mmol) and dry triethylamine (40 μL, 0.30 mmol) in dry THF (5 mL), and the mixture was stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane. The solution was washed sequentially with water and brine, dried ($MgSO_4$), and concentrated. The residue was taken up in dry methanol–hydrochloric acid [prepared by addition of acetyl chloride (50 μL) in anhydrous MeOH (5 mL)] and was refluxed under nitrogen for 1 h. The reaction medium was diluted with chloroform, and washed with 1% $NaHCO_3$, water, and brine. Evaporation of the dried organic phase gave a yellowish residue which was purified by PLC (benzene–EtOH–concentrated ammonia, 40:10:1) to give 1 (54 mg, 58%) as a colorless amorphous powder, identical with natural cuanzine on comparison of spectroscopic ^1H NMR, UV, MS, and TLC data.

Registry No. (±)-1, 132015-34-0; (±)-4, 131905-75-4; (±)-5, 131905-76-5; (±)-6, 131905-77-6; (±)-7, 131905-78-7; 8, 122835-08-9; 9, 4894-26-2; 10, 131905-79-8; 13, 65946-60-3; (±)-14, 131905-81-2; (±)-*cis*-15, 131905-80-1; (±)-*trans*-15, 131905-82-3; 16, 131905-83-4; (±)-17, 131905-84-5; (±)-19, 132015-35-1; (±)-20, 131932-50-8; (±)-21, 125160-81-8; (±)-22, 125160-62-5; (±)-23, 131905-85-6; $ClCO(CH_2)_2SPh$, 51849-21-9; methyl isocyanoacetate, 39687-95-1.

Supplementary Material Available: NMR spectra for compounds 4–7, 10, 14, 16, 21, and 23 (9 pages). Ordering information is given on any current masthead page.

Regioselective Oxidation of Piperidine-3 Derivatives: A Synthetic Route to 2,5-Substituted Piperidines

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Mercuric acetate oxidation of 1-benzyl-3,3-(ethylenedioxy)piperidine (1) and of 3-CO_2Et- and 3-CH_2OH-substituted piperidines 7–9 was shown to occur regioselectively at the 6-position. Trapping of the resulting 6-iminium ions with cyanide yielded the corresponding 5-substituted 2-piperidinecarbonitriles 5, 10, and 11. However, the 2-iminium ion was formed in the reaction of the *N*-oxide of 1 with trifluoroacetic anydride; with cyanide this afforded the regioisomeric 3,3-(ethylenedioxy)-2-piperidinecarbonitrile (2). Plausible mechanisms are advanced to explain this contrasting behavior. 1-Benzyl-5,5-(ethylenedioxy)-2-piperidinecarbonitrile (5) was transformed into other piperidine-2,5 derivatives by reaction of the α-amino nitrile anion with electrophoresis, followed by reductive decyanation.

The piperidine ring forms an integral feature of many alkaloid structures. Efforts in drug synthesis have been directed at simplifying the complex substitution pattern of piperidine rings in morphine (1,2,3,4-substituted), reserpine (1,2,4,5-substituted), and LSD (1,2,3,5-substituted). These efforts eventually resulted in the preparation of many highly efficient drugs characterized by nonchiral 1,4-substituted piperidine and piperazine structures.[1] The selectivity required in binding to the asymmetric receptor site calls for chiral and flexible guest molecules. Therefore, we became interested in the synthesis of 2,5-substituted piperidines, which share a regioisomeric substitution pattern but not the conformational rigidity with the polycyclic alkaloids. Flexibility in fitting the receptor site is a property common to both 1,4- and 2,5-substituted piperidines. General methods for the synthesis of the latter compounds are not available.[2] In this context we investigated a route consisting of selective oxidation at the 6-position of 3-substituted piperidines and trapping of the resulting iminium ions with cyanide.[3]

The ethylenedioxy-protected derivative 1 of 1-benzyl-3-piperidinone was chosen as the first substrate since the electronic and steric effects of the acetal group were expected to direct the course of oxidation in a regioselective way. However, transformation of 1 to the *N*-oxide, trifluoroacetylation, and trapping of the resulting iminium ion with cyanide exclusively yielded (70%) the 2,3-functionalized piperidine 2. This structure assignment is based on a singlet absorption at 3.52 ppm for H-2 in the ^1H NMR spectrum and a doublet absorption for the CN group in the ^1H-coupled ^{13}C spectrum (Table I). Probably, regioselectivity is governed by the higher acidity of protons H-2 versus H-6. In the analogous reactions of 3-alkyl-substituted piperidines [R = Et, $CH_2CH_2CO_2Me$, $CH(OCH_2CH_2O)$, etc.], invariably mixtures of the 2- and 6-regioisomers were obtained.[4] An E_2 type mechanism (vis.3) is generally accepted[5] for this Polonovski-Potier reaction.[6] Our result would imply the development, at an early stage of the reaction, of a partial negative charge on the C-2 atom stabilized both by the positively charged N-atom and the inductive effect of the acetal O-atoms.

