were 50- or 100-mL volumetric flasks fitted with threaded necks that were closed with Mininert values (Precision Sample Co).

Blank solutions (no initiator) were heated (additional aliquots stored cold) to demonstrate that no PC or PIP was lost by volatilization. Oxidation experiments were prepared by diluting solutions of ACP or ABN in PC or PIP stock solutions to give the desired concentrations of reactants and heated at 50 ± 0.01 °C. Reaction blanks and oxidized solution were stored at 4 °C in a refrigerator until analyses could be made.

Analytical Methods. We analyzed reaction solutions of PC or PIP by using reverse-phase HPLC with gradient elution. Two Waters Associates M6000A pumps controlled by an M660 solvent programmer were used to pump the solvent through a 4 mm × 30 cm μBondapak C18 column at 2 mL/min. Solvents were high-purity water and Burdick and Jackson "Distilled in Glass" UV-grade acetonitrile (AN) for *p*-cresol. The solvent gradients were 20–35% AN/H_2O for 15 min with linear programming. Analyses were run at 2 mL/min total flow. Detection by UV photometer at 254 nm was with a Shoeffel Instruments SF770 flow monitor or Waters Associates M440 detector. Analyses for ABN or ACP were done at 330 nm.

Field ionization mass spectra were prepared from 10–30 μL of CH_2Cl_2 solutions of compounds injected into the cooled inlet part of the SRI-designed spectrometer. The molecular-weight profile for reaction mixtures was scanned from 90–490 amu. The temperature was raised ~ 2°/min from –30 to 300 °C at 8 kV. Data from repeated scans of 400 amu each were fed into a 4000-channel analyzer, stored, and collectively printed as a single spectrum. Molecular ions (P) or P + 1 peaks were used to detect the presence of ACP coupling products, PC dimers, PC peroxycyclohexadienone and *p*-hydroxybenzoic acid.

An LKB Model 9000 GC/MS with a PDP-11 computer was used to identify the phenol PIP dimer and peroxycyclohexadienone.

^{1}H NMR spectra were measured on a Varian 100-mHz NMR spectrometer.

Acknowledgment. We thank Drs. David Thomas and Sidney "Bud" Buttrill at SRI for preparation of mass spectral data. This work was supported by NSF Grant No. ENV76-11153. Maria Buyco prepared the several drafts of the manuscript.

Registry No. 1, 85553-41-9; 4, 85553-42-0; PIP, 99-89-8; PC, 106-44-5; ACP, 2589-57-3; ABN, 78-67-1; Cu^{2+} ion, 15158-11-9; Fe^{2+} ion, 15438-31-0.

Supplementary Material Available: table of NMR Analysis of ACP decomposition products (1 page). Ordering information is given on any current masthead page.

Stereochemistry of Cyanide Ion Addition to 3,4,5,6-Tetrahydropyridinium Derivatives

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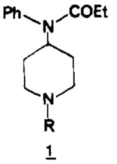
The stereochemistry of cyanide ion addition to 1-alkyl-4-(*N*-phenylpropanamido)-3,4,5,6-tetrahydropyridinium salts 2 was investigated by analysis of the ^{1}H NMR spectra of the isolated α-amino nitriles. The data obtained, together with epimerization studies, indicated that the addition occurred in a stereospecific manner to afford the trans diastereoisomers.

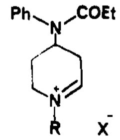
We have previously reported[1] on a convenient synthetic method for the α-cyanation of tertiary amines. The procedure consisted of reacting the corresponding amine oxide with trifluoroacetic anhydride followed by the addition of cyanide ion to the iminium intermediate that had been generated in the reaction. This procedure was successfully applied to a number of piperidine-containing opioids. We now report on the stereochemical consequences of this reaction when conducted on 1,4-disubstituted piperidine derivatives 1.



