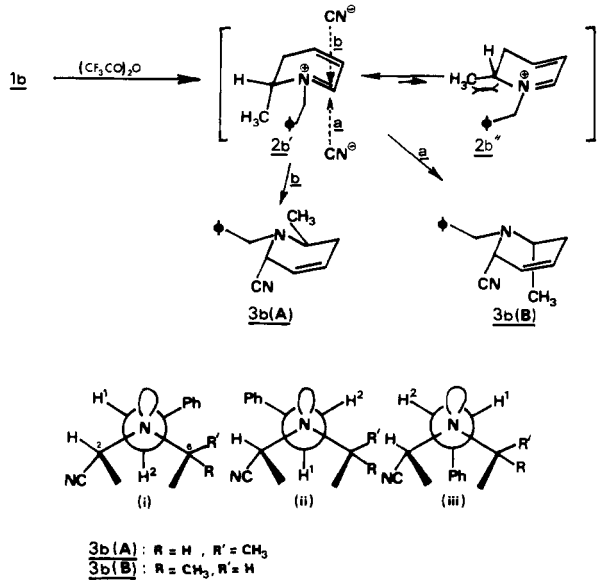
For the 6-alkyl substituted amino nitriles **3b,c,f**, epimeric mixtures were obtained. These mixtures proved to be inseparable by column chromatography, however the 400-MHz ^1H NMR spectrum of **3b** (3:2 mixture) was highly resolved, permitting assignments of structures **3b(A)** and **3b(B)** to the components of this mixture (Scheme II).

In the ^1H NMR spectrum of **3b** an AB resonance system was observed at δ 3.40, 4.23 (J_{AB} = 14 Hz) for the benzyl methylene protons of the major epimer **A**. In contrast a singlet absorption was observed at δ 3.89 for the same protons of the minor epimer **B**. By analogy with the study of Chan and Hill[13] on the ^1H NMR spectral characteristics of *N*-benzyl-2,6-dialkylpiperidines, it was concluded that in **3b(A)** the 2-cyano and 6-methyl substituents were "unsymmetrically" oriented, i.e., trans, and that in the minor epimer **3b(B)** they were "symmetrically" oriented, i.e., cis.

A more detailed examination of the spectrum of **3b** revealed that these assignments were correct. For both epimers **A** and **B** narrow multiplet absorptions were observed for the protons at C-2. On separate irradiation of these signals a vicinal coupling of 5 Hz and homoallylic couplings of 2.5–3 Hz and 1.0–1.5 Hz were lost from the corresponding resonances for H-3,[14] H-$5_{ax'}$, and H-$5_{eq'}$, respec-

(13) Hill, R. K.; Chan, T. H. *Tetrahedron* **1965**, *21*, 2015–2019.

Scheme II



3b(A): R = H, R′ = CH_3
3b(B): R = CH_3, R′ = H

tively. The magnitudes of these coupling constants were in good agreement with estimated values based upon an equatorial orientation of H-2[15] and hence an axial orientation of the cyano group in each molecule. By subsequent irradiation of the C-6 methyl proton resonance (δ 1.27, d) for the trans epimer **3b(A)**, the H-6 absorption (δ 2.98, m) collapsed to a doublet of doublets ($J_{6,5_{ax'}}$ = 10 Hz, $J_{6,5_{eq'}}$ = 4.5 Hz). The large value for $J_{6,5_{ax'}}$ clearly indicated that the methyl group was equatorial. In contrast, irradiation of the C-6 methyl proton resonance of the minor epimer **3b(B)** simplified the H-6 absorption giving a doublet of doublets with a small value for $J_{6,5_{ax'}}$ (6 Hz) which demonstrated that in this molecule both the cyano and methyl groups were axial.

Important similarities were apparent between the spectrum of **3b** and the spectra of **3c** and **3f** which revealed that corresponding mixtures of epimers **A** and **B** were also produced during the formation of these amino nitriles.

At this point further mention should be made concerning the use of the benzyl methylene proton absorption as a probe for determining stereochemistry α to nitrogen in

(14) Note that the presence of a cyano group at C-2 produces a significant upfield shift in the position of the H-3 absorption such that the H-4 resonance is now at lowest field.

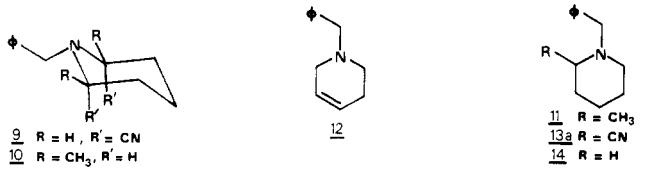
(15) (a) Garbisch, Jr., E. W. *J. Am. Chem. Soc.* **1964**, *86*, 5561–5564. (b) Cameron, D. W.; Kingston, D. G. I.; Sheppard, N.; Lord Todd *J. Chem. Soc.* **1964**, 98–103.

Table I. ^{13}C NMR Spectral Data

product	$NCH_2C_6H_5$	C-2	C-3	C-4	C-5	C-6	CH_3	CN
12	63.0	52.9	125.6[b]	125.4[b]	26.2	49.7		
3a	59.9	51.0	130.2	120.7	25.9	45.9		115.2
3b(A)	53.8	50.6	130.1	119.9	34.6	50.2	19.5	116.7
3b(B)	57.2	50.2	129.0[b]	118.9	32.0	46.9	12.7	
14	64.0	54.6	26.0	24.5	26.0	54.6		
13a	60.7	52.0	28.6	20.5	25.0	49.7		116.6
13b(A)	55.2	51.2	28.7	21.1	34.5	53.3	21.1	117.1
13b(B)	56.0	53.4	29.4	16.6	31.5	47.1	13.0	
15a	60.3	48.4	29.5	121.5	125.8	49.2		117.5
15b	55.9	47.7	29.2	120.7	132.3	53.0	20.1	117.2

[a] Data given in δ. [b] Refers to carbon absorptions whose assignments may be interchangeable.

Chart II



piperidine rings. It can be seen from the Newman projections (Scheme II) that for disubstituted systems such as **3b(A)** and **3b(B)** where the cyano group is axial, the conformer (iii) will be high in energy, and the appearance of the $CH_2C_6H_5$ resonance thus depends upon the orientation of the CH_3 group and consequently on its interaction with the phenyl ring. For epimer **3b(A)** the conformer (ii) wherein the two groups are opposed represents the only low-energy conformation available to the benzyl side chain. In this conformation the methylene protons are nonequivalent and thus give rise to a quartet signal. In contrast, for epimer **3b(B)** there is no particular interaction between the methyl and phenyl groups in either conformations i and ii and the benzyl protons are thus equivalent. It should be noticed however that if **3b(B)** adopted the cis diequatorial conformation a singlet absorption would also be observed. It is thus not possible to distinguish between a symmetrical diaxial compound such as **9**[16] and a diequatorial compound such as **10**[13] on the basis of the $NCH_2C_6H_5$ signal alone (Chart II).

Singlet absorptions were also expected for the benzyl methylene protons in the spectra of the monosubstituted amino nitriles **3a,d,e**.[17] In fact distinct AB quartets were observed for these resonances.[18] This may be due to an interaction of the π-electron clouds of the phenyl and cyano groups which results in a conformational bias. Such an effect may be sufficiently weak that it is destroyed when a methyl group is introduced axially at C-6. In any event the separation ($\Delta\delta_{AB}$) between the two doublet components of these AB systems was much less than that observed for *N*-benzyl-2-methylpiperidine (**11**) ($\Delta\delta_{AB}$, **3a** 0.12; **3d** 0.11; **3c** 0.13; **11** 0.8) and may be used as an indication that the cyano substituents are axial.

The ^{13}C NMR data of amino nitriles **3a–f** were in agreement with the assigned structures. A calculation of the chemical shift differences between the carbon resonances for tetrahydropyridine **12** and amino nitrile **3a** (Table I) revealed that substitution at C-2 by a cyano group produced a negative upfield γ-effect shift of the benzyl carbon (−3.1 ppm) and in particular of the C-6 resonance (−3.8 ppm). Such characteristic upfield shifts provide a good indication that the cyano group of **3a** is pseudoaxial. Similar γ-effects were observed in the spectra of compounds **3d** and **3e** after comparison with the appropriate tetrahydropyridines.