Mercuric acetate oxidation of 1,3-dialkylpiperidines in aqueous acetic acid was reported to give nonregioselective oxidation at both the 2- and 6-position.[7] Upon alkaline extraction, the resulting 2-iminium products were converted to the 3-substituted enamines, whereas the 6-iminium products reacted to form the (enamine + iminium) dimers. This dimerization problem could be avoided by further oxidation to the lactam using a mercuric ace-

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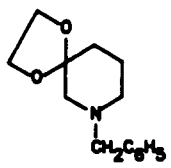

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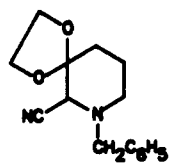

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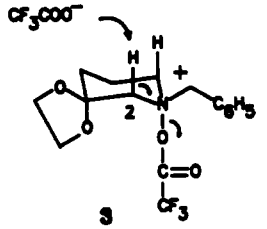
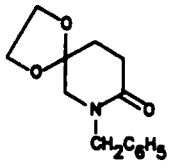


3

tate–EDTA reagent; for 3-acyl-substituted piperidines, the lactam carbonyl group was introduced regioselectively at the 6-position.[8]

When we applied the latter method to 1, lactam 4 was obtained in 30% yield only. This was converted into the desired nitrile 5 by partial reduction with $LiAlH_4$ and further treatment with cyanide. However, when using the original mercuric acetate method,[7] we were able to isolate 5 in 85% yield by trapping the 6-iminium product under acidic conditions.[3] This was effected, after completion of the Hg^{2+} oxidation of 1, simply by adding cyanide to the cooled aqueous acetic acid reaction medium. Probably the poor yield for lactam 4 was due in part to the enhanced rate of acidic cleavage of the acetal group of the neutral 4 as compared to that for the iminium ion leading to nitrile 5.



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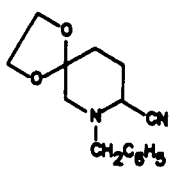

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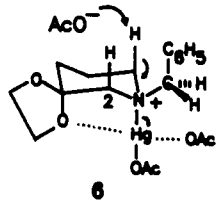

6

The observed regioselectivity cannot be ascribed solely to the steric effect of the acetal group since 3,3-dimethyl-substituted piperidines gave rise to oxidation at both the 2- and 6-position.[7] Rather, we suppose transition state 6 in which the mercuric ion is coordinated to both the N-atom and an axially oriented O-atom. By taking part in this five-membered ring coordination, the C-2 atom acquires more rigidity than the C-6 atom and therefore cannot readily attain the planar geometry of the iminium product. Furthermore, the phenyl group in 6 will assume an antiperiplanar orientation relative to the tetracoordinated axial Hg ligand, so that benzylic H-atoms are not available for antielimination.

The ^1H and ^{13}C NMR spectra of the regioisomeric amino nitriles 2 and 5 and the parent compound 1 are assembled in Table I for comparison. For both regioisomers an axial orientation is preferred for the cyano group due to repulsion between the π electrons and the free electron pair on the N-atom.[4,9] In the ^1H NMR spectrum of 5, the equatorial proton H-2eq appeared as a multiplet ($\sum^3J$ = 7 Hz), showing additional long-range coupling with protons H-4eq and H-6eq. The axial position of the CN group was confirmed by a ddd pattern in the ^{13}C spectrum, corresponding to coupling with H-2eq (^2J = 6 Hz), H-3ax (^3J = 10.5 Hz), and H-3eq (^3J = 2 Hz).

For regioisomer 2, the occurrence of either the CNax or CNeq form was revealed by the differentiation of protons H-6 (^2J = 11 Hz) into H-6eq ($\sum^3J$ = 7 Hz) and H-6ax ($\sum^3J$ = 15 Hz). When using C_6D_6 as a solvent instead of $CDCl_3$, separate signals were observed also for protons H-4ax, H-4eq, H-5ax, and H-5eq (δ = 1.84, 1.52, 1.70, and 1.26 ppm) characterized by $\sum J$ values of 29, 21, 43, and 23 Hz, respectively.

The orientation of the CN group was determined through comparison of the $^1J_{CH}$ coupling constants for the CH and CH_2 groups α to the ring N-atom of 1, 2, and 5 (table I). Similar measurements for CH α to the ring O-atom have been used previously to assign the anomeric configuration in 1-cyano[10] and other sugars[11] ($^1J_{CHax} < {}^1J_{CHeq}$; difference ca. 10 Hz). For regioisomers 2 and 5, equal values $^1J_{C\text{-}2,H\text{-}2}$ = 149 Hz were obtained, showing that proton H-2 for 2 had the same equatorial orientation as that established for compound 5. The validity of this method for anomeric assignment, when applied to α-substituted piperidines, was ascertained by the characteristic $^1J_{CH}$ values measured for the conformationally fixed α-protons H-6ax and H-6_{eq} of compound 5 (131 and 139 Hz). The 8 Hz difference is similar to the sugar difference values.[10,11] The mean value (135 Hz) should be compared to the single values obtained for the α-CH_2 group of piperidine (133.7 Hz)[12a] and the 2- and 6-CH_2 groups of 1 (133 Hz). Finally, the high value corresponding to H-6eq (139 Hz) nicely fits that mentioned above for H-2_{eq} (149 Hz), when taking into account the increment for CN (11 Hz).[12b]

Application of the Hg^{2+} oxidation and the cyanide trapping method to the commercial ethyl ester 7a and alcohol 8 and to the benzoylated analogue 9 in each case afforded a mixture of diastereoisomers 10 and 11. Regioisomeric products were not detected. The epimeric compounds were separated by column chromatography using hexane–ethyl acetate as the eluent. An equilibrium mixture was again established by dissolving the pure compounds in methanol.

The ^1H NMR spectra of compounds 10 and 11 uniformly revealed an axial orientation for the cyano group. The equatorial proton H-2eq appeared as a triplet with $\sum({}^3J_{2e,3e} + {}^3J_{2e,3a})$ = 7–8 Hz. The trans-diaxial structure 11 was assigned to the minor and less polar isomers on the basis of the coupling constants observed for protons H-6eq and H-6ax (^2J = 12 Hz, $^3J_{6e,5e}$ = 4 Hz, and $^3J_{6a,5e}$ = 4 Hz). For the major cis compounds 10 the R group had the equatorial orientation ($^3J_{6a,5a}$ = 11 Hz and $^3J_{6e,5a}$ = 4 Hz).

