

Synthesis of 4,4-Disubstituted Piperidine Analogs of (\pm)-*cis*-*N*-[1-(2-Hydroxy-2-phenylethyl)-3- methyl-4-piperidyl]-*N*-phenylpropanamide

G. A. Brine*, P. A. Stark and F. I. Carroll*

Chemistry and Life Sciences Unit, Research Triangle Institute,
Research Triangle Park, North Carolina 27709-2194

P. Singh

Department of Chemistry, North Carolina State University,
Raleigh, North Carolina 27695-8204

Received October 5, 1993

Condensation of (\pm)-1-benzyl-3-methyl-4-piperidone (**1**) with aniline followed by trapping of the intermediate imine with cyanide generated a mixture of isomeric nitriles **2A** and **2B**, the structures of which were established unambiguously by obtaining an X-ray crystal structure on nitrile **2B**. Subsequent elaboration of the nitrile intermediates provided analogs of (\pm)-*cis*-*N*-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide having a second substituent (carbomethoxy, carboethoxyl, methoxymethyl) at the piperidine 4-position. The conversion of the carboxamide intermediates **3A** and **3B** to the carboalkoxyl intermediates **5A**, **5B** and **6A** was accomplished utilizing a modified esterification procedure. Proton nmr data are presented for both the final products and the key synthetic intermediates.

J. Heterocyclic Chem., **31**, 513 (1994).

As part of our structure/activity studies on (\pm)-*cis*-*N*-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide, an extremely potent member of the 4-anilidopiperidine class of analgesics [1-3], we wanted to synthesize analogs containing a 4,4-disubstituted piperidine ring. Earlier studies have shown that the introduction of a second substituent at the piperidine 4-position in the 4-anilidopiperidines can affect the analgesic potency, the duration of action and the compound toxicity [4,5]. Because of their presence in the clinically useful compounds carfentanil [4], sufentanil [4] and alfentanil [6], we were particularly interested in the introduction of the carbomethoxy and methoxymethyl substituents into the piperidine 4-position of (\pm)-*cis*-*N*-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide. In addition, we wanted to maintain the *cis* relationship between the 3-methyl substituent and the 4-propionanilide substituent which was present in the lead compound.

Our synthetic starting material was (\pm)-1-benzyl-3-methyl-4-piperidone (**1**) (*cf.* Scheme I), which we prepared using slight modifications of literature procedures [7]. Condensation of compound **1** with aniline followed by trapping of the intermediate imine with cyanide [5] produced a mixture of nitriles **2A** ("cis") and **2B** ("trans") in 65% yield. (The designations "cis" and "trans" here refer to the spatial relationship of the piperidine 3-methyl group and the 4-anilino group.) Chromatographic separation followed by recrystallization provided the pure compounds. Typically we obtained nitriles **2A** and **2B** in a 1:2 ratio using this procedure. Use of trimethylsilyl cyanide [8] as the trapping agent afforded a higher overall yield (84%); however, the product was almost exclusively the "trans" nitrile **2B**. Since we desired primarily the "cis"

nitrile **2A**, we routinely utilized cyanide as the trapping agent.

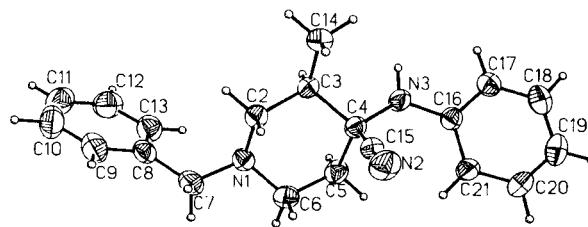
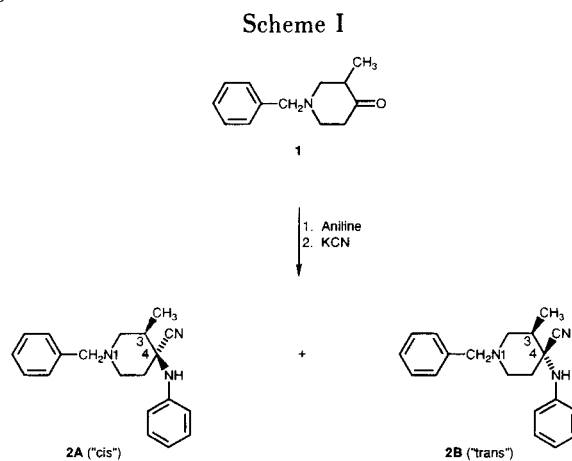


Figure 1. ORTEP drawing of nitrile **2B** showing the relative stereochemistries at the piperidine C-3 and C-4 positions. Thermal ellipsoids for non-hydrogen atoms are drawn at the 50% probability level. Hydrogen atoms are shown as small open circles. The atomic numbering sequence used in the drawing is also utilized in Tables III-VII.

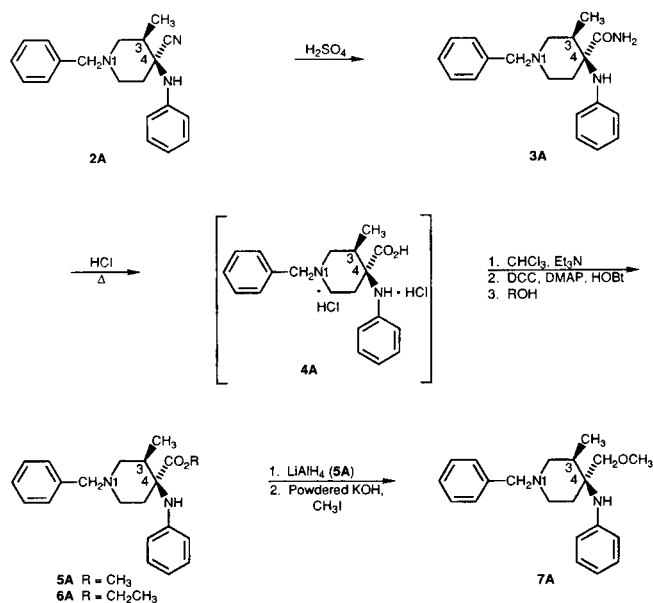
Table I
Crystal Data on Nitrile **2B**

Empirical formula	C ₂₀ H ₂₃ N ₃
Color; habit	Colorless needles
Crystal size (mm)	0.62 x 0.30 x 0.24
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	<i>a</i> = 6.010(2) Å <i>b</i> = 10.744(4) Å <i>c</i> = 14.170(0) Å <i>α</i> = 79.19(3)° <i>β</i> = 85.34(3)° <i>γ</i> = 73.46(3)°
Volume	861.2(5) Å ³
Density (calculated)	1.18 g cm ⁻³
Formula weight	305.43
Z	2
λ(MoKα)	0.71069 Å
μ	0.66 cm ⁻¹

The structures of the isomeric nitriles were established unambiguously by obtaining an X-ray crystal structure on "trans" nitrile **2B**. The pertinent crystal data are summarized in Table I, and an ORTEP [9] drawing of the molecule is presented in Figure I. The *trans* relationship between the piperidine C-3 methyl group and the C-4 anilino group is clearly evident from the drawing. Additional crystallographic data are presented in the Experimental.