The ^{13}C signals of the major component (**A**) in the **3b** mixture were then compared with those of **3a**. α-, β-, and γ-effect shifts of 4.3, 8.7, and −0.4 ppm (C-2), respectively, were found to be produced by the C-6 methyl group, consistent with its equatorial orientation.[19]

For the minor component **3b(B)** the axial methyl group produced an α-effect shift of +1.0 ppm, a +6.1 ppm β shift in the C-5 absorption, and interestingly a γ-shift of only −0.8 ppm in the position of the C-2 absorption. A negligible γ-effect is known to occur in systems where the methyl group is 1,3-syn axial to a functionality other than H.[20] This provided further evidence that the cyano group at C-2 of this compound is pseudoaxial.

Also interesting, the presence of the CH_3 group in **3b(A)** produced a larger upfield shift (−6 ppm, relative to **3a**) of the benzyl carbon resonance than was produced by the axial CH_3 group in **3b(B)**. As discussed above (Scheme II), in epimer **3b(A)** the benzyl group is restricted in its motion and occupies conformation ii. In this conformation one of the benzyl hydrogens is fixed in a 1,3-syn axial arrangement with the cyano group at C-2 and thus experiences the full γ-effect produced by this substituent. In epimer **3b(B)** the benzyl side chain has greater mobility and the γ-effect produced by the C-2 and C-6 substituents is consequently much smaller.

Similar conclusions were arrived at for the more complex amino nitriles **3c** and **3f** after an analysis of their ^{13}C NMR spectra.

The important point to note from the structures of compounds **3a–f** is that in each molecule a conformation is preferred wherein the cyano group is pseudoaxial.[18] This is particularly striking for the minor epimer (**B**) of amino nitriles **3b,c,f** in which *both* the C-2 cyano and C-6 alkyl substituents are axial (see also **9**). Evidently there is a gain in stabilization energy when the cyano group is pseudoaxial, which is sufficiently large to prevent ring inversion to the alternate and a priori more stable diequatorial conformer.[21] This preferred orientation of the nitrile

(16) Compound **9** was previously believed to adopt a cis diequatorial conformation [Johnson, H. E.; Crosby, D. G. *J. Org. Chem.* **1962**, *27*, 1298–1313]. However from the observation of a narrow multiplet resonance (δ 3.90) for H-2 in the ^1H NMR spectrum of **9** and from the upfield position of the C-4 absorption (δ 16.9) in the ^{13}C NMR, it was clear that this molecule adopts a cis diaxial conformation.

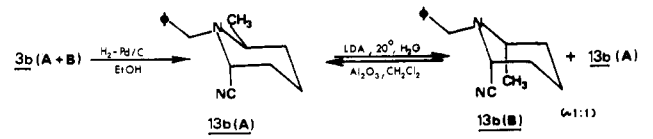
(17) Lyle, R. E.; Thomas, J. J. *Tetrahedron Lett.* **1969**, 897–900.

(18) The low-temperature (−55 °C) ^1H NMR spectra of **3a–d, 3e**, and **13a** did not reveal the occurrence of an equilibrium mixture of axial and equatorial cyano conformers.

(19) Wehrli, F. W.; Wirthlin, T. "Carbon-13 NMR spectra"; Heyden and Sons Ltd.: London, 1978; p 45.

(20) Grover, S. H.; Strothers, J. B. *Can. J. Chem.* **1974**, *52*, 870–878. Compare compounds **6** and **7** with **8** and **9** and **16** and **17**.

Scheme III



group in piperideine (and piperidine) amino nitriles appears to be a general phenomenon which we believe can be likened to the "anomeric effect" observed in pyranose sugars.[23]

Concerning the mechanism of formation of these 2-cyano-Δ^3-piperideines, it is felt that two factors are dominant in the transition state which determine the stereochemical outcome of these reactions. Firstly, the presence of an alkyl group at C-6 in the dihydropyridinium intermediate **2** will lock the molecule in the more stable C-6 pseudoaxial alkyl conformation **2'** (the pseudoequatorial conformer **2''** being destabilized by severe allylic $A^{1,2}$ strain interactions between the N-1 and C-6 substituents[24]). Secondly, in the absence of overriding steric interactions the approach of cyanide ion to **2** will occur under stereoelectronic control from the axial direction.[25]

Such an axial approach of CN^- to the dihydropyridinium intermediates **2a,d,e** adequately accounts for the formation of the corresponding amino nitriles **3a,d,e**. Similarly, an axial approach of CN^- to the pseudoaxial methyl conformer **2b'** of dihydropyridinium salt **2b** would lead to the minor epimer (**B**) of **3b**. However as an important 1,3-diaxial interaction develops during this reaction it is not unexpected that the approach of cyanide ion to **2b'** would occur predominantly from the electronically less favorable, but sterically less hindered equatorial direction (pathway b)[26] giving the epimer **3b(A)** as the major product (after ring inversion).

As equilibrating reaction conditions were employed (CH_2Cl_2–H_2O, KCN, H^+, pH 4.0) for the condensation of CN^- and **2b** one might expect (if the differences in product stabilities are large) that over a long reaction time an equilibration of **3b(B)** to the "a priori" more stable trans epimer **3b(A)** will occur. However, on reacting **2b** with KCN over a 24-h period no appreciable change in the original epimer distribution (established by reaction for <1 min) was observed.

Table II. Isomerization of 2-Cyano-Δ^3-piperideines

3	conditions[a]	yield, % (product)
a	12 h, RT	50 (**15a**)
b	2 h, RT	90 (**15b**)
c	2 h, RT	90 (**15c**)
d	8 h, RT	60 (**15d**)
e	>24 h, 60 °C	no rxn[b]
f	2 h, 60 °C	50 (**19f**)
b (NCH_3)	5 h, RT	80 (**15b**) (N-CH_3)

[a] Merck (Art. 1097) activity II–III alumina (activated at 110 °C, 1 h) and compound **3** (1 mmol) stirred as a thick slurry in CH_2Cl_2 for time and temperature indicated. [b] Decomposition.

Further experiments showed that an equilibrium between the amino nitrile and iminium forms could readily be achieved under certain reaction conditions leading to the thermodynamically more stable and/or isomerized products.

Hydrogenation of the amino nitriles **3b** did not lead to a mixture of the corresponding saturated compounds **13(A)** and **13(B)**. Instead, a single product **13b(A)** was produced being isolated in >91% yield (Scheme III).[27] Apparently a conversion of the cis to trans amino nitrile system occurred during this reaction, presumably through epimerization of the nitrile center (C-2) on the catalyst surface. By treatment of **13b(A)** with LDA at −30 °C and reaction of the resultant anion with water at room temperature it was possible however to obtain the cis diaxial epimer **13b(B)** as a 1:1 mixture with **13b(A)** (addition of H_2O at −40 °C gave **13b(A)** only). When an attempt was made to separate this mixture by column chromatography on alumina a cis → trans epimerization was again observed, and **13b(A)** was isolated in 95% yield.

The structures of these two epimers were deduced from the appearance of the respective $NCH_2C_6H_5$ signals (**13b-(A)** (AB quartet, J = 14 Hz, $\Delta\delta$ = 1.05) **13b(B)** (AB quartet, J = 14 Hz, $\Delta\delta$ = 0.06)) and from selective irradiation of the H-5,6 and C-6 methyl proton signals. Narrow multiplet absorptions were observed for H-2_{eq} of both compounds.

An analysis of the ^{13}C NMR spectra was made by comparing compounds **13a**,[28] **14**, and **13b(A** and **B)** (Table I) in an identical manner as for the unsaturated amino nitriles **3**. As expected a large negative γ-effect shift was produced at C-4 of the epimer **B** by the axial cyano and methyl substituents, and only a minor γ-shift was observed in the position of the signal of C-2.[19,20]

By column chromatography of the 2-deuterio derivatives of amino nitrile **13b** and by determining that no deuterium was lost in the product **13b(A)**, we were able to demonstrate that the epimerization **13b(B)** → **13b(A)** occurred through an alumina-assisted removal of CN^- and formation of the corresponding iminium ion rather than through loss of the deuterium at C-2.

(21) Molecular mechanics calculations using the program SCRIPT[22] in which the anomeric effect is not considered showed that the two alternative chair conformations of both the cis and the trans epimers of **3b** are effectively equal in their thermodynamic energies, ie., the differences in energies are of the order of 0.2–0.4 Kcal/mol, which is close to the limits of experimental error of the technique. In the trans system **3b(A)** the smaller steric volume (A factor) of the cyano group would tend to favor the conformer in which this substituent is axial so as to minimize 1,3-diaxial interactions. However this tendency is counterbalanced by the decrease in the gauche interactions that occur with the *N*-benzyl group when the cyano group is equatorial. This later effect is accentuated in N-substituted piperidines relative to the cyclohexane system due to the shorter C–N bond length. In the cis epimer **3b(B)** the 1,3-diaxial interactions present in the diaxial conformer are again counterbalanced by the important gauche interaction of the two α-substituents with the *N*-benzyl group present in the diequatorial conformer. On the basis of steric effects alone therefore one would expect these molecules to be conformationally mobile. The observation of preferred conformations in which the cyano group is pseudoaxial is thus a good argument in favor of the occurrence of an anomeric effect in the α-amino nitrile system.