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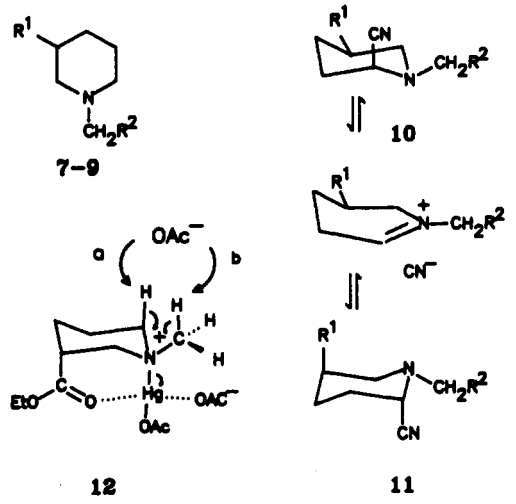
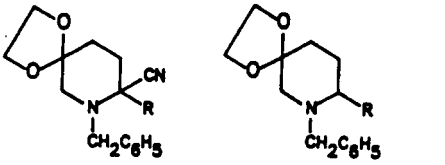


7–9 10 12 11

7a: R^1 = CO_2Et, R^2 = H
7b: R^1 = CO_2Et, R^2 = Ph
8: R^1 = CH_2OH, R^2 = H
9: R^1 = CH_2OCOPh, R^2 = H
10a, 11a: R^1 = CO_2Et, R^2 = H (55%)
10b, 11b: R^1 = CH_2OH, R^2 = H (isolated as 10c, 11c, 43%)
10c, 11c: R^1 = $CH_2OCOC_6H_5$, R^2 = H (58%)
10d, 11d: R^1 = CO_2Et, R^2 = Ph (67%)

The regioselective Hg^{2+} oxidation of **7a**, 8, and 9 may involve a six-membered ring coordination (e.g., **12**, pathway a) of the mercuric ion with the piperidine N-atom and an O-atom of the axially oriented 3-substituent.[13] However, in regard to the decreased yields obtained for **10a–c** and **11a–c** (43–58% as compared to 85% for 5), formation and subsequent degradation of alternative iminium ions cannot be ruled out. Especially hydrolytic loss may occur for methylene iminium ions formed via abstraction of a methyl H-atom (**12**, pathway b). In contrast to the benzylic H-atoms in **6**, one H-atom can be oriented anti relative to the Hg ligand. The resulting secondary amines remain undetected as they are water-soluble and easily oxidizable compounds. In order to verify the supposed concurrent oxidation of the *N*-methyl group, Hg^{2+} oxidation was applied to **7b**,[14] the *N*-benzyl analogue of **7a**. As expected, suppression of the side reaction resulted in a substantially increased yield (67%) for the epimeric *N*-benzyl compounds **10d** and **11d**.

The α-amino nitrile can be transformed in several ways, e.g., by alkylation of the corresponding anion.[15] Treatment of **5** with LDA in THF at low temperature in the presence of HMPTA, and further reaction of the resulting anion with phenethyl bromide or ethyl chloroformate, gave **13** and **14** in high yield. The alkylated compound **13** readily lost cyanide to form the alkyl-substituted iminium ion. This was indicated by trailing on TLC and the fast reductive decyanation with $NaBH_4$ in ethanol to yield **16**. In contrast, the electron-withdrawing ester group in **14** prevented formation of the iminium ion. Accordingly, the first attack of the $NaBH_4$ reducing agent occurred on the activated ester, and alcohol **15** was detected as an intermediate in the conversion of 14 to the final decyanated product **17**.



13: R = $C_6H_5CH_2CH_2$
14: R = CO_2Et
15: R = CH_2OH
16: R = $C_6H_5CH_2CH_2$
17: R = CH_2OH

In conclusion, Hg^{2+} oxidation of 3,3-(ethylenedioxy), 3-CO_2Et-, and 3-CH_2OH-substituted piperidines and trapping of the intermediate iminium ions with cyanide opens a way to various 2,5-substituted piperidines. The regioselective formation of the iminium ion at ring position 6 appears to be governed mainly by coordination of the axial Hg ligand to an α-O-atom of the 3-substituent. For N-benzylic compounds, the ring regioselectivity is enhanced further by the antiperiplanar position of the phenyl group. Further synthetic work on **5** will be oriented toward transformations of the α-amino nitrile function and toward deprotection and functionalization of the 5-ketone group.

Experimental Section

IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrophotometer. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker WM 250 instrument operating at 250 MHz for ^1H and 63 MHz for ^{13}C measurements. The ^1H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. Mass spectra were run on a Kratos MS50 instrument and DS90 data system; the ion source temperature was 150–250 °C as required. Exact mass measurements were performed at a resolution of 10 000. Besides the spectral and analytical data mentioned below, the purity of all compounds was checked by TLC.

1-Benzyl-3,3-(ethylenedioxy)piperidine (1). A mixture of 1-benzyl-3-piperidinone·HCl (11.3 g, 50 mmol), ethylene glycol (128 mL, 2.3 mol), and *p*-toluenesulfonic acid (0.2 g, 1.05 mmol) in 500 mL of toluene was refluxed overnight under nitrogen with azeotropic removal of water. The reaction mixture was cooled, and the ethylene glycol layer was separated and poured into 200 mL of an ice-cold solution of K_2CO_3 in water. The alkaline solution was extracted with CH_2Cl_2 (400 mL). The organic phase was washed with water (2 × 200 mL), filtered, and evaporated, yielding 11.6 g of crude 1 as an oil, which can be used directly in the next step.