The conversion of the nitrile group to the methyl ester group in similar 4,4-disubstituted compounds (e.g., carfen-tanil) has been accomplished by different methods [5,8,10]. After some exploration, we chose a reaction sequence

Scheme II



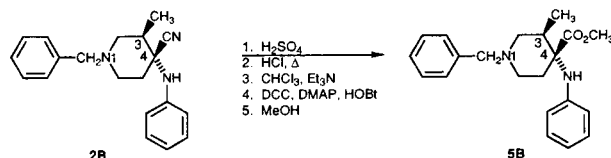
Only one of the two possible arrangements of the piperidine C-3 and C-4 substituents is shown.

which involved a two-step acid hydrolysis to an amino acid intermediate followed by esterification under coupling conditions. Thus, hydrolysis of nitrile **2A** with sulfuric acid [5] yielded the corresponding amide **3A** (cf. Scheme II). In our hands the yield of amide **3A** was significantly improved when the reaction was run under a nitrogen atmosphere. Treatment of amide **3A** with concentrated hydrochloric acid under reflux conditions [11] afforded the free acid **4A**, presumably as a dihydrochloride salt. Without characterization, the crude acid **4A** was neutralized with triethylamine, then coupled with methanol using 1,3-dicyclohexylcarbodiimide in the presence of 4-(dimethylamino)pyridine to activate the acyl group. The overall yield of methyl ester **5A** from nitrile **2A** using this sequence was 52%. Use of ethanol in place of methanol gave the corresponding ethyl ester **6A**, albeit it much lower overall yield (28%). However, this lower yield may not reflect a limitation of the method, since we prepared ethyl ester **6A** only once.

The reduction of methyl ester **5A** with lithium aluminum hydride yielded the corresponding hydroxymethyl intermediate. Subsequent treatment of this intermediate with iodomethane in the presence of powdered potassium hydroxide completed the synthesis of intermediate **7A**, which had the methoxymethyl substituent at the piperidine 4-position. The yield of compound **7A** from methyl ester **5A** was 83%. No methylation of the anilino nitrogen was observed.

Starting with the isomeric nitrile **2B**, the same sequence of reactions was employed to prepare the isomeric methyl ester **5B** (cf. Scheme III). Both the sulfuric acid hydrolysis to amide **3B** (not shown) and its subsequent conversion to methyl ester **5B** proceeded in slightly lower yields in this series. The overall yield (**2B** → **5B**) was 39%.

Scheme III

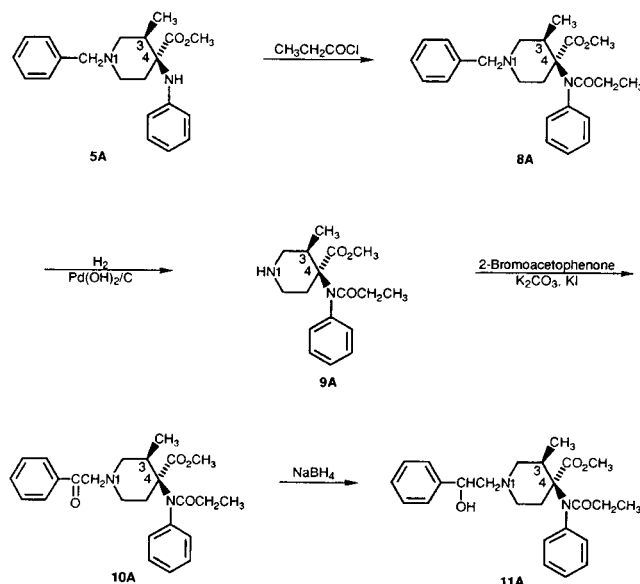


Only one of the two possible arrangements of the piperidine C-3 and C-4 substituents is shown.

The conversion of synthetic intermediates **5A**, **5B**, **6A** and **7A** to the corresponding target compounds involved a four-step sequence which we had developed in conjunction with the synthesis of other analogs of (±)-*cis*-N-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenylpropanamide [1,12]. Thus, acylation of methyl ester **5A** with propionyl chloride provided the propanamide intermediate **8A** (cf. Scheme IV). Cleavage of the 1-benzyl group was achieved by hydrogenolysis over palladium hydroxide (Pearlman's catalyst), affording intermediate **9A**. Subse-

quent alkylation with 2-bromoacetophenone to introduce the 1-(2-oxo-2-phenylethyl) group produced intermediate **10A**. Sodium borohydride reduction of the ketone gave the desired analog **11A**, thereby completing the synthesis. Typically the intermediates in this four-step sequence were purified by flash chromatography (as necessary) and used directly in the next reaction. The yields for the conversions of the four intermediates to the respective target compounds are summarized in Table II. Once again the yield for the "trans" series (**5B** \rightarrow **11B**) was slightly lower.

Scheme IV



Only one of the two possible arrangements of the piperidine C-3 and C-4 substituents is shown.

Table II
Conversion of Key Synthetic Intermediates to Final Products

Intermediate		Product		Yield (4 Steps)
No.	R	No.	R	
5A	$-\text{CO}_2\text{CH}_3$	11A	$-\text{CO}_2\text{CH}_3$	42%
5B	$-\text{NH}-\text{C}_6\text{H}_5$	11B	$-\text{NCOCH}_2\text{CH}_3$	37%
6A	$-\text{CO}_2\text{CH}_2\text{CH}_3$	12A	$-\text{CO}_2\text{CH}_2\text{CH}_3$	44%
7A	$-\text{CH}_2\text{OCH}_3$	13A	$-\text{CH}_2\text{OCH}_3$	42%

The final products were mixtures of four possible isomers (two diastereoisomeric pairs) as was the lead compound, (\pm)-*cis*-*N*-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide [1]. As a consequence,