(22) Cohen, N. C.; Colin, P.; Lemoine, G. *Tetrahedron* **1981**, *37*, 1711–1721.

(23) (a) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527. (b) Lemieux, R. U.; Koto, S.; Voisin, D. *ACS Symp. Ser.* **1979**, *87*, 17.

(24) (a) Overman, L. E.; Freeks, R. L. *J. Org. Chem.* **1981**, *46*, 2833–2835. (b) Matsumara, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1982**, *23*, 1929–1932. (c) Bonin, M.; Besselièvre, R.; Grierson, D. S.; Husson, H-P. *Tetrahedron Lett.* **1983**, *24*, 1493–1496.

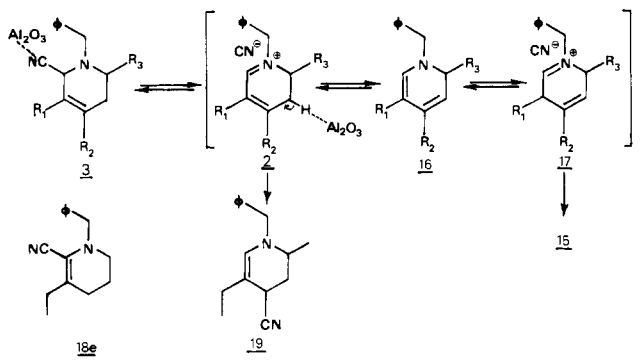
(25) Eisenstein, O.; Klein, J.; Lefour, J. M. *Tetrahedron* **1979**, *35*, 225–228.

(26) For examples of this mode of reaction due to steric factors see: (a) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 227–238. (b) Goutas, W. C.; Essawi, M.; Portoghese, P. S. *Synth. Commun.* **1980**, *10*, 495.

(27) This reaction was originally described as producing a 9:1 mixture of **13b(A)/13b(B)**, see: Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H-P. *Tetrahedron Lett.* **1982**, *23*, 3369–3372. The minor component formed occasionally has since been identified as *N*-benzyl-4-cyano-6-methylpiperidine and not as the cis epimer (**B**) of **13b**. This product was most probably formed by elimination of CN^- on the catalyst surface followed by its reintroduction at C-4 giving **19b** and reduction of the enamine double bond.

(28) A comparison of the α (−2.6 ppm) and β (+2.6 ppm) effect shifts produced by the cyano group in **13a** with the values determined for an axial or equatorial cyanocyclohexane (CN_{eq}, α + 1, β + 3; CN_{ax}, α + 0, β − 1)[19] revealed that an assignment of stereochemistry could not be made on the basis of the α and β shifts using this model.

Scheme IV



This can be viewed as involving a coordination of the cyano group of **13b(B)** with alumina followed by departure of CN^-, eliminating in the process the diaxial steric interaction with the C-6 methyl group. Reapproach of CN^- to the pseudoaxial conformer of the iminium intermediate then occurs from the opposite or equatorial direction. Since simple contact with alumina resulted in conversion of the mixture of amino nitriles **13b** to a single epimer, experiments were carried out on the unsaturated amino nitriles **3b** to see whether pure epimer **3b(A)** could be obtained by this method.

Stirring a slurry of Merck alumina and the **3b** mixture in CH_2Cl_2 at room temperature for 2 h did not lead to an equilibration to **3b(A)**. Rather, an isomerization of the $\Delta^{3,4}$-double bond occurred, giving a single product, 2-cyano-Δ^4-piperideine **15b** in 90% yield (Table II, Scheme I).

The 2,6-trans arrangement of the side chain substituents in this molecule was deduced from the presence of a broad AB resonance system δ 3.30, 4.20 (J_{AB} = 14 Hz) in its ^1H NMR spectrum. Small couplings $J_{2,3_{ax'}}$ = 6 Hz and $J_{2,3_{eq'}}$ = 2 Hz were established in the H-2_{eq} (dd, δ 3.70) absorption after successive irradiation of H-$3_{ax'}$ (δ 2.44) and H-$3_{eq'}$ (δ 2.17). Irradiation of these proton absorptions also resulted in the loss of the homoallylic couplings ($J_{6,3_{ax'}}$ = 4 Hz, $J_{6,3_{eq'}}$ = 2 Hz) in the signal for H-6. Finally, a small coupling (2 Hz) was found between the signals for H-6 and the olefinic protons, consistent with an axial position for H-6.

Comparing the ^{13}C NMR spectra of **15a** and **15b** (Table I), the equatorial methyl group produced an α-shift of +3.8 ppm in carbon-6 and a negligible γ-effect shift (0.7 ppm) in the position of C-2. The methylene carbon absorption at 29 ppm was not affected by the methyl substitution at C-6, in complete agreement with its position δ to this center in **15b**.

Apparently in this reaction the alumina not only assisted in the removal of the cyano group but also in the deprotonation–equilibration of the resultant dihydropyridinium intermediate **2b** to the corresponding 1,2-dihydropyridine **16b** (Scheme IV). The formation of **15b** from this intermediate can be envisaged to involve its reprotonation at C-3 which deconjugates the dienamine system, giving **17b** followed by reapproach of the CN^- group to this iminium ion from the equatorial direction.

The remarkable efficiency of this transformation suggests that the amino nitrile molecules are well separated from each other on the alumina surface, and that the entire sequence of reactions takes place at the coordination sites. The sensitive dihydropyridinium salt **2b** and the 1,2-dihydropyridine **16b** are thus transient intermediates only in a reaction which leads to a stable product species **15b**. Attempts to achieve the direct isomerization of dihydropyridinium salts **2** to 1,2-dihydropyridines **16** in solution results in the rapid formation of dimeric, polymeric, and disproportionation products only.

As 2-cyano-Δ^4-piperideines are synthetically useful molecules[7] it was of interest to examine the generality of the alumina-assisted isomerization method as a new approach for the preparation of these molecules. Reaction of the 6-propyl amino nitrile **3c** with alumina (CH_2Cl_2, room temperature, 2 h) was also very efficient, giving **15c** in 90% yield. However, it proved difficult at first to obtain reproducible results for the unsubstituted amino nitrile **3a**. This situation was remedied eventually by preactivating the alumina at 110 °C for 1 h. With this more active alumina, moderate yields of **15a** were obtained after reaction for 12 h. The difference between the rate of isomerization of **3a** and **3b** (or **3c**) may result from an acceleration in reaction rate in the latter mixture due to a release in steric strain when the C_2–nitrile bond is cleaved in the minor isomer.

The C-4 methyl substituted amino nitrile **3d** was observed to isomerize readily, giving **15d** in 60% yield after 8 h at room temperature. The increase in reaction rate in this case is presumably due to the presence of the alkyl group at C-4 which is known to facilitate migration of a $\Delta^{3,4}$-double bond to the $\Delta^{4,5}$-position (and vice versa).

Unfortunately, when **3e** was treated with alumina in CH_2Cl_2, even at reflux, the presence of **15d** in the product mixture could not be confirmed (decomposition products form in significant quantities after heating for 24 h). Formation of the undesired cyano enamine **18e** (~90%) was however observed when **3e** was reacted with basic alumina (prepared by addition of 20% NaOH to alumina, and activation at 110 °C). As previously described[2] this double bond shift occurs by a deprotonation of the amino nitrile at C-2 and a thermodynamic reprotonation of the resultant ambident anion at C-4.

Interestingly when the 3-ethyl-6-methyl amino nitrile **3f** was reacted at reflux with alumina, the 4-cyano-Δ^2-piperideine **19f** was obtained (60%) (^1H NMR δ 5.82 (H-2, br s), 3.28 (H-4, br t); ^{13}C NMR δ 32.6 (C-4), 132.5 (C-2); IR 1650 cm^{-1} (enamine)). This synthetically useful transformation has only recently been achieved for related compounds by using Lewis acid conditions (Et_2AlCN, C_6H_6, 2–3 h, room temperature).[3c] From this result it would appear that either the equilibration of the 5,6-dihydropyridinium intermediate **2f** to the 1,2-dihydropyridine **16f** is prevented or that the presence of the ethyl side chain directs reprotonation of **16f** to C-5 rather than to the substituted 3-position.