The crude product was purified by column chromatography on silica gel (chloroform–ethyl acetate, 4:1) to give 1 as a yellow oil (11 g, 94%): ^1H NMR ($CDCl_3$) δ 7.28 (m, 5 H, Ar), 3.92 (m, 4 H, OCH_2CH_2O), 3.60 (s, 2 H, NCH_2Ph), 2.42 (t, 2 H, $^3J_{6,5}$ = 5 Hz, H-6), 2.40 (s, 2 H, H-2), 1.73 (m, 2 H, H-5), 1.60 (m, 2 H, H-4); MS *m/z* 233 (M^+), 188, 160, 134 (100), 99, 91, 86; exact mass calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1420.

1-Benzyl-3,3-(ethylenedioxy)-2-piperidinecarbonitrile (2). Excess of 30% H_2O_2 (7 mL) was added to a solution of 1 (2 g, 8.58 mmol) in 40 mL of 1:1 CH_2Cl_2–MeOH, and the resulting solution was stirred at 55 °C for 24 h. Excess peroxide was destroyed by the addition of 200 mg of 10% Pd/C and 2 h of stirring at 55 °C. The mixture was filtered and concentrated. The residue was dissolved in 40 mL of CH_2Cl_2 and the solution dried over $MgSO_4$. Filtration, evaporation, and drying in vacuo gave the *N*-oxide of 1 (2.1 g, 98%) as a white solid (TLC on silica gel, R_f = 0.25 with 1:19 MeOH–EtOAc).

To a stirred and cooled (0 °C) solution of the *N*-oxide of 1 (2.1 g, 8.43 mmol) in 10 mL of dry CH_2Cl_2 was added trifluoroacetic anhydride (3 mL, 21.1 mmol) dropwise over a period of 20 min (N_2 atmosphere). Stirring was continued at 0 °C for 1 h; then

(13) In accordance with our hypothesis, mercuric acetate oxidation and cyanide trapping of the 3-CH_2CO_2Et and 3-CH_2CH_2OH homologues of **7a** and 8 gave rise to 1:9 and 1:2 regioisomeric mixtures of 2,3- and 2,5-substituted cyanopiperidines in low total yield (34–42%) (our unpublished results).

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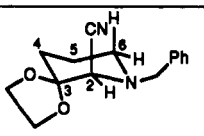
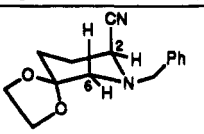
Table I. ^1H and ^{13}C NMR Spectral Data of 1, 2, and 5 in $CDCl_3$



2

atom	δ (mult, no. of protons)
H-2	3.52 (br s, Σ^4J = 2 Hz, 1 H)
H-4, H-5	1.64–1.98 (m, 4 H)
H-6ax	2.52 (trm, ΣJ = 26 Hz, 1 H)
H-6eq	2.80 (ddm, ^2J = 11 Hz, ΣJ = 18 Hz, 1 H)
CH_2Ph	3.52 and 3.83 (AB q, ^2J = 13 Hz, 2 H)
OCH_2CH_2O	3.82–4.06 (m, 4 H)
C_6H_5	7.2–7.32 (m, 5 H)
C-2	58.8 (^1J = 149 Hz)
C-3	105.3
C-4	30.8
C-5	22.0
C-6	48.3
CH_2Ph	59.7
OCH_2CH_2O	64.9/64.7
CN	114.7 (^2J = 6 Hz)



5

atom	δ (mult, no. of protons)
H-2	3.78 (m, Σ^3J = 7 Hz, 1 H)
H-3, H-4	1.8–2.17 (m, 4 H)
H-6ax	2.54 (d, ^2J = 12 Hz, 1 H)
H-6eq	2.75 (br d, ^2J = 12 Hz, Σ^4J = 2 Hz, 1 H)
CH_2Ph	3.64 and 3.76 (AB q, ^2J = 13 Hz, 2 H)
OCH_2CH_2O	3.8–4.2 (m, 4 H)
C_6H_5	7.05–7.25 (m, 5 H)
C-2	51.0 (^1J = 149 Hz)
C-5	105.5
C-4	30.6
C-3	26.6
C-6	55.8 (^1J = 131, 139 Hz)
CH_2Ph	60.4
OCH_2CH_2O	64.8/64.6
CN	116.0 (^2J = 6 Hz, ^3J = 10.5, 2 Hz)

1

atom	δ (mult, no. of protons)
H-2	3.62 (s, 2 H)
H-4, H-5	1.5–1.7 (m, 4 H)
H-6	2.45 (t, 2 H)
CH_2Ph	2.4 (s, 2 H)
OCH_2CH_2O	3.8–4.0 (m, 4 H)
C_6H_5	7.2–7.4 (m, 5 H)
C-2	62.4 (^1J = 133 Hz)
C-3	106.2
C-4	33.1
C-5	22.6
C-6	52.2 (^1J = 133 Hz)
CH_2Ph	59.1
OCH_2CH_2O	64.0

an aqueous solution of KCN (900 mg, 13.8 mmol) in 6 mL of water was added dropwise. The aqueous layer was adjusted to pH 5 by the addition of solid NaOAc. The mixture was stirred at room temperature for 30 min, made alkaline (pH 8) with aqueous K_2CO_3, and extracted with CH_2Cl_2 (2 × 200 mL). The combined extracts were evaporated, and the residue was purified on a silica column using 1:9 EtOAc–$CHCl_3$ as the eluent to afford **2** (1.6 g, 72%) as an oil: ^1H and ^{13}C NMR, see Table I; MS *m/z* 258 (M^+), 218, 167, 159, 99 (100), 91; exact mass calcd for $C_{15}H_{18}N_2O_2$ 258.1368, found 258.1372.