1

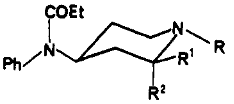
a, R = Me
b, R = CH_2Ph
c, R = CH_2CH_2Ph

Results and Discussion



2

Since the cyanation procedure using 1 involved the formation of the iminium intermediate 2, cis and trans diastereomeric products (3–5) can be envisaged as arising from the addition of cyanide ion to either side of 2.



a, R^1 = H , R^2 = CN
b, R^1 = CN , R^2 = H

3 R = Me
4 R = CH_2Ph
5 R = CH_2CH_2Ph

Moreover, molecular models revealed that both faces of the iminium double bond in 2 are equally accessible to nucleophilic attack when the bulky 4-(*N*-phenylpropanamido) group[2] is in the thermodynamically preferred equatorial conformation.

It was therefore unexpected to find that only one diastereomer 3a (38%) had formed in this reaction in view

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[1] Groutas, W. C.; Essawi, M.; Portoghese, P. S. *Synth. Commun.* **1980**, *10*, 495.

[2] Maryanoff, B. E.; McComsey, D. E.; Taylor, R. J., Jr.; Gardoki, J. *J. Med. Chem.* **1981**, *24*, 79 and references therein.

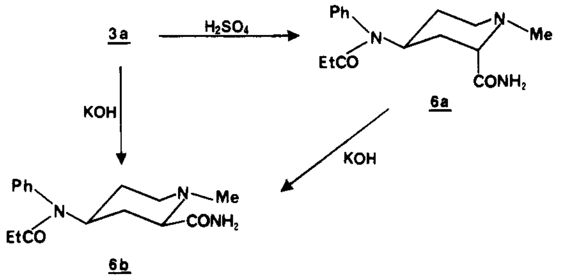
0022-3263/83/1948-2138$01.50/0

of the small conformational preference of the CN group.[3] This was verified by chromatographic analysis of the crystalline product *3a* and the reaction mixture. A second product (48%) was identified as *N*-phenylpropanamide.[4]

The NMR spectrum of **3a** showed the C-4 proton resonance at δ 4.9 (J_{ax-ax} = 12.45 and J_{ax-eq} = 3.84 Hz). This clearly reflected the equatorial orientation of the *N*-phenylpropanamido group. The signal for the C-2 proton appeared as a multiplet at δ 3.85 (W_H = 8.5 Hz). This suggested an equatorial disposition of this proton and therefore an axial orientation of the cyano group. The other N-substituted analogues (**1b**, **1c**) afforded cyano compounds (**4a**, **5a**) with similar spectral properties as the only isolable diastereomers.

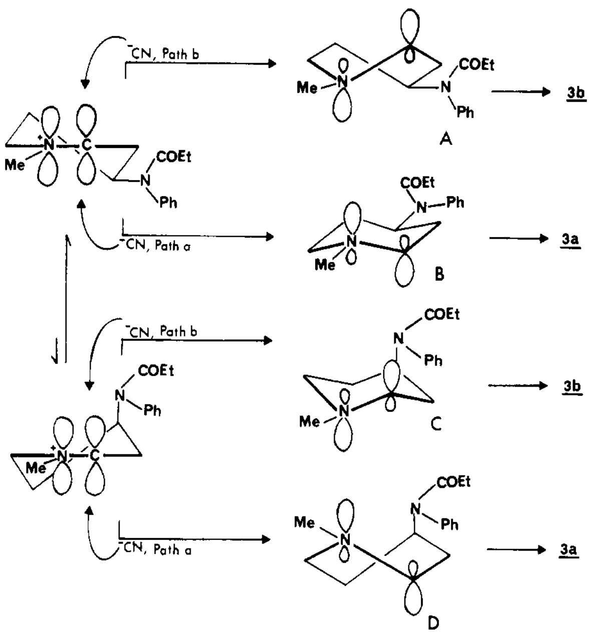
Efforts to epimerize the trans isomer **3a** to its presumably more stable cis isomer **3b** were unsuccessful because of the facile elimination of the cyano group with the subsequent formation of *N*-phenylpropanamide when NaH in refluxing THF was employed. Further, attempts to effect base-promoted deuterium exchange at the C-2 center (in C_2D_5OD) gave inconclusive results because the exchange rate appeared to be slow[5] relative to the elimination process.