As a final example the isomerization of 2-cyano-1,6-dimethyl-Δ^3-piperideine **3b** (NCH_3) was examined. Although the time required to isomerize this compound was twice that necessary for **3b**, it was evident that the presence of the *N*-benzyl group was not critical for activation of the amino nitrile system.

To summarize briefly the results, isomerization to the 2-cyano-Δ^4-piperideine system occurs on reaction of the nonsubstituted amino nitrile **3a** and the alkyl substituted amino nitriles **3b–d** with alumina. Optimum yields and reaction rates are observed when there is a substituent at position-6. However the desired products are not obtained when a substituent is present at C-3.

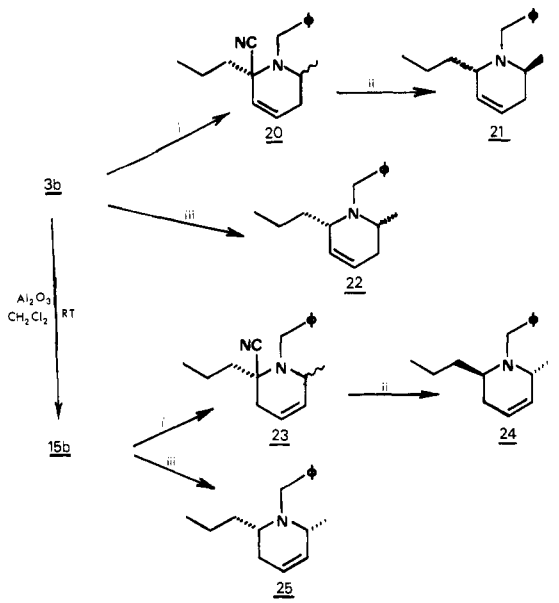
In a recent publication we described a method for the synthesis of either the cis or the trans epimer of 6-methyl-2-propylpiperidine from 1-benzyl-2-cyano-6-methyl-Δ^3-piperideine (**3b**).[27] As an evergrowing number of piperidine alkaloids are known[8–11] which possess, in addition to the substituents at the 2- and 6-positions, either an endocyclic double bond ($\Delta^{3(5)}$) or a hydroxyl group (C-3(5)) (Chart I) it was of interest to extend the above

Table III. ^{13}C NMR Chemical Shift Values (δ)[a] for the *cis*-and *trans*-2-Propyl-6-methyl-Δ^3- and -Δ^4-*N*-benzylpiperideines

product	$NCH_2C_6H_5$[c]	C-2	C-3	C-4	C-5	C-6	CH_3	C-1′	C-2′	C-3′[b]
21	50.8	56.7	129.9	124.8	29.5	46.7	16.7	36.2	19.1	14.2
22	56.2	60.6	129.9	123.9	31.9	53.0	21.6	37.1	19.1	14.3
24	50.4	52.5	27.2	124.8	131.1	50.9	19.9	33.4	20.2	14.1
25	54.5	57.0	27.7	123.8	131.2	54.8	20.8	36.2	20.2	14.2

[a] All assignments were supported by off-resonance experiments. [b] Carbons-1′, 2′, and 3′ refer to the carbons of the 2-propyl side chain. [c] Average values for the aromatic carbons of the $NCH_2C_6H_5$ groups are δ 128, 129, 131, and 142.

Scheme V[a]



[a] i, LDA, THF, *n*-PrBr; ii, $NaBH_4$, EtOH; iii, *n*-PrMgBr, THF.

synthesis to molecules having these functionalities.

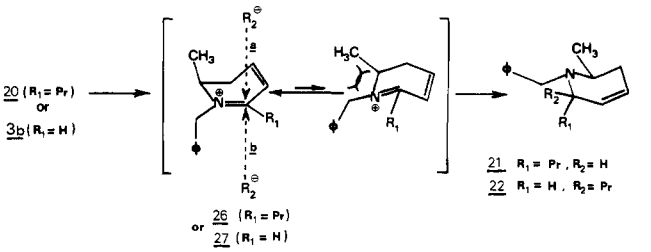
When the synthetic equivalence of a double bond and a hydroxyl group[12] were considered, our objective was to develop conditions for the preparation of the *cis*- and *trans*-6-methyl-2-propyl-Δ^3- and -Δ^4-piperideines **21**–**22** and **24**–**25** from the common starting material **3b** (Scheme V). A key step in an approach to the compounds having the Δ^4-double bond was the isomerization of **3b** to **15b**.

Reaction of amino nitriles **3b** with LDA in THF at −30 °C and of the resultant anion with propyl bromide at room temperature (1 h) led to the formation of a single product **20** as determined from the ^1H NMR spectrum of the crude reaction mixture. So as to avoid any possibility of isomerization of **20** to **23**, the crude mixture was treated immediatly with $NaBH_4$ in ethanol (30 min, room temperature). The expected 2,6-*trans*-Δ^3-piperideine **21** formed stereoselectively during this reaction (**21**/**22**, 86/14, GLC analysis) was isolated in 50% overall yield from **3b** after preparative-layer chromatography on alumina.

Conversely, reaction of the **3b** mixture with PrMgBr led directly to the formation of the 2,6-*cis*-Δ^3-piperideine **22** (**22**/**21**, 83/17) in 76% yield after purification.

The high and opposite stereoselectivities observed in the reaction of **20** with BH_4^- and **3b** with PrMgX were predicted on the basis of a mechanism involving prior formation of the iminium ions **26** and **27** (Scheme VI). The strong preference for the C-6 methyl pseudoaxial conformations of these intermediates would confer rigidity to the cyclic iminium system in the transition state during the subsequent reaction with H^- and Pr^-. Stereoelectronically controlled approach of the incoming nucleophile from the axial direction (a) would lead in each case to formation of the major reaction product.

Scheme VI



That only small quantities of the epimeric products were formed in each case resulting from the unhindered equatorial approach (b) of the nucleophile may reflect the irreversible nature of these reactions (compare with the formation of **3b**).

Preparation of the corresponding Δ^4-piperideines involved initial use of the high yielding isomerization of **3b** to **15b** (90%). Subsequent reaction of the anion of **15b** with propyl bromide at −40 °C for 3 h then led to the formation of a sensitive product **23** which was treated immediately after isolation with $NaBH_4$ in ethanol (30 min, room temperature). GLC analysis of the crude reaction mixture revealed that the 2,6-trans compound **24** was formed in only slight excess (**24**/**25**, 54/46). Product **24** could be purified however by preparative-layer chromatography on alumina.

Finally the reaction of **15b** with PrMgBr gave the epimeric 2,6-*cis*-Δ^4-piperideine **25** in 59% yield after purification. In contrast to the two-step sequence leading to **24**, the formation of **25** was highly stereoselective (**25**/**24**, 92/8). This latter result is in keeping with the proposed mechanism invoking a preferred conformation for a piperideinium intermediate and stereocontrolled axial approach of the nucleophile. The lack of significant stereoselectivity in the former case is not yet clearly understood.

The two pairs of *cis*- and *trans*-piperideines were readily distinguished by the differences in the appearances of the benzyl CH_2 resonances in their ^1H NMR spectra. For the *trans*-piperideines **21** and **24** two well-separated AB quartet absorptions were observed ($\Delta\delta_{AB}$ 0.24). In contrast for the cis compounds **22** and **25** a narrow AB quartet ($\Delta\delta_{AB}$ 0.07) and a singlet absorption, respectively, were observed. Product stereochemistry could also be deduced from the differences observed in the chemical shift positions of the benzyl carbon resonances in the ^{13}C NMR spectra (Table III). This resonance occurred at higher field in the spectra of the *trans*-piperideines **21** and **24** due to an upfield γ-effect shift produced by the axial ring substituent.

Intermediate values were determined for the ring proton coupling constants ($J_{a,e}$ and $J_{e,e}$ = 5–8 Hz) in the ^1H NMR spectra of **21** and **24** indicating that these products were conformationally flexible. The ^{13}C spectra provided a more sensitive probe of these molecules however suggesting that one conformer predominated in their equilibration. For the *cis*-piperideines **22** and **25** the chemical shifts observed for the 6-methyl carbon (δ 21), and the 1′-carbon of the

2-propyl side chain (δ 37) were typical for an equatorial orientation of both substituents. In the spectrum of **21** however, the 6-methyl carbon resonance was found at δ 16.7, i.e., nearly 5 ppm upfield from the position observed for this carbon resonance in **22** or **25**, which suggested that the methyl group preferred an axial orientation in this 2,6-*trans*-Δ^3-piperideine. In contrast, in the spectrum of **24** the C-1′ carbon resonance of the propyl side chain occurred ~4 ppm to higher field (δ 33.4) suggesting in this case that it was the propyl side chain and not the methyl group which preferred to be axial. Interestingly in each molecule it is the side chain at the position homoallylic to the double bond which prefers the axial orientation.