1-Benzyl-5,5-(ethylenedioxy)-2-piperidinone (4). A stirred mixture of **1** (2 g, 8.58 mmol), 1% aqueous acetic acid (100 mL), disodium EDTA·$2H_2O$ (8 g, 21.5 mmol), and $Hg(OAc)_2$ (6.9 g, 21.7 mmol) was heated under reflux for 1.5 h. After cooling, the reaction mixture was extracted with $CHCl_3$ (300 mL). The $CHCl_3$ extract was evaporated, and the residue was chromatographed on a silica column using EtOAc as the eluent to give **4** (655 mg, 31%) as an oil; IR 1650 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.24 (s, 5 H, Ph), 4.56 (s, 2 H, NCH_2Ph), 3.88 (m, 4 H, OCH_2CH_2O), 3.16 (s, 2 H, H-6), 3.62 (t, 2 H, ^3J = 6 Hz, H-3), 1.94 (t, 2 H, H-4); MS *m/z* 247 (M^+), 174, 91; exact mass calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1203.

1-Benzyl-5,5-(ethylenedioxy)-2-piperidinecarbonitrile (5). (a) From 1. A stirred mixture of crude **1** (11.6 g) and mercuric acetate (57 g, 0.179 mol) in 750 mL of 5% aqueous acetic acid was heated at 85 °C until complete consumption of **1** (monitored by TLC detection of **1** and of cyanide adduct **5**, prepared by addition of KCN to a sample of the reaction mixture). After about 5 h, the reaction mixture was cooled to 0 °C and KCN (38 g, 0.585 mol) dissolved in 5% aqueous acetic acid was added slowly. After 1 h, 500 mL of dichloromethane was added and the aqueous phase, still kept at 0 °C, was made alkaline with K_2CO_3. The aqueous phase was further extracted with CH_2Cl_2 (2 × 300 mL), and the combined extracts were filtered and evaporated. Column chromatography of the residue on silica gel with 1:19 EtOAc–$CHCl_3$ as the eluent, yielded compound **5** as slightly yellow crystals (11 g, 85% from 1-benzyl-3-piperidinone), mp 95 °C ($CHCl_3$): IR 2220 cm^{-1}; ^1H and ^{13}C NMR, see Table I; MS *m/z* 258 (M^+), 232, 231, 159, 158, 99 (100), 91, 86; exact mass calcd for $C_{15}H_{18}N_2O_2$ 258.1367, found 258.1367. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.02; N, 10.84. Found: C, 69.38; H, 7.00; N, 10.67.

Caution: While we have not experienced any problems handling KCN in cold dilute aqueous acetic acid in the presence of mercury salts, appropriate care should be exercised in avoiding inhalation of possibly evolved HCN vapors and in waste disposal of mercury salts and cyanide solutions.

(b) From Lactam 4. To a cooled (0 °C) suspension of $LiAlH_4$ (98 mg, 2.58 mmol) in dry ether (3 mL) was added a solution of lactam **4** (1.92 g, 7.8 mmol) in dry THF at once. After 1 h, methanol was added and the solvents were evaporated. The residue was treated with an ice-cold solution of KCN (1.56 g, 24 mmol) in water. Extraction with $CHCl_3$ and chromatographic purification yielded **5** (1.21 g, 60%).

Ethyl 1-Methyl-6-cyano-3-piperidinecarboxylate (10a and 11a). A stirred mixture of **7a** (1 g, 5.84 mmol) and mercuric acetate (7.44 g, 23.4 mmol) in 100 mL of 5% aqueous acetic acid was heated at 90 °C for 4 h. Then KCN (4.5 g, 62.2 mmol) dissolved in 5% aqueous acetic acid was added over 15 min to the cooled (0 °C) and vigorously stirred reaction mixture. The mixture was kept at 0 °C for 30 min and worked up in the usual way (as for **5**). Column chromatography of the residue on silica gel (gradient elution, 10% to 50% EtOAc–hexane) afforded the two diastereomers **10a** and **11a**. Compound **11a** was eluted first (oil, 160 mg, 14%), followed by **10a** (oil, 464 mg, 40.5%). The compounds were equilibrated in a methanol solution.

10a: IR 2220, 1735 cm^{-1}; ^1H NMR (C_6D_6) δ 3.9 (q, 2 H, ^3J = 6.5 Hz, OCH_2CH_3), 3.07 (t, 1 H, $\Sigma^3J_{6,5}$ = 7 Hz, H-6e), 2.7 (dm, 1 H, ^2J = 11 Hz, H-2e), 2.37 (t, 1 H, ^2J = 11 Hz, $^3J_{2ax,3ax}$ = 11 Hz, H-2ax), 2.26 (tt, 1 H, $^3J_{3ax,2ax}$ = 11.5 Hz, $^3J_{3ax,4ax}$ = 11.5 Hz, $^3J_{3ax,2e}$ = 4 Hz, $^3J_{3ax,4e}$ = 4 Hz, H-3ax), 1.98 (s, 3 H, NCH_3), 1.4–1.7 (m, 3 H, H-5ax + H-4e + H-5e), 1.3 (m, 1 H, H-4ax), 0.92 (tr, 3 H, ^3J = 6.5 Hz, CH_2CH_3); ^{13}C NMR δ 172.6 (COOEt), 115.9 (CN, ddd, $^2J_{CNax,H6e}$ = 6.5 Hz, $^3J_{CNax,H5ax}$ = 10.5 Hz, $^3J_{CNax,H5e}$ = 2 Hz), 60.6 (OCH_2CH_3), 53.9 (C-6), 52.0 (C-2), 44.1 (NCH_3), 41.2 (C-3), 27.8 (C-5), 22.6 (C-4), 14.2 (CH_3CH_2O); MS *m/z* 196 (M^+), 195, 181, 169, 167, 151, 142, 123, 96, 70; exact mass calcd for $C_{10}H_{16}N_2O_2$ 196.1212, found 196.1217.