Table III
Bond Lengths (\AA) for Nitrile **2B**

N(1)-C(2)	1.458(2)
N(1)-C(6)	1.459(2)
N(1)-C(7)	1.462(2)
C(2)-C(3)	1.523(2)
C(3)-C(4)	1.551(2)
C(3)-C(14)	1.522(2)
C(4)-C(5)	1.539(2)
C(4)-C(15)	1.492(2)
C(4)-N(3)	1.448(2)
C(5)-C(6)	1.512(2)
C(7)-C(8)	1.509(2)
C(8)-C(9)	1.385(2)
C(8)-C(13)	1.387(2)
C(9)-C(10)	1.379(2)
C(10)-C(11)	1.370(3)
C(11)-C(12)	1.371(3)
C(12)-C(13)	1.380(2)
C(15)-N(2)	1.132(2)
N(3)-C(16)	1.394(1)
C(16)-C(17)	1.395(2)
C(16)-C(21)	1.398(2)
C(17)-C(18)	1.376(2)
C(18)-C(19)	1.378(2)
C(19)-C(20)	1.375(2)
C(20)-C(21)	1.387(2)

Table IV
Bond Angles ($^\circ$) for Nitrile **2B**

C(2)-N(1)-C(6)	110.3(1)	C(2)-N(1)-C(7)	110.4(1)
C(6)-N(1)-C(7)	111.7(1)	N(1)-C(2)-C(3)	113.6(1)
C(2)-C(3)-C(4)	110.4(1)	C(2)-C(3)-C(14)	109.5(1)
C(4)-C(3)-C(14)	113.6(1)	C(3)-C(4)-C(5)	108.5(1)
C(3)-C(4)-C(15)	107.7(1)	C(5)-C(4)-C(15)	109.0(1)
C(3)-C(4)-N(3)	109.1(1)	C(5)-C(4)-N(3)	111.8(1)
C(15)-C(4)-N(3)	110.6(1)	C(4)-C(5)-C(6)	112.6(1)
N(1)-C(6)-C(5)	109.7(1)	N(1)-C(7)-C(8)	112.8(1)
C(7)-C(8)-C(9)	121.3(1)	C(7)-C(8)-C(13)	120.2(1)
C(9)-C(8)-C(13)	118.4(1)	C(8)-C(9)-C(10)	120.7(2)
C(9)-C(10)-C(11)	120.2(2)	C(10)-C(11)-C(12)	120.0(1)
C(11)-C(12)-C(13)	120.1(2)	C(8)-C(13)-C(12)	120.6(2)
C(4)-C(15)-N(2)	179.7(1)	C(4)-N(3)-C(16)	125.7(1)
N(3)-C(16)-C(17)	117.6(1)	N(3)-C(16)-C(21)	124.1(1)
C(17)-C(16)-C(21)	118.3(1)	C(16)-C(17)-C(18)	120.7(1)
C(17)-C(18)-C(19)	120.7(1)	C(18)-C(19)-C(20)	119.5(1)
C(19)-C(20)-C(21)	120.6(1)	C(16)-C(21)-C(20)	120.3(1)

the ^1H nmr spectra of the final products (free bases) were fairly complex with many of the signals due to the piperidine ring protons integrating for approximately 0.5 proton. Our assignments in the case of analogs **11A** and **12A** were made in part by comparison to the nmr spectrum of the lead compound [1]. For analog **13A** our assignments

Table V
Atomic Coordinates ($\times 10^4$) and Isotropic Thermal Parameters ($\text{\AA}^2 \times 10^3$)

	X	Y	Z	U [a]
N(1)	5793(2)	1357(1)	8243(1)	40(1)
C(2)	6459(2)	1426(1)	7226(1)	38(1)
C(3)	7407(2)	2594(1)	6812(1)	33(1)
C(4)	5651(2)	3900(1)	7000(1)	33(1)
C(5)	4910(2)	3738(1)	8071(1)	44(1)
C(6)	3999(2)	2548(1)	8398(1)	46(1)
C(7)	5040(2)	170(1)	8603(1)	44(1)
C(8)	7045(2)	-1054(1)	8807(1)	41(1)
C(9)	6919(3)	-2257(1)	8633(1)	54(1)
C(10)	8678(3)	-3389(2)	8903(1)	70(1)
C(11)	10590(3)	-3332(2)	9339(1)	71(1)
C(12)	10772(3)	-2145(2)	9497(1)	62(1)
C(13)	9023(3)	-1008(1)	9224(1)	49(1)
C(14)	8063(3)	2571(2)	5754(1)	46(1)
C(15)	3575(2)	4128(1)	6413(1)	36(1)
N(2)	1995(2)	4300(1)	5971(1)	55(1)
N(3)	6726(2)	4966(1)	6722(1)	42(1)
C(16)	5565(2)	6307(1)	6583(1)	34(1)
C(17)	6814(2)	7187(1)	6152(1)	42(1)
C(18)	5792(3)	8525(1)	6013(1)	51(1)
C(19)	3512(3)	9024(1)	6295(1)	54(1)
C(20)	2251(2)	8172(1)	6722(1)	48(1)
C(21)	3252(2)	6820(1)	6867(1)	41(1)

[a] Equivalent isotropic U is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

Table VI
Anisotropic Thermal Parameters ($\text{\AA}^2 \times 10^3$) [a]

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	46(1)	34(1)	35(1)	-3(1)	4(1)	-10(1)
C(2)	43(1)	32(1)	37(1)	-7(1)	4(1)	-9(1)
C(3)	29(1)	30(1)	38(1)	-5(1)	-0(1)	-4(1)
C(4)	29(1)	31(1)	38(1)	-7(1)	-0(1)	-7(1)
C(5)	55(1)	37(1)	38(1)	-11(1)	2(1)	-7(1)
C(6)	50(1)	44(1)	37(1)	-7(1)	11(1)	-7(1)
C(7)	47(1)	43(1)	43(1)	0(1)	1(1)	-17(1)
C(8)	51(1)	39(1)	31(1)	-1(1)	6(1)	-17(1)
C(9)	74(1)	48(1)	46(1)	-7(1)	5(1)	-27(1)
C(10)	105(1)	39(1)	63(1)	-10(1)	16(1)	-18(1)
C(11)	81(1)	50(1)	59(1)	2(1)	13(1)	6(1)
C(12)	55(1)	65(1)	54(1)	-1(1)	0(1)	-5(1)
C(13)	54(1)	45(1)	46(1)	-6(1)	-0(1)	-14(1)
C(14)	48(1)	43(1)	44(1)	-8(1)	13(1)	-10(1)
C(15)	29(1)	33(1)	44(1)	-4(1)	3(1)	-7(1)
N(2)	39(1)	57(1)	69(1)	-10(1)	-11(1)	-10(1)
N(3)	29(1)	31(1)	64(1)	-10(1)	6(1)	-9(1)
C(16)	34(1)	32(1)	37(1)	-7(1)	-2(1)	-9(1)
C(17)	41(1)	41(1)	45(1)	-5(1)	0(1)	-14(1)
C(18)	63(1)	40(1)	55(1)	-0(1)	-4(1)	-23(1)
C(19)	67(1)	33(1)	59(1)	-6(1)	-12(1)	-7(1)
C(20)	43(1)	40(1)	56(1)	-15(1)	-2(1)	-1(1)
C(21)	37(1)	36(1)	48(1)	-10(1)	3(1)	-9(1)

[a] The anisotropic temperature factor exponent takes the form: $-2\pi^2(h^2a^*2U_{11} + \dots + 2hka^*b^*U_{12})$.