In conclusion, by the above short sequence of reactions the Δ^3-piperideines **21** and **22**, and the Δ^4-piperideines **24** and **25** were readily prepared from the *N*-benzyl-2-cyano-Δ^3-piperideine **3b**. The 2,6-cis or trans configurations of these products were readily established on the basis of the benzyl CH_2 proton absorption in their ^1H NMR spectra. These assignments were confirmed by a more detailed examination of the ^{13}C NMR signals. It is felt that through a combination of the appropriate reaction steps and an acquired confidence in the analysis of the product spectra that the future efforts to synthesize the more complex piperidine alkaloid systems such as **4–8** from 2-cyano-Δ^3-piperideine synthons should be facilitated considerably.

Experimental Section

"Normal extractive workup" indicates that the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 times), and that the combined CH_2Cl_2 layers were washed with water, dried over sodium sulfate, and concentrated using a rotary evaporator. Column chromatography was carried out by using silica gel (Merck, Art. 7734) and Aluminoxid-90 (Merck, activity II–III). The *N*-benzylpyridinium salts used to synthesize *N*-oxides **1a,b,d–f** were prepared by reaction of commercially available pyridines with benzyl bromide (~100% yields). 2-Propylpyridine was prepared according to ref 24c. Infrared spectra (IR) were recorded neat (except where noted) on a Perkin-Elmer 257 spectrophotometer. Infrared absorption bands are expressed in reciprocal centimeters (cm^{-1}) by using polystyrene calibration. Ultraviolet spectra (UV) were run in ethanol solution on a Jobin-Yvon DUOSPAC 203 spectrometer. ^1H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (tetramethylsilane as an internal standard, δ = 0) on either a Brücker WP-80 (80 MHz), or a I.E.F. (Institut d'Electronique Fondamentale, Université de Paris-Sud, 91405 Orsay, France) spectrometer (400 MHz). Chemical shift data are reported in parts per million (ppm) downfield from tetramethylsilane, where s, d, t, q, qn, and m designate singlet, doublet, triplet, quartet, quintet, and multiplet, respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ (δ, ppm Me_4Si) on either a Brücker HX 90 E (22.63 MHz) or WP 60 (15.08 MHz). High-resolution mass spectrometry was performed by the mass spectrometry service at Gif on a KRATOS MS 80 RF instrument.

Preparation of 1-Benzyl-1,2,5,6-tetrahydropyridine *N*-Oxides (1a–f). The required tetrahydropyridine *N*-oxides (**1a–f**) were prepared in 75–85% yields according to an established general procedure.[2,3c] The preparation of **1b** outlined below represents a typical experiment.

1-Benzyl-6-methyl-1,2,5,6-tetrahydropyridine *N*-Oxide (1b). Sodium borohydride (2.8 g) was added in portions over 30 min to a cooled (0 °C) solution of 1-benzyl-6-methylpyridinium bromide (10 g, 0.037 mol) in ethanol (250 mL). Once addition of borohydride was complete the reaction mixture was stirred at room temperature for 1.5 h. After a normal extractive workup the crude reaction mixture was separated by column chromatography on silica (260 g, CH_2Cl_2, MeOH). 1-Benzyl-6-methyl-1,2,5,6-tetrahydropyridine (5.3 g, 75%) was obtained as a pale yellow liquid.

m-Chloroperbenzoic acid (5.50 g, 1 equiv) dissolved in CH_2Cl_2 was added dropwise over 15 min to a solution of the pure tetrahydropyridine in CH_2Cl_2(60 mL). After stirring for an additional 15 min at 40 °C an excess of solid potassium carbonate was added to the reaction and stirring was continued for 30 min at room temperature. The mixture was then suction filtered and the solid material was washed copiously with CH_2Cl_2. After concentration of the CH_2Cl_2 solution and column chromatography on silica gel (170 g, CH_2Cl_2/MeOH 10% → CH_2Cl_2/MeOH 80%) *N*-oxide **1b** was obtained as a viscous oil (4.60 g, 80%).

Preparation of 1-Benzyl-2-cyano-3-piperideines (3a–f). Amino nitriles **3a–f** were prepared by an established general procedure as detailed below for the preparation of **3b**.

1-Benzyl-2-cyano-6-methyl-3-piperideine (3b). Trifluoroacetic anhydride (12 mL, 88.0 mmol) was added slowly to a cooled (−5 °C) solution of *N*-oxide **1b** (4.60 g, 22.0 mmol) in dry CH_2Cl_2 (50 mL). The resultant mixture was stirred at room temperature under a nitrogen atmosphere for 1 h. An aqueous solution of potassium cyanide (7.15 g, 0.11 mol) was then added carefully to the reaction, the pH was adjusted to 4.0 by the addition of NaOAc or acetic acid, and vigorous stirring was maintained for an additional 30 min (room temperature). The two-phase mixture was then basified with aqueous sodium carbonate and subjected to a normal workup. The crude product (red oil) was rapidly filtered through a short column of alumina (40 g). Essentially pure **3b** (~3:2 mixture of epimers) was obtained as an orange oil (2.7 g, 57%). **Major epimer (A)**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, J = 6 Hz, 3 H, CH_3), 2.06 (ddq, J = 18, 10, 3, 2.5, 2.5 Hz, 1 H, H-5_{ax}), 2.17 (br dt, J = 18, 4.5, 4.5 Hz, 1 H, H-5_{eq}), 2.98 (m, 1 H, H-6), 3.86 (m, 1 H, H-2), 3.40, 4.23 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 5.54 (m, 1 H, H-3), 5.93 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) (Table I) δ 19.5, 34.6, 50.2, 50.6, 53.8, 116.7, 119.9, 127.7, 128.7, 129.2, 130.1, 136.9. **Minor epimer (B)**: ^1H NMR δ 1.20 (d, J = 6 Hz, 3 H, CH_3), 1.89 (dd, J = 18, 6 Hz, 1 H, H-5_{eq}), 2.48 (m, 1 H, H-5_{ax}), 3.23 (br qn, J ~ 6 Hz, 1 H, H-6), 3.89 (s, 2 H, $NCH_2C_6H_5$), 4.03 (m, 1 H, H-2), 5.62 (m, 1 H, H-3), 5.93 (m, 1 H, H-4); ^{13}C NMR δ 12.7, 32.0, 46.9, 50.2, 57.2, 118.9, 127.8, 128.6, 129.0, 136.7; MS, m/e (relative intensity) 212 ($M^{+\cdot}$, 25%), 197 (38%), 91 (100%); exact mass, m/e 212.1319; calcd for $C_{14}H_{16}N_2$, m/e 212.1313.

1-Benzyl-2-cyano-3-piperideine (3a): pale yellow liquid (65%); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.03 (br dt, J = 18, 6.5, 5 Hz, 1 H, H-5_{eq}), 2.32 (m, 1 H, H-5_{ax}), 2.61 (td, J = 12, 12, 5 Hz, 1 H, H-6_{ax}), 2.82 (dd, J = 12, 6.5 Hz, 1 H, H-6_{eq}), 3.68, 3.80 (2d, J_{AB} = 13 Hz, 2 H, $NCH_2C_6H_5$), 3.98 (br s, 1 H, H-2), 5.60 (m, 1 H, H-3), 5.98 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) (Table I) δ 25.9, 45.9, 51.0, 59.9, 115.2, 120.7, 127.9, 128.8, 129.2, 130.2, 136.9; MS, m/e (relative intensity) 198 ($M^{+\cdot}$, 6%), 271 (5%), 91 (50%); exact mass, m/e 198.1167; calcd for $C_{13}H_{14}N_2$, m/e 198.1156.

1-Benzyl-2-cyano-6-propyl-3-piperideine (3c): orange oil (63%) (55:45 mixture of epimers). **Major epimer (A)**: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, J = 6 Hz, 3 H, CH_3), 3.03 (m, 1 H, H-6), 3.55, 3.95 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 3.90 (dm, J = 5 Hz, 1 H, H-2), 5.54 (dqn, J = 10, 5, 2, 2, 2 Hz, 1 H, H-3), 5.99 (dm, J = 10, 5, 3, 2 Hz, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 14.6, 21.1, 28.6, 34.7, 51.9, 53.9, 55.2, 119.8, 130.2. **Minor epimer (B)**: ^1H NMR δ 0.90 (t, J = 6 Hz, 3 H, CH_3), 1.2–2.2 (6 m, 6 H, H-5, CH_2 CH_2 CH_3 (both epimers)), 2.98 (m, 1 H, H-6), 3.93 (s, 2 H, $NCH_2C_6H_5$), 4.02 (dm, J = 4 Hz, 1 H, H-2), 5.61 (br dt, J = 10, 3.5 Hz, 1 H, H-3), 5.92 (ddt, J = 10, 6, 2, 2 Hz, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 14.6, 18.8, 28.6, 29.7, 47.0, 50.1, 57.3, 119.6, 127.7, 127.4, 128.5, 128.6, 137.2; MS, m/e (relative intensity) 240 ($M^{+\cdot}$, 10%), 213 (10%), 197 (73%), 170 (22%), 91 (100%); exact mass, m/e 240.1623; calcd for $C_{16}H_{20}N_2$, m/e 240.1626.