11a: MS and IR, the same data as for **10a**; ^1H NMR (C_6D_6) δ 3.9 (q, 2 H, ^3J = 6.5 Hz, OCH_2CH_3), 2.92 (t, 1 H, $\Sigma^3J_{6,5}$ = 7 Hz, H-6e), 2.7 (dd, 1 H, ^2J = 12 Hz, $^3J_{2e,3e}$ = 4 Hz, H-2e), 2.14 (t, 1 H, $^3J_{3e,2ax}$ = 3.7 Hz, $^3J_{3e,4ax}$ = 3.7 Hz, H-3e), 2.40 (dd, 1 H, ^2J = 12 Hz, $^3J_{2ax,3e}$ = 3.7 Hz, H-2ax), 2.00 (s, 3 H, NCH_3), 1.8 (m, 2 H, H-5e + H-4e), 1.4 (m, 2 H, H-4ax + H-5ax), 0.94 (t, 3 H, ^3J = 6.5 Hz, CH_2CH_3); ^{13}C NMR δ 172.9 (COOEt), 116.5 (CN), 60.6 (OCH_2), 54.5 (C-6), 52.3 (C-2), 44.4 (NCH_3), 39.2 (C-3), 26.2 (C-5), 21.3 (C-4), 14.2 (CH_2CH_3); exact mass calcd for $C_{10}H_{16}N_2O_2$ 196.1212, found 196.1210.

1-Methyl-5-[(benzoyloxy)methyl]-2-piperidinecarbonitrile (10c and 11c). (a) To a stirred solution of **8** (2 g, 15.5 mmol) in 10 mL of pyridine was added benzoyl chloride (5 mL, 43.1 mmol) dropwise. After 15 min the solidifed mixture was treated with aqueous K_2CO_3 at 0 °C, and the mixture was stirred for 1 h. The solution then was extracted with CH_2Cl_2 (300 mL), and the organic phase washed with water (2 × 50 mL). Evaporation of dichloromethane and chromatography of the residue on silica gel (gradient elution 1% to 6% of MeOH–$CHCl_3$) afforded **9** as an oil (3.54 g, 98%). This was subjected to mercuric acetate oxidation in the usual manner (see preparation of **5**) using Hg-

$(OAc)_2$ (19 g, 59.6 mmol) and KCN (12.84 g, 0.20 mol). Chromatography over silica gel (gradient elution 5% to 20% EtOAc–hexane) yielded 219 mg (5.5%) of **11c** and 2.1 g (52.6%) of **10c**, both as crystalline products, mp 70 °C (ether) and 101 °C (ether).

9: ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.1 (dd, 2 H, $^3J_{Ho,Hm}$ = 7 Hz, $^4J_{Ho,Hp}$ = 2 Hz, H-ortho:*Ph*CO), 7.47 (m, 3 H, Ar), 4.18 (d, 2 H, ^3J = 7 Hz, CH_2O), 2.75 (t, br, 2 H, ^2J = ^3J = 13.5 Hz, H-2) 2.2 (s, 3 H, NCH_3), 1.5–2 (m, 6 H, H-4,5,6).

10c: IR 2220, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–8.05 (5 H, Ar), 4.2 (2 × q, 2 H, ^3J = 6.5 Hz, ^3J = 5 Hz, $COOCH_2$), 3.85 (t, $\sum^3J_{2e,3}$ = 7 Hz, H-2e), 2.9 (dd, 1 H, ^2J = 11 Hz, $^3J_{6e,5ax}$ = 4 Hz, H-6e), 2.22 (t, 1 H, ^2J = 11 Hz, $^3J_{6ax,5ax}$ = 11 Hz, H-6ax), 1.9 (m, 4 H, H-6ax, H-4e, H-3), 1.41 (qd, 1 H, ^2J = 12.5 Hz, $^3J_{4ax,5ax}$ = 12 Hz, $^3J_{4ax,3ax}$ = 12 Hz, $^3J_{4ax,3e}$ = 4 Hz, H-4ax); MS *m/z* 258 (M^+), 231, 153, 136, 126, 109, 108, 105, 96 (100), 83; exact mass calcd. for $C_{15}H_{18}N_2O_2$ 258.1368, found 258.1367. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.02; N, 10.84. Found: C, 69.58; H, 7.06; N, 10.82.

11c: IR, MS, same data as for **10c**; ^{1}H NMR ($CDCl_3$) δ 7.45–8.05 (5 H, Ar), 4.4 (d, 2 H, ^2J = 7 Hz, $COOCH_2$), 3.55 (t, 1 H, $^3J_{2e,3ax}$ = 4 Hz, $^3J_{2e,3e}$ = 4 Hz, H-2e), 2.73 (dd, 1 H, ^2J = 12 Hz, $^3J_{6ax,5e}$ = 3.5 Hz, H-6ax), 2.47 (dd, 1 H, ^2J = 12 Hz, $^3J_{6e,5e}$ = 4 Hz, H-6e), 2.4 (s, 3 H, NCH_3), 2.2 (m, 1 H, H-5e), 2.1 (m, 1 H, H-3e), 1.85 (m, 2 H, H-4e, H-3ax), 1.6 (m, 1 H, H-4ax); exact mass calcd for $C_{15}H_{18}N_2O_2$ 258.1368, found 258.1367.