Chemical evidence for the trans stereochemistry of **3a** was obtained from its hydrolysis under acidic and basic conditions. Treatment with concentrated H_2SO_4 afforded the trans amide **6a** (80%), which, when treated with KOH in ethylene glycol, was converted quantitatively into the more stable cis isomer **6b**.[6] When hydrolysis of the nitrile **3a** was conducted with KOH in *t*-BuOH,[7] the cis isomer **6b** was obtained together with a trace amount of its diastereomer **6a** and some *N*-phenylpropanamide.



The NMR spectra of the diastereomeric amides (**6a**, **6b**) also were consistent with the proposed stereochemistry. The C-4 proton resonance of the trans isomer **6a** appeared at δ 4.63 (J_{ax-ax} = 11.25 and J_{ax-eq} = 4.48 Hz). The multiplet at δ 3.29 (W_H = 12 Hz) corresponds to the C-2 equatorial proton. The cis isomer **6b** possessed chemical shifts and coupling constants at δ 4.71 (J_{ax-ax} = 12.3, J_{ax-eq} = 3.5 Hz) and δ 2.97 (J_{ax-ax} = 11.6, J_{ax-eq} = 3.0 Hz) for the C-4 and C-2 protons, respectively. The fact that the C-4 diaxial proton coupling in **6b** is somewhat larger than that in **6a**, while the reverse is true for J_{ax-eq} at this center, is consistent with a greater population of the flip conformer of **6a** due to the counterbalancing effect of the axial 2-aminocarbonyl group. The 2,4-diequatorial orientation of substituents in **6b** renders it essentially conformationally homogeneous.

Scheme I



In view of the inability to obtain both isomers of **3**, and thereby to ascertain the stability of **3b** to the reaction conditions, it is not clear whether the isolation of **3a** is the result of preferential addition kinetic control of cyanide ion to **2** to form **3a** or the result of preferential destruction of **3b**. We favor the former explanation (Scheme I). Thus, addition of cyanide ion by paths a or b to either side of **2**, when the *N*-phenylpropanamido group is in the equatorial or axial conformations, gives four possible transition states (A–D)[8] that maintain maximum orbital overlap with respect to the approaching cyanide ion and the developing lone pair on nitrogen. Two of these transition states (B–C) are chair-like, with the latter being less favorable due to diaxial interaction between the *N*-phenylpropamido group and incoming cyanide ion. On the other hand, B can accomodate the incoming cyanide ion without steric interference of the 4-substituent, thereby leading to the trans product (e.g., **3a**). Precedent for kinetic control in the addition of nucleophiles to iminium compounds has been reported.[8] The present study confirms and extends the generality of the stereochemistry of this reaction to cyanide addition.

Experimental Section

Proton NMR spectra were obtained by using a 300 NIC spectrometer on solutions of ca. 10% containing 1% tetramethylsilane as an internal standard. Mass spectra were recorded on AEI MS-30 or Finnigan spectrometers. IR spectra were obtained on Perkin-Elmer 281 spectrometer. Melting points (uncorrected) were determined with a Thomas-Hoover apparatus. Elemental analyses were performed by M-H-W Lab., Phoenix, AZ. GLC analyses were conducted on a Varian 2100 Aerograph. TLC analyses were carried out on precoated silica gel (GF) plates (0.25 mm) obtained from Analtech Inc., Newark, DE. Silica gel (60–200 mesh) from Baker Chemical Co., Phillipsburg, NJ, was

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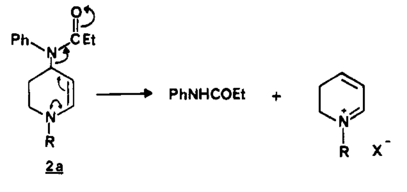
(3) Hirsh, J. A. *Top. Stereochem.* **1967**, *1*, 199.