1-Benzyl-2-cyano-4-methyl-3-piperideine (3d): orange oil (60%); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.73 (s, 3 H, CH_3), 1.94 (dd, J = 17, 5 Hz, 1 H, H-5_{eq}), 2.33 (m, 1 H, H-5_{ax}), 2.66 (td, J = 12, 12, 5 Hz, 1 H, H-6_{ax}), 2.88 (dd, J = 12, 7 Hz, 1 H, H-6_{eq}), 3.71, 3.82 (2d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 3.98 (m, 1 H, H-2), 5.38 (m, 1 H, H-3); ^{13}C NMR ($CDCl_3$) δ 22.5, 30.6, 46.1, 51.3, 59.6, 114.9, 116.2, 127.5, 128.5, 129.0, 138.0; MS, m/e (relative intensity) 212 ($M^{+\cdot}$, 30%), 197 (26%), 185 (30%), 135 (20%), 121 (100%), 91 (100%); exact mass m/e 212.1319; calcd for $C_{14}H_{16}N_2$, m/e 212.1313.

1-Benzyl-2-cyano-3-ethyl-3-piperideine (3e): colorless oil (65%); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, J = 6 Hz, 3 H, CH_3), 1.97, 2.05, 2.15, 2.31 (4 m, 4 H, H-5, CH_2CH_3), 2.57 (td, J = 12, 12, 5 Hz, 1 H, H-6_{ax}), 2.82 (dd, J = 12, 6.5 Hz, 1 H, H-6_{eq}), 3.73,

3.80 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 3.83 (br s, 1 H, H-2), 5.65 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 11.6, 25.4, 26.6, 45.8, 54.6, 59.8, 118.5, 122.5, 127.8, 128.7, 129.2, 136.0, 139.0; MS, *m/e* (relative intensity) 226 ($M^{+\cdot}$, 80%), 221 (45%), 199 (39%), 135 (100%), 91 (100%); exact mass, *m/e* 226.1477; calcd for $C_{15}H_{18}N_2$, *m/e* 226.1469.

1-Benzyl-2-cyano-3-ethyl-6-methyl-3-piperideine (3f): orange oil (63%). **Major epimer (A)**: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, J = 6 Hz, 3 H, CH_2CH_3), 1.25 (d, J = 6 Hz, 3 H, CH_3), 2.98 (m, 1 H, H-6), 3.72 (br s, 1 H, H-2), 3.45, 4.22 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 5.60 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 11.5, 19.7, 26.3, 34.3, 50.3, 53.7, 53.8, 117.1, 122.5, 133.0, 127.7, 128.8, 129.2, 137.8. **Minor epimer (B)**: ^1H NMR δ 1.06 (t, J = 6 Hz, 3 H, CH_2CH_3) 1.19 (d, J = 6 Hz, 3 H, CH_3), 1.89, 2.06, 2.17, 2.50 (4 m, 4 H, H-5, CH_2CH_3 (both epimers)), 3.22 (br qn, 1 H, H-6), 3.93 (br s, 3 H, H-2, $NCH_2C_6H_5$), 5.65 (m, 1 H, H-4); ^{13}C NMR δ 11.7, 12.5, 26.2, 31.8, 50.1, 57.1, 118.1, 120.6; MS, *m/e* (relative intensity) 240 ($M^{+\cdot}$, 20%), 225 (45%), 91 (100%); exact mass, *m/e* 240.1630; calcd for $C_{16}H_{20}N_2$, *m/e* 240.1626.

1,6-Dimethyl-2-cyano-3-piperideine (3b (NCH_3)): orange oil from *N*-oxide **1b** (NCH_3) (65%). **Major epimer (A)**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (d, J = 6 Hz, 3 H, CH_3), 1.92 (ddq, J = 18, 10, ~2.5 Hz, 1 H, H-5_{ax}), 2.10 (br dt, J = 18, 6, 4 Hz, 1 H, H-5_{eq}), 2.41 (s, 3 H, NCH_3), 2.67 (m, 1 H, H-6), 4.09 (m, 1 H, H-2), 5.63 (m, 1 H, H-3), 5.91 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 19.2, 34.4, 39.3, 50.7, 54.6, 117.0, 120.7, 130.0. **Minor epimer (B)**: ^{13}C NMR δ 15.4, 32.7, 40.3, 52.0, 52.6, 120.1, 128.5; MS, *m/e* (relative intensity) 136 ($M^{+\cdot}$, 8%), 121 (15%), 110 (10%), 94 (25%), 57 (20%); exact mass, *m/e* 136.1022; calcd for $C_8H_{12}N_2$, *m/e* 136.1000.

1-Benzyl-2-cyano-4-piperideine (15a). Alumina (10 g) (Merck, preactivated at 110 °C, 30 min) was added to a solution of amino nitrile **3a** (0.200 g, 1 mmol) in CH_2Cl_2 (15 mL) and the resulting suspension was stirred at room temperature for 12 h. The mixture was then filtered, the supranatant was concentrated, and the crude product was separated by simple filtration down a short column of alumina. Pure **15a** (0.100 g, 50%) was obtained as a pale yellow liquid: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.25 (dm, J = 18 Hz, 1 H, H-3_{eq}), 2.57 (dm, J = 18 Hz, 1 H, H-3_{ax}), 3.05 (dm, J = 18 Hz, 1 H, H-6_{ax}), 3.31 (dm, J = 18 Hz, 1 H, H-6_{eq}), 3.55, 3.78 (2d, J_{AB} = 13 Hz, 2 H, $NCH_2C_6H_5$), 3.80 (dd (overlapped), J = 6, 1.5 Hz, 1 H, H-2), 5.68 (m, 1 H, H-5), 5.75 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) (Table I) δ 29.5, 48.4, 49.2, 60.3, 117.5, 121.5, 125.8, 127.9, 128.8, 129.3, 136.8; MS, *m/e* (relative intensity) 198 ($M^{+\cdot}$, 60%), 172 (20%), 91 (100%); exact mass, *m/e* 198.1135; calcd for $C_{13}H_{14}N_2$, *m/e* 198.1156.

1-Benzyl-2-cyano-6-methyl-4-piperideine (15b). Amino nitrile **3b** (0.30 g) was treated with activated alumina (2 h) and purified as above. Pure **15b** was obtained as a yellow liquid (0.27 g, 90%): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, J = 5 Hz, 3 H, CH_3), 2.17 (dqn, J = 18, 5, 2, 2 Hz, 1 H, H-3_{eq}), 2.44 (dm, J = 18 Hz, 1 H, H-3_{ax}), 3.25 (m, 1 H, H-6), 3.30, 4.20 (2 d, J = 14 Hz, 2 H, $NCH_2C_6H_5$), 3.70 (dd, J = 6, 2 Hz, 1 H, H-2), 5.62 (dt, J = 10, 2, 2 Hz, 1 H, H-5), 5.67 (ddm, J = 10, 5 Hz, 1 H, H-4); ^{13}C NMR ($CDCl_3$) (Table I) δ 20.1, 29.2, 47.7, 53.0, 55.9, 117.2, 120.7, 127.5, 128.5, 128.7, 132.3, 137.4; MS, *m/e* (relative intensity) 212 ($M^{+\cdot}$, 8%), 197 (80%), 91 (100%); exact mass, *m/e* 212.1288; calcd for $C_{14}H_{16}N_2$, *m/e* 212.1313.