Table VII
Hydrogen Atom Coordinates ($\times 10^4$) and Isotropic Thermal Parameters ($\text{\AA}^2 \times 10^3$)

	X	Y	Z	U
H(2A)	5021(21)	1483(12)	6845(9)	44(3)
H(2B)	7656(22)	614(13)	7149(9)	47(4)
H(3)	8791(24)	2510(13)	7163(10)	47(4)
H(5A)	6284(23)	3637(13)	8432(10)	53(4)
H(5B)	3747(23)	4526(14)	8212(10)	47(4)
H(6A)	2504(23)	2650(13)	8048(10)	53(4)
H(6B)	3591(22)	2470(13)	9088(9)	53(4)
H(7A)	4021(24)	64(14)	8149(10)	57(4)
H(7B)	4136(23)	319(13)	9231(10)	55(4)
H(9)	5557(24)	-2248(14)	8335(10)	58(4)
H(10)	8513(30)	-4234(18)	8762(13)	89(6)
H(11)	11783(30)	-4103(17)	9523(13)	93(5)
H(12)	12173(30)	-2100(16)	9772(13)	90(5)
H(13)	9142(24)	-154(15)	9324(10)	54(4)
H(14A)	6675(27)	2608(16)	5363(12)	81(5)
H(14B)	8663(27)	3284(16)	5419(11)	71(4)
H(14C)	9191(28)	1744(16)	5652(12)	74(5)
H(3N)	7978(26)	4807(14)	6391(11)	54(4)
H(17)	8443(23)	6823(14)	5975(10)	49(4)
H(18)	6723(25)	9082(15)	5728(11)	67(4)
H(19)	2856(26)	9936(15)	6204(11)	71(4)
H(20)	699(24)	8461(13)	6926(10)	56(4)
H(21)	2286(23)	6249(13)	7156(9)	48(4)

were aided by obtaining a COSY spectrum on the free base. While we believe that our assignments are correct, we acknowledge that more detailed studies could result in some piperidine ring proton assignments being changed, especially those for protons bonded to C-2 and C-6.

The nmr data on analogs **11A**, **12A** and **13A** are consistent with a solution conformation (under the conditions of the nmr experiments) similar to that of the lead compound [1] in which the piperidine ring is in a chair conformation, the bulky 1-(2-hydroxyl-2-phenylethyl) and 4-propionanilide substituents occupy equatorial positions, the 3-methyl group *cis* to the 4-propionanilide substituent is axial, and the second piperidine 4-substituent occupies an axial position on the opposite side of the piperidine ring from the 3-methyl group. In the case of analog **11B**, in which the positions of the 4-propionanilide and 4-carbomethoxyl substituents are reversed relative to analog **11A**, the nmr spectrum suggests that the piperidine ring is distorted from the chair conformation. In this structure, the bulky 4-propionanilide substituent cannot occupy an equatorial position without causing serious steric interactions between the 4-carbomethoxyl and 3-methyl substituents.

Biological studies on compounds **11A**, **11B**, **12A** and **13A** are in progress. The biological studies will be the subject of a later report.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary apparatus and are uncorrected. The ^1H nmr spectra were recorded in deuteriochloroform on a Bruker AM 250 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. In reporting the nmr data, the following abbreviations are used: a, axial; e, equatorial; d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet; br, broad; dq, doublet of quartets; and dt, doublet of triplets. Thin layer chromatographic (tlc) analyses were done on analytical silica gel plates (E. Merck). Unless otherwise noted, anhydrous sodium sulfate was used to dry organic solutions. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

(\pm)-1-Benzyl-*t*-4-cyano-*r*-3-methyl-*N*-phenyl-4-piperidinamine (**2A**) and (\pm)-1-Benzyl-*c*-4-cyano-*r*-3-methyl-*N*-phenyl-4-piperidinamine (**2B**).

Method A.

A stirred solution of (\pm)-1-benzyl-3-methyl-4-piperidone [7] (204 g, 1.0 mole) and aniline (94 g, 1.0 mole) in glacial acetic acid (700 ml) was cooled in an ice bath. A solution of potassium cyanide (72 g, 1.1 moles) in water (200 ml) was added dropwise over a 15 minute period. Following the addition, the ice bath was removed and the resultant mixture stirred 2 days at room temperature. Afterwards, the reaction mixture was poured onto crushed ice (1,000 g), neutralized by the addition of concentrated ammonium hydroxide (1,300 ml), and extracted with chloroform (4 x 250 ml). The combined organic extracts were dried and evaporated to obtain an amber oil (226 g). Crystallization of the oil from ethyl acetate/hexanes gave 198 g (65%) of a slightly tan solid, tlc: two spots, R_f 0.60 and R_f 0.40 [ethyl acetate:hexane (1:1) containing 5 drops of concentrated ammonium hydroxide].

The above mixture was further purified in 40 g batches by flash chromatography on silica gel (900 g) utilizing an ethyl acetate:hexane (25:75) solvent system. A typical chromatography provided compound **2A** (10 g, 25%), compound **2B** (20 g, 50%) and some recovered mixture (8 g, 20%). Subsequent recrystallization of the compound **2A** fractions from ethyl acetate/hexane afforded a white crystalline solid, mp 140-141 $^\circ$; tlc: single spot, R_f 0.60 [ethyl acetate:hexane (1:1) containing 5 drops of concentrated ammonium hydroxide]; ^1H nmr: δ 1.14 (d, $J = 6.9$ Hz, 3H, CH_3), 1.60 (s, 1H), 1.99 (m, 1H), 2.38-2.54 (overlapping m, 3H), 2.66 (dd, 1H), 3.50-3.55 (overlapping m, 3H, ArCH_2 and piperidine CH), 6.82-6.92 (m, 2H, ArH), 7.12-7.35 (m, 8H, ArH).

Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.56; H, 7.64; N, 13.69.

Recrystallization of the compound **2B** fractions from ethyl acetate/hexane afforded a white crystalline solid, mp 115-118 $^\circ$; tlc: single spot, R_f 0.40 [ethyl acetate:hexane (1:1) containing 5 drops of concentrated ammonium hydroxide]; ^1H nmr: δ 1.20 (d, $J = 6.6$ Hz, 3H, CH_3), 1.69 (m, 1H), 1.95-2.55 (overlapping m, 4H), 2.84 (m, 2H), 3.48-3.60 (overlapping m, 3H, ArCH_2 and piperidine CH), 6.88-6.95 (m, 3H, ArH), 7.21-7.36 (m, 7H, ArH). A sample of this material was submitted for X-ray crystallographic analysis.

Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.60; H, 7.63; N, 13.73.

Method B.

Trimethylsilyl cyanide (100 g, 1.0 mole) was added dropwise

over a 15 minute period to a stirred solution of (\pm)-1-benzyl-3-methyl-4-piperidone [7] (100 g, 0.49 mole) and aniline (54 g, 0.58 mole) in glacial acetic acid (500 ml). Following the addition, the resultant mixture was stirred 45 minutes at room temperature, then poured onto crushed ice (1,000 g). The mixture was adjusted to pH 10 by the addition of concentrated ammonium hydroxide and extracted with chloroform (4 x 250 ml). The combined organic extracts were dried and evaporated to give an amber oil (147 g). Crystallization of the oil from ethyl acetate/hexanes afforded 126.5 g (84%) of a slightly tan solid, tlc: essentially one spot, R_f 0.40 [ethyl acetate:hexane (1:1) containing 5 drops of concentrated ammonium hydroxide]. A minor spot was observed at R_f 0.60.

(\pm)-1-Benzyl-*r*-3-methyl-*c*-4-(*N*-phenyl)aminoisonipecotamide (**3A**).

Under nitrogen compound **2A** (15.7 g, 0.0515 mole) was added to concentrated sulfuric acid (50 ml) which had been cooled to 0 $^\circ$. Although the solid did not completely dissolve upon addition, it gradually went into solution. Following the addition, the ice bath was removed and the reaction mixture stirred 2 days at room temperature. Afterwards, the mixture was poured onto crushed ice (1,000 g). Concentrated ammonium hydroxide (approximately 250 ml) was added until pH 10, and the mixture was extracted with chloroform (4 x 250 ml). The combined chloroform extracts were dried and evaporated to obtain the title compound (12.6 g, 76%) as a white solid, mp 244-246 $^\circ$; tlc: single spot, R_f 0.40 (ethyl acetate containing 4 drops of concentrated ammonium hydroxide); ^1H nmr: δ 0.95 (d, $J = 7.1$ Hz, 3H, CH_3), 1.78 (m, 1H), 1.99 (t, 1H), 2.30-2.58 (overlapping m, 4H), 2.79 (dd, 1H), 3.45 (s, 2H, ArCH_2), 3.77 (s, 1H, amide NH), 5.63 (br s, 1H, NH), 6.67 (m, 2H, ArH), 6.81 (m, 2H, ArH), 6.93 (br m, 1H, amide NH), 7.15-7.30 (m, 7H, ArH).

Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.27; H, 7.81; N, 13.02.

(\pm)-1-Benzyl-*r*-3-methyl-*t*-4-(*N*-phenyl)aminoisonipecotamide (**3B**).

The sulfuric acid hydrolysis of compound **2B** was carried out utilizing the same procedure described above for the hydrolysis of compound **2A**. The title compound was obtained in 68% yield as a white solid, mp 220-224 $^\circ$; tlc: single spot, R_f 0.30 [ethyl acetate:hexane (75:25) containing 4 drops of concentrated ammonium hydroxide]; ^1H nmr: δ 1.18 (d, $J = 7.0$ Hz, 3H, CH_3), 1.78-2.11 (overlapping m, 3H), 2.40-2.73 (overlapping m, 4H), 3.45 (q, 2H, ArCH_2), 4.06 (s, 1H, amide NH), 5.51 (br s, 1H, NH), 6.63 (m, 2H, ArH), 6.78 (overlapping m, 2H, ArH and amide NH), 7.14-7.31 (m, 7H, ArH).

Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.26; H, 7.83; N, 12.98.

(\pm)-1-Benzyl-*r*-3-methyl-*c*-4-(*N*-phenyl)aminoisonipecotic Acid Methyl Ester (**5A**).

A solution of compound **3A** (10.0 g, 0.031 mole) in concentrated hydrochloric acid (100 ml) was refluxed overnight, then concentrated *in vacuo*. The residue was dissolved in absolute ethanol (200 ml), then the solution was concentrated to dryness. This process was repeated three more times, after which the residual solid (presumably compound **4A**) was vacuum dried overnight to remove the last traces of water.

The dried solid was dissolved in chloroform (300 ml) and treated with triethylamine (10 ml, 0.072 mole). After stirring several minutes at room temperature, the mixture was filtered to remove the triethylamine hydrochloride. The clear filtrate was then cooled in an ice bath and the following reagents were added: 1,3-dicyclohexylcarbodiimide (5.2 g, 0.025 mole), 4-(dimethylamino)pyridine (6.1 g, 0.050 mole) and 1-hydroxybenzotriazole hydrate (3.4 g, 0.025 mole). The resultant solution was stirred 30 minutes at low temperature, then treated with methanol (50 ml). Following the latter addition, the ice bath was removed and the reaction mixture stirred overnight at room temperature. Afterwards, the volatiles were evaporated to dryness and the residue partitioned between toluene (400 ml) and 10% aqueous sodium bicarbonate (400 ml). The toluene layer was separated, dried and evaporated to obtain the crude product. Subsequent flash chromatography on silica gel using an ethyl acetate:hexane (95:5) → ethyl acetate gradient yielded the title compound (7.1 g, 68%). Crystallization from ethyl acetate/hexane gave a white solid, mp 75-76°; ¹H nmr: δ 0.95 (d, J = 7.0 Hz, 3H, CH₃), 2.17-2.52 (overlapping m, 6H), 2.66 (dd, 1H), 3.47 (s, 2H, ArCH₂), 3.71 (s, 3H, OCH₃), 3.75 (s, 1H, NH), 6.53 (dd, 2H, ArH), 6.72 (m, 1H, ArH), 7.09-7.31 (m, 7H, ArH).