(4) This byproduct presumably arises from the base-promoted generation of enamine 2a (from 2 or from 3a or 3b), which undergoes elimination of the 4-(*N*-phenylpropanamido) group.



(5) Similarly, it has been reported that base-promoted D exchange of *cis*- or *trans*-4-*tert*-butylcyclohexylcarbonitrile is slow. Rickborn, B.; Jensen, F. R. *J. Org. Chem.* **1962**, *27*, 4606.

(6) The *A* value for COOH group (1.35 kcal/mol, see ref 3) may be taken as a reasonable approximation for the *A* value of CONH$_2$, which, to our knowledge, has not been reported.

(7) Hall, J. H.; Gisler, M. *J. Org. Chem.* **1976**, *41*, 3769.

(8) Stevens, R. F.; Lee, A. W. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

used for column chromatography. Evaporation was performed under reduced pressure on a rotary evaporator.

***trans*-(±)-*N*-(2-Cyano-1-methyl-4-piperidyl)-*N*-phenylpropanamide (3a).** This compound was prepared by modification of the published procedure.[1] To a stirred suspension of the *N*-oxide of **1a**[1] (24.5 g, 0.0935 mol) in dry MeCN (150 mL) at −30 °C under nitrogen, MsCl (7.23 mL, 0.0935 mol) was added dropwise over a period of 1 h. After the addition, the mixture was stirred for 1 h at −30 °C, and then the temperature was allowed to rise to −10 °C over an additional 0.5 h. The mixture was cooled to −30 °C, Me_3SiCN (25 g, 0.252 mol) was added gradually, and stirring was continued for 1 h during which the temperature was allowed to rise to 0 °C. The mixture was allowed to stand overnight at −15 °C. Potassium cyanide (5 g, 0.077 mmol) was added, and the mixture was stirred for 3 h at 10 °C. The mixture was evaporated and the residue was ice cooled, mixed with 5% HCl (100 mL), and extracted with ether (2 × 100 mL). Evaporation of the ether gave 6.45 g (46%) of *N*-phenylpropanamide [mp 105 °C (lit.[9] mp 105–106 °C)]. The aqueous layer was cooled, basified (pH 9.5) with Na_2CO_3, and extracted with EtOAc (2 × 150 mL). The extract was washed with saturated NaCl solution and dried (Na_2SO_4), and EtOAc was evaporated. The oily residue containing only one diastereoisomer (**3a**) and low-R_f products was chromatographed on a column of silica gel (*n*-hexane/EtOAc/NH_4OH, 3:7:0.1), and the crude product was recrystallized from ether to give 9.6 g (38%) of **3a** as prisms: mp 125 °C; t_R 2.0 min (glass column, 6 ft × 2 mm; packing, 3% OV-17 on 100/120 Chromosorb W-HP; column temperature 170 °C; detector temperature 200 °C; flow rate, 15 mL/min of nitrogen); R_f 0.32 (*n*-hexane/EtOAc/NH_4OH, 3:7:0.1); IR (KBr) 2205 (CN), 1660 (C═O, anilide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.9 (tt, *J* = 12.45 and 3.84 Hz, H-4), 3.85 (t, *J* = 4.3 and 3.3 Hz, H-2); mass spectrum, *m/e* 271 (M$^+$). Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.81; H, 7.79; N, 15.48. Found: C, 70.79; H, 7.88; N, 15.45.