1-Benzyl-2-cyano-6-propyl-4-piperideine (15c). Amino nitrile **3c** (0.30 g) was treated with activated alumina (2 h) and purified as described above. Compound **15c** was obtained pure as an orange liquid (0.27 g, 90%): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, J = 6 Hz, 3 H, CH_3), 1.35, 1.55, 1.60, 1.75 (4 m, 4 H, $CH_2CH_2CH_3$), 2.18 (dqn, J = 18, 5, 2, 2 Hz, 1 H, H-3_{eq}), 2.42 (dm, J = 18 Hz, 1 H, H-3_{ax}), 3.25 (m, 1 H, H-6), 3.32, 4.20 (2d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 5.70 (dt, J = 10, 2.5, 2.5 Hz, 1 H, H-5), 5.78 (ddt, J = 10, 5, 2, 2 Hz, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 14.8, 17.6, 29.2, 35.0, 47.9, 55.7, 57.3, 117.0, 121.4, 127.5, 128.6 (2), 130.6, 137.4; MS, *m/e* (relative intensity) 240 ($M^{+\cdot}$, 8%), 213 (9%), 197 (60%), 170 (15%), 91 (100%); exact mass, *m/e* 240, 1642; calcd for $C_{16}H_{20}N_2$, *m/e* 240.1626.

1-Benzyl-2-cyano-4-methyl-4-piperideine (15d). Amino nitrile **3d** (0.30 g) was treated with activated alumina (8 h) and purified as above. Compound **15d** was obtained pure as a yellow oil (0.18 g, 60%): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.72 (s, 3 H, CH_3), 2.11 (br d, J = 18 Hz, 1 H, H-3_{eq}), 2.57, 3.05, 3.30 (3 dm, J = 18 Hz, 1 H each, H-3_{ax}, 6_{eq}, 6_{ax}), 3.57, 3.80 (2 d, J_{AB} = 13 Hz, 2 H, $NCH_2C_6H_5$), 3.84 (dd, J = 6, 1.5 Hz, 1 H, H-2), 5.49 (br s, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 22.6, 33.9, 48.8, 49.2, 60.0, 119.5, 127.9, 128.8, 129.0, 129.2, 136.9; MS, *m/e* (relative intensity) 212 ($M^{+\cdot}$, 14%), 197 (8%), 185 (20%), 172 (8%), 121 (50%), 91 (100%); exact mass, *m/e* 212.1320; calcd for $C_{14}H_{16}N_2$, *m/e* 212.1313.

1-Benzyl-2-cyano-3-ethyl-6-methyl-4-piperideine (15f). Amino nitrile **3f** (0.30 g) was treated with activated alumina (2 h, 60 °C) and purified as above. Pure **15f** (0.15 g, 50%) was obtained as a pale yellow liquid: IR (film) ν_{max} 2220 (CN), 1650 cm^{-1} (enamine); UV (EtOH) λ_{max} 252 nm; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_2CH_3), 1.22 (d, J = 6 Hz, 3 H, CH_3), 2.02, 2.10 (2 m, 4 H, CH_2CH_3, H-5), 3.10 (m, 1 H, H-6), 3.28 (br t, J = 6 Hz, 1 H, H-4), 4.05 (s, 2 H, $NCH_2C_6H_5$), 5.82 (br s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 13.0, 16.9, 25.0, 25.7, 32.6, 48.0, 54.0, 132.5; MS, *m/e* (relative intensity) 240 ($M^{+\cdot}$, 100%), 225 (75%), 211 (8%), 91 (100%); exact mass, *m/e* 240.1649; calcd for $C_{16}H_{20}N_2$, *m/e* 240.1626.

1,6-Dimethyl-2-cyano-4-piperideine (15b (NCH_3)). Amino nitrile **3b** (NCH_3) (0.30 g) was treated with activated alumina (5 h) and purified as described above. Pure **15b** (NCH_3) (0.24 g, 80%) was obtained as a pale yellow liquid: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6 Hz, 3 H, CH_3), 2.28 (dm, J = 18 Hz, 1 H, H-3_{eq}), 2.76 (do, J = 18, 6, 4, 2, 2 Hz, 1 H, H-3_{ax}), 2.98 (m, 1 H, H-6), 3.82 (dd, J = 6, 2 Hz, 1 H, H-2), 5.57 (dt, J = 10, 2, 2 Hz, 1 H, H-5), 5.67 (ddt, J = 10, 5, 2, 1.5 Hz, 1 H, H-4); ^{13}NMR ($CDCl_3$) δ 19.5, 29.5, 41.4, 52.8, 54.0, 117.5, 120.3, 132.2; MS, *m/e* (relative intensity) 136 ($M^{+\cdot}$, 2%), 121 (30%), 110 (3%), 94 (12%); exact mass, *m/e* 136.1019; calcd for $C_8H_{12}N_2$, *m/e* 136.1000.

1-Benzyl-2-cyano-6-methylpiperidine (13b(A)). Amino nitriles **3b** (0.250 g, 1.2 mmol) in methanol (10 mL) were hydrogenated for 18 h at atmospheric pressure and room temperature by using 10% palladium on carbon (0.03 g) as catalyst. The reaction mixture was then filtered through a Celite bed and concentrated to give a near colorless oil. The crude product was purified by simple filtration through a short column of alumina. Pure **13b(A)** was obtained as a colorless oil (0.235 g, 91%): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 6 Hz, 3 H, CH_3), 1.3, 1.7, 1.8 (3 m, 6 H, H-3, 4, 5), 2.64 (m, 1 H, H-6), 3.20, 4.25 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 3.65 (narrow m, 1 H, H-2); ^{13}C NMR ($CDCl_3$) (Table I) δ 21.1 (2), 28.7, 34.5, 51.2, 53.3, 55.2, 117.1, 127.4, 128.5, 128.9, 137.8; MS, *m/e* (relative intensity) 214 ($M^{+\cdot}$, 27%), 199 (100%), 173 (50%), 123 (97%), 91 (100%); exact mass, *m/e* 214.1466; calcd for $C_{14}H_{18}N_2$, *m/e* 214.1469.

1-Benzyl-2-cyano-6-methylpiperidine (13b(B)). A solution of amino nitrile **13b(A)** (0.235 g, 1.10 mmol) in THF (1 mL) was added via syringe to a solution of LDA (2.20 mmol) in THF (10 mL) (–30 °C, N_2 atmosphere). The resultant solution containing the anion of **13b** was warmed to room temperature over 30 min then quenched by the addition of an aqueous solution of NH_4Cl. After a normal extractive workup a pale yellow oil was obtained containing the desired product **13b(B)** in a 1:1 mixture with **13b(A)**. Attempts to obtain compound **13b(B)** pure by column chromatography on alumina resulted in its reconversion to epimer **13b(A)**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, J = 6 Hz, 3 H, CH_3), 1.5–1.9 (m, 6 H, H-3, 4, 5), 3.12 (m, 1 H, H-6), 3.53 (m, 1 H, H-2), 3.82, 3.88 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) (Table I) δ 13.0, 16.6, 29.4, 31.5, 47.1, 53.4, 56.0, 128.3, 128.8, 128.9, 137.8; MS, *m/e* (relative intensity) 214 ($M^{+\cdot}$, 27%), 199 (100%), 173 (50%), 123 (97%), 91 (100%); exact mass, *m/e* 214.1476; calcd for $C_{14}H_{18}N_2$, *m/e* 214.1469.

1-Benzyl-*trans*-2-propyl-6-methyl-3-piperideine (21). A solution of amino nitriles **3b** (0.250 g, 1.18 mmol) in THF (1 mL) was added to a solution of LDA (2.36 mmol) in THF (10 mL) at –55 °C (N_2 atmosphere). After the solution stirred for 5 min propyl bromide (0.5 mL) was added, and the reaction mixture was allowed to warm to room temperature over a 1-h period. The reaction was then stopped by the addition of water and extracted with CH_2Cl_2 as normal. The crude product **20** (0.245 g) was immediately dissolved in ethanol (15 mL) and reacted with an excess of $NaBH_4$ (30 min, room temperature). The reaction was then diluted with water, and the aqueous mixture was extracted with CH_2Cl_2. After rewashing, drying, and concentration of the organic fractions a near colorless oil (0.160 g) was obtained. GC analysis of the crude product mixture (SE-30, 155 °C, 1.2 bar) revealed the presence of two products **21** (T_R = 6.5 min) and **22** (T_R = 6.9 min) in a 86:14 ratio. The desired product **22** was

isolated pure by preparative layer chromatography on alumina (elution 3 times with hexane) (0.116 g, 50%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.70 (t, J = 6 Hz, 3 H, CH_3), 1.07 (d, J = 6 Hz, 3 H, CH_3), 1.25, 1.40, 1.60 (4 m, 4 H, H-7, 8), 1.82, 1.96 (2 dm, 2 H, H-$5_{ax,eq}$), 2.88 (m, 1 H, H-2), 3.09 (m, 1 H, H-6), 3.42, 3.65 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 5.55 (ddt, J = 10, 3.5, 2.5, 1.5 Hz, 1 H, H-3), 5.72 (dtd, J = 10, 4, 3.5, 2 Hz, 1 H, H-4), 7.3 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) (Table III); MS, m/e (relative intensity) 229 ($M^{+\cdot}$, 20%), 214 (22%), 177 (100%), 91 (90%); exact mass, 229.1830; calcd for $C_{16}H_{23}N$, m/e 229.1830.