Anal. Calcd. for C₂₁H₂₆N₂O₂: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.43; H, 7.78; N, 8.34.

(±)-1-Benzyl-*r*-3-methyl-*t*-4-(*N*-phenyl)aminoisonipecotic Acid Methyl Ester (**5B**).

The title compound was prepared in 58% overall yield following the same procedure used for methyl ester **5A** except that compound **3B** was used as the starting material. Crystallization of the title compound from ethyl acetate/hexanes provided a white solid, mp 132-133°; ¹H nmr: δ 1.09 (d, J = 6.9 Hz, 3H, CH₃), 1.94 (m, 1H), 2.10-2.37 (overlapping m, 3H), 2.51-2.71 (overlapping m, 3H), 3.45 (q, 2H, ArCH₂), 3.66 (s, 3H, OCH₃), 3.87 (s, 1H, NH), 6.56 (dd, 2H, ArH), 6.72 (t, 1H, ArH), 7.09-7.33 (m, 7H, ArH).

Anal. Calcd. for C₂₁H₂₆N₂O₂: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.46; H, 7.77; N, 8.31.

(±)-1-Benzyl-*r*-3-methyl-*c*-4-(*N*-phenyl)aminoisonipecotic Acid Ethyl Ester (**6A**).

The title compound was prepared in 37% overall yield following the same procedure used for methyl ester **5A** except that ethano was added in place of methanol in the esterification step. The product was isolated from the chromatography as a clear oil; ¹H nmr: δ 0.97 (d, J = 7.0 Hz, 3H, CH₂), 1.19 (t, 3H, OCH₂CH₃), 2.14-2.50 (overlapping m, 6H), 2.66 (dd, 1H), 3.47 (s, 2H, ArCH₂), 3.73 (s, 1H, NH), 4.20 (m, 2H, OCH₂CH₃), 6.55 (dd, 2H, ArH), 6.72 (m, 1H, ArH), 7.08-7.31 (m, 7H, ArH). This material was utilized in the subsequent conversion to target compound **12A** with no further purification or characterization.

(±)-1-Benzyl-*t*-4-methoxymethyl-*r*-3-methyl-*N*-phenyl-4-piperidinamine (**7A**).

Methyl ester **5A** (1.0 g, 0.0030 mole) was dissolved in dry tetrahydrofuran (100 ml) and the solution cooled in an ice bath. To this solution was added a solution of lithium aluminum hydride in tetrahydrofuran (5 ml of a 1M commercial solution). After stirring for 2 hours, the reaction was quenched by the addition of 0.1N sodium hydroxide solution. Precipitated solids were removed by filtration and the filtrate was evaporated. The residue

was partitioned between ethyl acetate and 10% aqueous sodium bicarbonate solution. The ethyl acetate layer was separated, dried and evaporated to obtain 0.9 g (98%) of (±)-1-benzyl-*t*-4-hydroxymethyl-*r*-3-methyl-*N*-phenyl-4-piperidinamine as an oil; ¹H nmr: δ 1.05 (d, J = 6.6 Hz, 3H, CH₃), 1.55 (m, 1H), 1.91-2.27 (overlapping m, 4H), 2.48 (m, 2H), 3.47 (q, 2H, ArCH₂), 3.75 (q, 2H, CH₂OH), 6.79 (m, 3H, ArH), 7.14-7.34 (m, 7H, ArH).

After vacuum drying, the crude alcohol was dissolved in dimethylsulfoxide (25 ml). Powdered potassium hydroxide (1 g) was added to the solution. The mixture was stirred 5 minutes, then iodomethane (0.2 ml, 0.0031 mole) was added. The resultant mixture was stirred 2 hours at room temperature, after which time the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (250 ml) and washed with 10% aqueous sodium bicarbonate (2 x 200 ml). The organic layer was dried and evaporated to obtain a crude oil. Subsequent flash chromatography on silica gel using ethyl acetate:hexane (25:75) yielded 0.8 g (90%) of the title compound as a clear oil; ¹H nmr: δ 0.99 (d, J = 6.6 Hz, 3H, CH₃), 1.75 (m, 1H), 2.03-2.34 (overlapping m, 4H), 2.53 (m, 2H), 3.30 (s, 3H, OCH₃), 3.32-3.57 (overlapping q, 4H, CH₂OCH₃ and ArCH₂), 6.75 (m, 3H, ArH), 7.09-7.33 (m, 7H, ArH). This material was used in the subsequent conversion to target compound **13A** with no further purification or characterization.

(±)-1-(2-Hydroxy-2-phenylethyl)-*r*-3-methyl-*c*-4-[*N*-(1-oxopropyl)-*N*(phenyl)amino]isonipecotic Acid Methyl Ester (**11A**) Hydrochloride.

A solution of methyl ester **5A** (3.0 g, 0.0089 mole) and propionyl chloride (5.1 ml, 0.059 mole) in chloroform (70 ml) was refluxed overnight, then cooled to room temperature. Following removal of the chloroform, the residue was dissolved in ethyl acetate (250 ml) and washed with 10% aqueous sodium bicarbonate (3 x 150 ml). The organic layer was dried and evaporated to obtain the crude product. Subsequent flash chromatography on silica gel utilizing ethyl acetate:hexane (25:75) afforded pure (±)-1-benzyl-*r*-3-methyl-*c*-4-[*N*-(1-oxopropyl)-*N*(phenyl)amino]isonipecotic acid methyl ester (**8A**) as an oil; ¹H nmr: δ 0.95 (t, 3H, CH₂CH₃), 1.25 (d, J = 7.3 Hz, 3H, CH₃), 1.32 (partially obscured m, 1H), 1.61 (dt, 1H), 1.90 (m, 2H, CH₂CH₃), 1.96 (m, 1H), 2.67 (overlapping m, 2H), 3.06 (dd, 1H), 3.30 (br m, 1H), 7.21-7.54 (m, 10H, ArH). The oil was dissolved in methanol (100 ml) and the solution treated with an equal volume of dioxane which had been saturated with hydrogen chloride gas. Removal of the volatiles afforded a solid hydrochloride salt. Subsequent recrystallization from methanol/ethyl acetate provided a white solid (2.1 g, 55%), mp 247-250°; tlc: single spot, R_f 0.35 [ethyl acetate:hexane (35:65) containing 4 drops of concentrated ammonium hydroxide].