***trans*-(±)-1-Methyl-4-(*N*-phenylpropanamido)piperidine-2-carboxamide (6a).** Compound **3a** (3.5 g, 12.91 mmol) was added in small portions to concentrated sulfuric acid (15 mL) while the temperature was kept below 5 °C. After the addition, the mixture was stirred for 2 h at 0–5 °C and 48 h at 25 °C. The mixture was ice cooled and added in small portions to about 30 g of crushed ice. The solution was basified (pH 12) by the dropwise addition of 10% NaOH and then extracted with EtOAc (3 × 75 mL). The extract was dried (Na_2SO_4), EtOAc was evaporated, and the resulting residue was crystallized from acetone/*n*-hexane to afford 2.91 g (79%) of **6a**: mp 145–147 °C; R_f 0.31 (*n*-hexane/EtOAc/MeOH/NH_4OH, 3:10:2:0.15); IR (KBr) 3372 (NH_2), 3320 (NH_2), 1690–1630 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.63 (tt, *J* = 11.25 and 4.48 Hz, H-4), 3.29 (m, W_H = 12 Hz, H-2); mass spectrum, *m/e* 290 (M$^+$ + 1). Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.69, H, 8.13, N, 14.74.

***cis*-(±)-1-Methyl-4-(*N*-phenylpropanamido)piperidine-2-carboxamide (6b).** To a stirred solution of **3a** (2.75 g, 0.01 mol) in *t*-BuOH (45 mL) under nitrogen was added finely powdered KOH (3.24 g, 0.057 mol). The mixture was stirred at 25 °C for 2 h and heated at 65–70 °C for 3 h. The solvent was removed in vacuo, and the residue was mixed with saturated NaCl solution (50 mL) and extracted with EtOAc (3 × 75 mL). The extract was dried (Na_2SO_4) and EtOAc was evaporated. The residue was washed with cold ether (2 × 30 mL) and then with cold acetone (2 × 20 mL) and dried to give 1.7 g (58%) of **6b**: mp 197–199 °C; R_f 0.36 (*n*-hexane/EtOAc/MeOH/NH_4OH, 3:10:2:0.15); IR (KBr) 3400 (NH_2), 3300 (NH_2), 1675 (C═O, anilide), 1640 (amide I band), 1623 (amide II band) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.71 (tt, *J* = 12.3 and 3.5 Hz, H-4), 2.97 (m, *J* = 11.6 and 3.0 Hz, H-2); mass spectrum, *m/e* 290 (M$^+$ + 1). Anal. calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.47; H, 8.10; N, 14.69.

Epimerization of 6a. To a solution of KOH (100 mg, 1.78 mmol) in ethylene glycol (5 mL) was added **6a** (35 mg, 0.12 mmol), and the mixture was stirred and heated at 65–70 °C for 7 h. The solvent was evaporated in vacuo, and the residue was mixed with H_2O (10 mL) and extracted with EtOAc (2 × 10 mL). The extract was dried (Na_2SO_4), EtOAc was evaporated, and the solid residue was washed with cold ether (2 × 5 mL) and dried to give 28 mg (80%) of a solid, mp 183–185 °C, whose IR and NMR spectra were identical with that of the cis isomer **6b**. TLC (*n*-hexane/EtOAc/MeOH/NH_4OH, 3:10:2:0.15) showed the presence of a trace amount of unconverted starting material **6a**.