1-Benzyl-*cis*-2-propyl-6-methyl-3-piperideine (22). *n*-Propylmagnesium bromide (4.7 mL, 2.35 mmol) was added dropwise to a cold (-40 °C) solution of amino nitriles **3b** (0.250 g, 1.18 mmol) in THF (10 mL) N_2 atmosphere). The resultant mixture was stirred for 15 min, at -40 °C followed by 45 min at room temperature. After addition of water and normal extractive workup with CH_2Cl_2 a near colorless oil (0.255 g) was obtained. GC analysis of the crude product mixture (SE-30, 155 °C, 1.2 bar) revealed the presence of two isomeric products **21** (T_R = 6.5 min) and **22** (T_R = 6.9 min) in a 17:83 ratio. The desired cis compound **22** was obtained pure after preparative layer chromatography on alumina (elution 3 times with hexane) (colorless oil, 0.170 g, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J = 6 Hz, 3 H, CH_3), 1.00 (d, J = 6 Hz, 3 H, CH_3), 1.25, 1.35, 1.5, 1.7, 1.88, 2.05 (6 m, 6 H, H-5, 7, 8), 2.85 (m, 1 H, H-6), 3.06 (m, 1 H, H-2), 3.70, 3.80 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 5.60 (dq, J = 10, 2, 2, 2 Hz, 1 H, H-3), 5.70 (dqn, J = 10, 4, 2, 2 Hz, 1 H, H-4), 7.3 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) (Table III); MS, m/e (relative intensity) 229 ($M^{+\cdot}$, 5%), 214 (8%), 177 (96%), 91 (100%); exact mass, m/e 229.1816; calcd for $C_{16}H_{23}N$, m/e 229.1830.

1-Benzyl-*trans*-2-propyl-6-methyl-4-piperideine (24). As described for the preparation of **21**, a solution of amino nitrile **15b** (0.250 g, 1.18 mmol) in THF was reacted with LDA (2.0 equiv), and propyl bromide (0.5 mL) (-40 °C, 3 h). After extraction the crude product (0.230 g) was reacted with $NaBH_4$ (30 min, room temperature). A near colorless oil (0.180 g) was obtained containing products **24** (T_R = 5.7 min) and **25** (T_R = 6.0 min) in a ratio of 54/46 (SE -30, 155 °C, 1.2 bar). Product **24** was isolated pure by preparative layer chromatography on alumina (elution 3 times with hexane) (0.067 g, 46%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 6 Hz, 3 H, CH_3), 1.08 (d, J = 6 Hz, 3 H, CH_3), 1.37, 1.53, 1.70, 1.88 (4 m, 6 H, H-3, 7, 8), 2.98 (br qn, J = 6 Hz, 1 H, H-2), 3.03 (m, 1 H, H-6), 3.45, 3.70 (2 d, J_{AB} = 14 Hz, 2 H, $NCH_2C_6H_5$), 5.52 (ddt, J = 10, 4, 2, 2 Hz, 1 H, H-5), 5.75 (dtd, J = 10, 4, 3, 2 Hz, 1 H, H-4), 7.30 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) Table III; MS, m/e (relative intensity) 229 ($M^{+\cdot}$, 10%), 214 (15%), 177 (100%), 91 (88%); exact mass, m/e 229.1828; calcd for $C_{16}H_{23}N$, m/e 229.1830.

1-Benzyl-*cis*-2-propyl-6-methyl-4-piperideine (25). *n*-Propylmagnesium bromide (4.7 mL, 2.35 mmol) was added dropwise to a cooled (0 °C) solution of amino nitrile **15b** (0.250 g, 1.18 mmol) in THF (10 mL) (N_2 atmosphere). The resulting mixture was stirred for 3 h at room temperature. After addition of water and normal extractive workup with CH_2Cl_2 a near colorless oil (0.210 g) was obtained. GC analysis (SE-30, 155 °C, 1.2 bar) revealed the presence of two isomeric products **25** (T_R = 6.0 min) and **24** (T_R = 5.7 min) in a 92:8 ratio. The desired cis compound **25** was obtained pure after preparative layer chromatography on alumina (elution 3 times with hexane) (colorless oil, 0.147 g, 59%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J = 6 Hz, 3 H, CH_3), 1.05 (d, J = 6 Hz, 3 H, CH_3), 1.25, 1.60 (2 m, 4 H, H-7, 8), 1.85, 2.15 (2 m, 2 H, H-$3_{ax,eq}$), 2.80 (m, 1 H, H-2), 3.30 (m, 1 H, H-6), 3.72 (s, 2 H, $NCH_2C_6H_5$), 5.52 (dq, J = 10, 2, 2, 2 Hz, 1 H, H-5), 5.70 (dtd, J = 10, 4, 4, 2 Hz, 1 H, H-4), 7.30 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) Table III; MS, m/e (relative intensity) 229 ($M^{+\cdot}$, 10%), 214 (22%), 177 (92%), 91 (100%); exact mass, m/e 229.1829; calcd for $C_{16}H_{23}N$, m/e 229.1830.

Acknowledgment. The authors would like to thank M. G. Lemoine (Roussel-Uclaf) for the computer calculations, and Dr. G. Lukacs for helpful discussions concerning the ^{13}C NMR results. We also thank S. K. Kan (Institut d'Electronique Fondamentale, Université de Paris-Sud, Orsay) for the use of his 400-MHz ^{1}H NMR spectrometer.

Registry No. **1a**, 89873-51-8; **1b**, 89873-52-9; **1c**, 89873-53-0; **1d**, 89873-54-1; **1e**, 60900-18-7; **1f**, 89873-55-2; **3a**, 85617-07-8; **3b(A)**, 89873-56-3; **3b(A)** (NCH_3), 89873-57-4; **3b(B)**, 89873-58-5; **3b(B)** (NCH_3), 89873-59-6; **3c(A)**, 89873-60-9; **3c(B)**, 89873-61-0; **3d**, 89873-62-1; **3e**, 73657-71-3; **3f(A)**, 89873-63-2; **3f(B)**, 89873-64-3; **13b(A)**, 89873-65-4; **13b(B)**, 89873-66-5; **15a**, 89873-67-6; *trans*-**15b**, 89873-68-7; **15b** (NCH_3), 89873-69-8; **15c**, 89873-70-1; **15d**, 89873-71-2; **15f**, 89873-72-3; **20**, 89873-73-4; **21**, 89873-74-5; **22**, 89873-75-6; **24**, 89873-76-7; **25**, 89873-77-8; 1-benzyl-6-methylpyridinium bromide, 2654-66-2; 1-benzyl-6-methyl-1,2,5,6-tetrahydropyridine, 89873-78-9.

2-Cyano-Δ^3-piperideines. 13.[1] Synthesis and Reactivity of N-Protected Dehydrosecodine Equivalents[2]

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Received November 7, 1983

A direct synthesis of 1-(phenylsulfonyl)secodine (**6**) is accomplished by lithiation of 1-(phenylsulfonyl)-3-[2-(5-ethyl-1,2,3,6-tetrahydropyridyl)ethyl]indole (**4**), reaction with methyl pyruvate, and dehydration. The 2-cyano-Δ^3-piperideine derivatives of both the carbinol precursor **9** and of 1-(phenylsulfonyl)dehydrosecodine **12** have been characterized. Various reaction conditions under which 1-(phenylsulfonyl)dehydrosecodine (**14**) could be generated have been examined but no products of either the *Aspidosperma* or *Iboga* structural type have been characterized. Instead, disproportionation of the dihydropyridine intermediate appears to be the dominant reaction. Reductive desulfonylation of the carbinol intermediate provides 16-hydroxy-16,17-dihydrosecodine (isosecodinol) (**19**) but under the same conditions 1-(phenylsulfonyl)secodine (**6**) generates 16,17-dihydrosecodine (**18**).

The role of dehydrosecodine (**2**) as an intermediate in the biosynthesis of indole alkaloids (*Corynanthé* → *Strychnos* → *Aspidosperma* and *Iboga*) was postulated by Wenkert in 1962.[4] This hypothesis has been supported

(1) For Part 12 see: Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.*, preceding paper in this issue.

(2) For a preliminary disclosure see: Husson, H.-P. In "Monoterpene Indole Alkaloids"; Saxton, J. E., Ed.; Wiley: New York, 1984.

0022-3263/84/1949-2400$01.50/0