(**b**) Mercuric acetate oxidation was performed directly on alcohol **8** (2 g, 15.5 mmol) in the usual way (see preparation of **5**). After reaction with KCN and extraction with CH_2Cl_2 (3 × 200 mL), the reaction mixture consisting of the polar **10b**, **11b** (M^+ 154) was benzoylated as described under (a) to give compounds **11c** (0.25g, 6%) and **10c** (1.45 g, 36%).

Ethyl 1-Benzyl-6-cyano-3-piperidinecarboxylate (10d and 11d). A mixture of **7b**[11] (2.00 g, 8.1 mmol) and mercuric acetate (12.89 g, 40.4 mmol) in 200 mL of 2.5% aqueous acetic acid was stirred at 90 °C for 5 h. The mixture then was cooled in an ice bath and KCN (6.85 g, 105.2 mmol), dissolved in aqueous acetic acid (pH 5), was added under vigorous stirring. The reaction mixture was kept for 1 h at 0 °C and worked up as described for **5**. After purification by column chromatography (silica gel, 15:85 EtOAc–hexane) the mixture of epimers **10d** and **11d** was obtained as a yellow oil (55/45 ratio, total yield 67%). In another experiment subfractions containing the pure epimers **11d** and **10d** were collected separately in this order.

10d: IR 2220, 1735 cm^{-1}; ^{1}H NMR (C_6D_6) δ 7.30–7.05 (m, 5 H, C_6H_5), 3.93 (q, 2 H, ^3J = 7 Hz, OCH_2CH_3), 3.46 and 3.38 (AB q, 2 H, ^2J = 13 Hz, NCH_2Ph), 3.24 (m, 1 H, $\sum^3J$ = 7 Hz, H-6e), 2.99 (ddm, 1 H, $^2J_{2e,2ax}$ = 12 Hz, $^3J_{2e,3ax}$ = 4 Hz, H-2e), 2.65 (t, 1 H, $^2J_{2ax,2e}$ = 12 Hz, $^3J_{2ax,3ax}$ = 12 Hz, H-2ax), 2.35 (m, 1 H, $^3J_{3ax,2ax}$ = 12 Hz, $^3J_{3ax,4ax}$ = 11 Hz, $^3J_{3ax,2e}$ = 4 Hz, $^3J_{3ax,4e}$ = 5 Hz, H-3ax), 1.62–1.21 (m, 2 H) and 1.12–1.39 (m, 2 H) (H-4, H-5), 0.96 (t, 3 H, ^3J = 7 Hz, OCH_2CH_3; ^{13}C NMR δ 172.4 (*C*OOEt), 136.4 (C-ipso), 128.7 (C-meta), 128.5 (C-ortho), 127.5 (C-para), 115.8 (CN), 60.3 (OCH_2), 50.9 (C-6), 50.7 (C-2), 41.3 (C-3), 27.6 (C-5), 23.2 (C-4), 14.0 (CH_3); MS *m/z* 272 (M^+), 227, 218, 199, 181, 135, 106, 91 (100); exact mass calcd for $C_{16}H_{10}N_2O_2$ 272.1525, found 272.1524.

11d: MS and IR, the same data as for **10d**; ^{1}H NMR (C_6D_6) δ 7.30–7.05 (m, 5 H, C_6H_5), 3.93 (q, 2 H, ^3J = 7 Hz, OCH_2CH_3), 3.46 and 3.38 (AB q, 2 H, ^2J = 13 Hz, NCH_2Ph), 3.23 (m, 1 H, $\sum^3J$ = 7 Hz, H-6e), 3.04 (dm, 1 H, $^2J_{2e,2ax}$ = 12 Hz, H-2e), 2.49 (dd, 1 H, $^2J_{2ax,2e}$ = 12 Hz, $^3J_{2ax,3e}$ = 3.5 Hz, H-2ax), 2.14 (m, 1 H, $\sum J$ = 13 Hz, H-3e), 2.20–1.87 (m, 2 H), 1.47 (m, 1 H, $\sum J$ = 39 Hz) and 1.31 (m, 1 H, $\sum J$ = 24 Hz) (H-4, H-5), 0.96 (t, 3 H, ^3J = 7 Hz, OCH_2CH_3); ^{13}C NMR δ 172.7 (*C*OOEt), 136.6 (C-ipso), 128.7 (C-meta), 128.3 (C-ortho), 127.4 (C-para), 116.3 (CN), 60.3 (OCH_2), 52.1 (C-6), 50.0 (C-2), 39.0 (C-3), 25.6 (C-5), 21.2 (C-4), 14.0 (CH_3).

1-Benzyl-5,5-(ethylenedioxy)-2-(2-phenylethyl)-2-piperidinecarbonitrile (13). To a solution of LDA, prepared from *n*-BuLi (1.21 mL of a 1.6 M solution in hexane; 2 mmol) and diisopropylamine (0.28 mL, 2 mmol) in 10 mL of anhydrous THF at 0 °C, was added dry HMPA (0.34 mL, 2 mmol). The mixture was cooled to −78 °C; then a solution of amino nitrile **5** (258 mg, 1 mmol) in 4 mL of anhydrous THF was added. After 5 min, (2-bromoethyl)benzene (0.56 mL, 4.7 mmol) was added and the reaction mixture was stirred for 1.5 h at −78 °C. The mixture then was allowed to come to room temperature and worked up by addition of 10 mL of aqueous NH_4Cl followed by extraction with $CHCl_3$ and filtration. The filtrate was evaporated, and the residue was chromatographed over silica (gradient elution, 1% to 8% EtOAc–$CHCl_3$) to give **13** (0.31 g, 86%) as a solid, mp 108–109 °C (ethyl acetate–ether); IR 2210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 10 H, Ar), 4.23 and 3.20 (AB q, 2 H, ^2J = 14 Hz, NCH_2Ph), 3.85 (m, 4 H, OCH_2CH_2O), 2.85 (m, 2 H, CH_2CH_2Ph), 2.68 (dd, 1 H, ^2J = 12 Hz, H-6e), 2.32 (d, 1 H, ^2J = 12 Hz, H-6a), 1.80-2.29 (m, 6 H, H-3, H-4, CH_2CH_2Ph); MS *m/z* 362 (M^+), 335, 334, 320, 306, 262, 258, 257, 249, 248, 244, 230, 167, 158, 99, 91 (100), 86; exact mass calcd for $C_{23}H_{26}N_2O_2$ 362.1994, found 262.1996. Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.82; H, 7.17; N, 7.52.