***trans*-(±)-*N*-(1-Benzyl-2-cyano-4-piperidyl)-*N*-phenylpropanamide (4a).** To a cooled (−30 °C) solution of **1b**[10] (12 g, 0.037 mol) was added dropwise with stirring an ice-cold suspension of *m*-chloroperoxybenzoic acid (85%) (7.56 g, 0.037 mol) in CH_2Cl_2 (60 mL). After complete addition, the mixture was stirred at −30 °C for 1 h. Stirring was continued for an additional 1 h during which the temperature was allowed to rise to −5 °C. The mixture was cooled to −30 °C, trifluoracetic anhydride (6 mL, 0.0396 mol) was added dropwise over a period of 20 min, and after an additional 45 min at −30 °C, the mixture was evaporated at 25 °C. To the oily residue was added at −10 °C a solution of KCN (5 g, 0.077 mol) in H_2O (20 mL), and the mixture was stirred for 20 min. The mixture was extracted with EtOAc (75 mL), and the extract was washed with saturated NaCl solution and dried (Na_2SO_4), and EtOAc was evaporated. The oily residue was dissolved with ether (100 mL), ice cooled, and acidified with ethereal HCl. The precipitated salt was washed with ether and dried to give 7.45 (52%) of crude **4a**·HCl: mp 175–178 °C; R_f 0.4 (*n*-hexane/EtOAc/NH_4OH, 10:5:0.15); mass spectrum, *m/e* 347 (M$^+$), 256 (M$^+$ − CH_2Ph). The base **4a** was obtained from **4a**·HCl (using Na_2CO_3) as an oil (NMR pure): IR (neat) 2200 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.93 (tt, *J* = 12.45 and 3.85 Hz, H-4), 3.85 (t, *J* = 4.0 and 3.0 Hz), 3.65 (s, 2 H, benzylic protons). This nitrile **4a** was converted to the cis carboxamide as described for **6b**, except that heating was continued for 7 h: yield 48% (the remaining material consisted of *N*-phenylpropanamide and a trace amount of the trans isomer); mp 214–215 °C (2-propanol/*n*-hexane); R_f 0.61 (*n*-hexane/EtOAc/MeOH/NH_4OH, 3:10:2:0.15); IR (KBr) 1695, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.72 (tt, *J* = 12.2 and 3.7 Hz, H-4), 3.5 (AB q, *J* = 13.68 Hz, benzylic protons), 2.99 (q, J_{AX} + J_{BX} = 14.36 Hz, H-2); mass spectrum, *m/e* 366 (M$^+$ + 1). Anal. calcd for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.44; N, 11.49. Found: C, 72.30; H, 7.43; N, 11.37.

***trans*-(±)-*N*-[2-Cyano-1-(2-phenethyl)-4-piperidyl]-*N*-phenylpropanamide (5a).** This compound was prepared in 20% yield according to the published procedures:[1] mp 167–168 °C (2-propanol/*n*-hexane); R_f 0.55 (*n*-hexane/EtOAc/MeOH/NH_4OH, 3:7:1:0.1); IR (KBr) 2218 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.9 (tt, *J* = 12.45 and 3.85, H-4), 3.85 (t, W_H = 8.01 Hz, H-2); mass spectrum, *m/e* 361 (M$^+$). Anal. calcd for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.52; N, 11.62. Found: C, 76.19; H, 7.40; N, 11.47. The remaining material from this reaction consisted of *N*-phenylpropanamide ~50%, as estimated from the NMR spectrum of the reaction mixture) and low-R_f decomposition products.

Acknowledgment. We thank Dr. B. E. Maryanoff, McNeil Labs, Springhouse, PA, for the supply of **1c**. This research was supported in part by NIDA Research Grant No. DA02220.

Registry No. **1a** oxide, 85893-35-2; **1b**, 1474-02-8; **1b** oxide, 85893-36-3; **1c**, 437-38-7; **1c** oxide, 85893-37-4; (±)-**2a**, 85893-38-5; (±)-**2b**, 85893-39-6; (±)-**2c**, 85893-40-9; (±)-**3a**, 85893-41-0; (±)-**4a**, 85893-45-4; (±)-**4a**·HCl, 85893-42-1; (±)-**4b** (carboxamide), 85893-46-5; (±)-**5a**, 85893-43-2; (±)-**6a**, 85893-44-3; (±)-**6b**, 85908-76-5; MsCl, 124-63-0; Me_oSiCN, 7677-24-9; potassium cyanide, 151-50-8.

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(9) "Handbook of Chemistry and Physics", 56th ed.; Weast, R. C., Ed.; CRC Press: Cleveland, OH, 1975; p C446.

(10) Janssen, P. A. J. U.S. Patent 3 141 823, 1964.