A mixture of compound **8A** hydrochloride (2.1 g, 0.0048 mole) and palladium hydroxide/carbon catalyst (0.7 g) in methanol was shaken 2 hours at 40 psi hydrogen on a Parr apparatus. The catalyst was then removed by filtration and the filtrate evaporated. The residue was taken up in water (400 ml). The solution was treated with concentrated ammonium hydroxide until pH 10, then extracted with chloroform (4 x 100 ml). The combined chloroform extracts were dried and evaporated to obtain (±)-*r*-3-methyl-*c*-4-[*N*-(1-oxopropyl)-*N*(phenyl)amino]isonipecotic acid methyl ester (**9A**) as an oil. To a solution of the oil in absolute ethanol (200 ml) were added 2-bromoacetophenone (1.0 g, 0.005 mole), potassium carbonate (5 g), and a few crystals of potassium iodide. The resultant mixture was stirred 1 hour at room temperature, then the solvent was evaporated. The residue was parti-

tioned between toluene (200 ml) and saturated sodium bicarbonate solution (200 ml). The toluene layer was separated and extracted with 10% citric acid (4 x 100 ml). The combined acid extracts were adjusted to pH 10 utilizing concentrated ammonium hydroxide, then extracted with chloroform (4 x 100 ml). The combined chloroform extracts were dried and evaporated to obtain (\pm)-*r*-3-methyl-1-(2-oxo-2-phenylethyl)-*c*-4-[*N*-(1-oxopropyl)-*N*-(phenyl)amino]isonipecotic acid methyl ester (**10A**) as an amber oil (2.9 g). The hydrochloride salt was prepared as described above and recrystallized from methanol/ethyl acetate to obtain a white solid (1.9 g, 85%), mp 205-207°.

A stirred solution of compound **10A** hydrochloride (1.9 g, 0.0041 mole) in methanol (100 ml) was treated with solid sodium borohydride (0.9 g, 0.024 mole), added in portions over 15 minutes. Following the final addition, the resultant mixture was stirred 1.5 hours at room temperature. The methanol was then evaporated and the residue dissolved in ethyl acetate (250 ml). The ethyl acetate solution was washed with 10% aqueous sodium bicarbonate (2 x 200 ml), dried and evaporated to obtain (\pm)-1-(2-hydroxy-2-phenylethyl)-*r*-3-methyl-*c*-4-[*N*-(1-oxopropyl)-*N*-(phenyl)amino]isonipecotic acid methyl ester (**11A**) as a clear oil; ¹H nmr: δ 0.97 (t, 3H, CH₂CH₃), 1.31 (d, J = 7.3 Hz, 3H, CH₃), 1.36 (m, 1H, 5He), 1.59 (dq, H, 5Ha), 1.80-2.00 (overlapping m, 2.5H, CH₂CH₃ and 6Ha), 2.18-2.49 (overlapping m, 3H, NCH₂, 2Ha and 6Ha), 2.59 (d, 0.5H, 2Ha), 2.82 (br d, 0.5H, 2He), 2.94 (d, 0.5H, 6He), 3.11 (dd, 0.5H, 2He), 3.36 (overlapping m, 1.5H, 3He and 2He), 3.81 (s, 3H, OCH₃), 4.58 and 4.67 (two dd, 1H, ArCHOH), 7.25-7.55 (m, 10H, ArH). The free base was converted to the hydrochloride salt by the above procedure. Subsequent crystallization from 2-propanol/isopropyl ether afforded the title compound as a white solid (1.8 g, 89%), mp 135-140°; tlc: single spot, R_f 0.40 [ethyl acetate:hexane (1:1) containing 5 drops of concentrated ammonium hydroxide]. The overall yield from methyl ester **5A** was 42%.

Anal. Calcd. for C₂₂H₃₃ClN₂O₄·0.5C₂H₆O: C, 64.82; H, 7.60; Cl, 7.22; N, 5.70. Found: C, 64.71; H, 7.64; Cl, 7.07; N, 5.58.

(\pm)-1-(2-Hydroxy-2-phenylethyl)-*r*-3-methyl-*t*-4-[*N*-(1-oxopropyl)-*N*-(phenyl)amino]isonipecotic Acid Methyl Ester (**11B**) Hydrochloride.

Using the same procedures described above for the preparation of compound **11A**, methyl ester **5B** was converted to (\pm)-1-(2-hydroxy-2-phenylethyl)-*r*-3-methyl-*t*-4-[*N*-(1-oxopropyl)-*N*-(phenyl)amino]isonipecotic acid methyl ester (**11B**). Following purification by flash chromatography [silica gel, ethyl acetate:hexane (1:1)], compound **11B** was isolated as a clear oil; ¹H nmr: δ 0.97 (t, 3H, CH₂CH₃), 1.07 and 1.12 (two d, J = 7.0 Hz, CH₃), 1.61 (br t, 1H), 1.88 (q, 2H, CH₂CH₃), 2.03 (m, 1H), 2.24-2.60 (overlapping m, 5.5H, NCH₂ and other CH), 2.73-2.91 (overlapping m, 1.5H), 3.77 (s, 3H, OCH₃), 4.58 and 4.67 (two dd, 1H, ArCHOH), 7.22-7.47 (m, 10H, ArH). Conversion to the hydrochloride salt followed by recrystallization from methanol/ethyl acetate yielded the title compound as a white solid (2.5 g), mp 204-206°; tlc: single spot, R_f 0.35 [ethyl acetate:hexane (1:1) containing 5 drops of concentrated ammonium hydroxide]. The overall yield from methyl ester **5B** was 37%.

Anal. Calcd. for C₂₅H₃₃ClN₂O₄: C, 65.14; H, 7.22; Cl, 7.69; N, 6.08. Found: C, 64.91; H, 7.25; Cl, 7.63; N, 6.04.

(\pm)-1-(2-Hydroxy-2-phenylethyl)-*r*-3-methyl-*c*-4-[*N*-(1-oxopropyl)-*N*-(phenyl)amino]isonipecotic Acid Ethyl Ester (**12A**) Hydrochloride.