1-Benzyl-5,5-(ethylenedioxy)-2-(ethoxycarbonyl)-2-piperidinecarbonitrile (14). Ethyl chloroformate (0.45 mL, 4.7 mmol) was added to the carbanion of amino nitrile **5** (258 mg, 1 mmol), prepared as described for **13**. After the usual workup, chromatography of the resulting product over silica gel (using gradient elution, 1% to 5% EtOAc–$CHCl_3$) yielded **14** (0.28 g, 85%) as a solid, mp 87–89 °C (ethyl acetate–ether): IR 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5 H, Ar), 4.33 (m, 2 H, CH_2CH_3), 3.84 (m, 4 H, OCH_2CH_2O), 3.83 and 3.34 (AB q, 2 H, ^2J = 12.5 Hz, NCH_2Ph), 2.68 (dd, 1 H, ^2J = 12 Hz, $^4J_{6e,4e}$ = 2 Hz, H-6e), 2.42 (td, 1 H, ^2J = 13 Hz, $^3J_{3a,4a}$ = 13 Hz, $^3J_{3a,4e}$ = 5 Hz, H-3ax), 2.30 (d, 1 H, ^2J = 12 Hz, H-6ax), 2.21 (dt, 1 H, ^2J = 13 Hz, $^3J_{3e,4a}$ = 4 Hz, $^3J_{3e,4e}$ = 3 Hz, H-3e), 1.98 (m, 1 H, H-4ax), 1.88 (m, 1 H, H-4e), 1.34 (t, 3 H, CH_3CH_2); MS *m/z* 330 (M^+), 304, 303, 257, 212, 99, 91 (100), 86; exact mass calcd for $C_{18}H_{22}N_2O_4$ 330.1579, found 330.1585. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.19; H, 6.63; N, 8.40.

1-Benzyl-5,5-(ethylenedioxy)-2-(2-phenylethyl)piperidine (16). To a stirred solution of **13** (0.18 g, 0.5 mmol) in 40 mL of ethanol and 20 mL of water was added $NaBH_4$ (1 g, 26.3 mmol). After being stirred for 10 h at room temperature, the reaction mixture was extracted with dichloromethane. The organic phase was washed with water and evaporated. The residue was purified by preparative TLC on silica gel with 1:9 ethyl acetate–chloroform as the solvent to give **16** (0.15 g, 89%) as an oil: IR 3050, 2400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 10 H, Ar), 3.99 and 3.55 (AB q, 2 H, ^2J = 13 Hz, NCH_2Ph), 3.86 (m, 4 H, OCH_2CH_2O), 2.68 (m, 3 H, CH_2CH_2Ph, H-6), 2.50 (m, 1 H, $\sum^3J$ = 22 Hz, H-2), 2.23 (d, 1 H, ^2J = 12 Hz, H-6), 1.50–2.15 (m, 6 H, CH_2CH_2Ph, H-3, H-4); MS *m/z* 337 (M^+), 238, 233, 232 (100), 160, 99, 91, 81; exact mass calcd for $C_{22}H_{27}NO_2$ 337.2042, found 337.2031.

1-Benzyl-5,5-(ethylenedioxy)-2-piperdinemethanol (17). To a solution of **14** (100 mg, 0.3 mmol) in 20 mL of ethanol and 5 mL of water was added $NaBH_4$ (0.7 g, 18.4 mmol). After being stirred for 4 h at room temperature, the reaction mixture was extracted with dichloromethane. The organic phase was filtered and the filtrate was evaporated. Preparative TLC on silica gel using ethyl acetate as the solvent gave **17** (70 mg, 89%) as an oil.

TLC (1:19 EtOAc–$CHCl_3$) and MS analysis of the reaction mixture after 5 min revealed a mixture of **14** (R_f = 0.5), **17** (R_f = 0.2), and an intermediate (**15**) (R_f = 0.3).

17: IR 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O)) δ 7.28 (m, 5 H, Ar), 4.04 and 3.65 (AB q, 2 H, ^2J = 14 Hz, NCH_2Ph), 3.78–3.96 (m, 4 H, OCH_2CH_2O), 3.68 (AB of ABX, m, 2 H, CH_2OD), 2.74 (dd, 1 H, ^2J = 12.5 Hz, ^4J = 1 Hz, H-6), 2.61 (m, 1 H, H-2), 2.31 (dd, 1 H, ^2J = 12.5 Hz, ^4J = 1.2 Hz, H-6), 1.55–2.0 (m, 4 H, H-3, H-4); MS *m/z* 263 (M^+), 245, 232, 188, 172, 164, 99, 91 (100), 86; exact mass calcd for $C_{15}H_{21}NO_3$ 263.1521, found 263.1525.

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Supplementary Material Available: ^{13}C and ^{1}H NMR spectra for compounds **2**, **4**, **10a**, **11a**, **10d**, and **11d** and ^{1}H NMR spectra for compounds **1**, **10c**, **11c**, **16**, and **17** (29 pages). Ordering information is given on any current masthead page.