Using the same procedures described above for the preparation of compound **11A**, ethyl ester **6A** was converted to (\pm)-1-(2-hydroxy-2-phenylethyl)-*r*-3-methyl-*c*-4-[*N*-(1-oxopropyl)-*N*-(phenyl)amino]isonipecotic acid ethyl ester (**12A**). Following workup of the sodium borohydride reduction reaction, compound **12A** was isolated as a clear oil; ¹H nmr: δ 0.95 (t, 3H, CH₂CH₃), 1.27-1.40 (overlapping m, 7H, CH₃, OCH₂CH₃, 5He), 1.57 (dq, 1H, 5Ha), 1.74-2.01 (overlapping m, 2.5H, CH₂CH₃ and 6Ha), 2.19-2.47 (overlapping m, 3H, NCH₂, 2Ha and 6Ha), 2.57 (d, 0.5H, 2Ha), 2.81 (br d, 0.5H, 2He), 2.92 (d, 0.5H, 6He), 3.12 (dd, 0.5H, 2He), 3.38 (overlapping m, 1.5H, 3He and 2He), 4.14-4.38 (m, 2H, OCH₂CH₃), 4.57 and 4.66 (two dd, 1H, ArCHOH), 7.21-7.55 (m, 10H, ArH). Conversion to the hydrochloride salt followed by recrystallization from 2-propanol/isopropyl ether yielded the title compound as a white solid (1.4 g), mp 172-175°, 179-181°; tlc: single spot, R_f 0.25 [ethyl acetate:hexane (25:75) containing 5 drops of concentrated ammonium hydroxide]. The overall yield from ethyl ester **6A** was 44%.

Anal. Calcd. for C₂₆H₃₅ClN₂O₄: C, 65.75; H, 7.43; Cl, 7.46; N, 5.90. Found: C, 65.75; H, 7.67; Cl, 7.22; N, 5.73.

(\pm)-*N*-[1-(2-Hydroxy-2-phenylethyl)-*t*-4-methoxymethyl-*r*-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**13A**) Oxalate.

Using the same procedures described above for the preparation of compound **11A**, (\pm)-1-benzyl-*t*-4-methoxymethyl-*r*-3-methyl-*N*-phenyl-4-piperidinamine (**7A**) was converted to (\pm)-*N*-[1-(2-hydroxy-2-phenylethyl)-*t*-4-methoxymethyl-*r*-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**13A**). Following purification by flash chromatography [silica gel, ethyl acetate:hexane (1:1)], compound **13A** was isolated as a clear oil; ¹H nmr: δ 0.95 (t, 3H, CH₂CH₃), 1.23-1.34 (overlapping m, 2H, 5He and 5Ha), 1.33 (d, J = 7.1 Hz, CH₃), 2.10 (dt, 0.5H, 6Ha), 2.29-2.69 (overlapping m, 4.5H, NCH₂, 6Ha, two 2Ha, 6He and 2He), 2.88 (overlapping m, 1H, 6He and 2He), 3.17 (m, 1H, 3He), 3.44 and 3.45 (two s, 3H, CH₂OCH₃), 3.82 and 4.45 (two d, J = 9.8 Hz, 2H, CH₂OCH₃), 4.61 and 4.66 (two dd, 1H, ArCHOH), 7.19-7.50 (m, 10H, ArH). A solution of the oil in a minimum volume of methanol was treated with an equivalent of oxalic acid, then evaporated to dryness. Subsequent crystallization from ethyl acetate afforded the title compound as a white solid (1.6 g), mp 135-148°; tlc: single spot, R_f 0.66 [ethyl acetate:hexanes (1:1) containing 10 drops of concentrated ammonium hydroxide]. The overall yield from intermediate **7A** was 42%.

Anal. Calcd. for C₂₂H₃₆N₂O₇: C, 64.78; H, 7.25; N, 5.60. Found: C, 64.55; H, 7.21; N, 5.55.

X-ray Crystallography of Nitrile **2B**.

The unit cell dimensions (*cf.* Table I) were obtained by refining the setting angles of 25 reflections with 2θ values between 20 and 30°; 5456 intensity data were collected between 3 and 60° by the ω -scan method at variable speeds between 3.9 and 29.3 deg min⁻¹ depending on intensity. Stationary backgrounds were measured on both sides of a peak each for 1/2 of the scan time. The number of unique intensity data measured was 5012; R_{int} = 0.015. The intensity data were reduced to observed structure factor amplitudes, F_o, in the usual manner. A Siemens/Nicolet P3/F4-circle

automatic diffractometer was used for all measurements.

The structure was solved by direct methods and difference Fourier techniques and refined by the blocked-cascade least-squares technique [13] using 3450 reflections with $F_o \geq 5\sigma(F_o)$. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, where $w = 1/[\sigma(F^2) + 0.0005F^2]$. The goodness-of-fit parameter was 1.6. An isotropic secondary extinction correlation was applied near the end of the refinement; the extinction coefficient was $5(1) \times 10^6$. The nonhydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were located from a difference Fourier map and refined isotropically. A total of 301 parameters were refined. The maximum shift/ σ in a parameter in the last cycle of refinement was 0.53. The final difference Fourier was featureless with residual peak excursions of -0.17 and $+0.19 \text{ e } \text{\AA}^{-3}$. The data to parameter ratio, 11.5, was excellent. The final residuals were $R = 0.0445$ and $wR = 0.0574$. The atomic scattering factors were taken from the International Tables for X-ray Crystallography [14]. All calculations were performed on a Data General microclipse desktop computer using Sheldrick's crystallographic program package SHELXTL [15].

The bond lengths, bond angles and other crystallographic data are presented in Tables III-VII.

Acknowledgment.

This work was supported by grant DA06317 from the National Institute on Drug Abuse. The X-ray diffractometer at North Carolina State University was upgraded with the help of grant CHE 8307022 from the National Science Foundation. The authors thank Ms. T. M. Richardson for her assistance with the syntheses.

REFERENCES AND NOTES

- [1] G. A. Brine, D. K. Sawyer, P.-T. Huang, P. A. Stark, K. D. Gaetano and F. I. Carroll, *J. Heterocyclic Chem.*, **29**, 1773 (1992).
- [2] M. D. Aceto, E. R. Bowman, L. S. Harris and E. L. May, in Problems of Drug Dependence, 1988, L. S. Harris, ed, NIDA Research Monograph 90, 1988, p 468.
- [3] R. B. Rothman, H. Xu, M. Seggel, A. E. Jacobson, K. C. Rice, G. A. Brine and F. I. Carroll, *Life Sci.*, **48**, PL111 (1991).
- [4] W. F. M. Van Bever, C. J. E. Niemegeers, K. H. L. Schellekens and P. A. J. Janssen, *Arzneim.-Forsch.*, **26**, 1548 (1976).
- [5] P. G. H. Van Daele, M. F. L. De Bruyn, J. M. Boey, S. Sanczuk, J. T. M. Agten and P. A. J. Janssen, *Arzneim.-Forsch.*, **26**, 1521 (1976).
- [6] F. Janssens, J. Torremans and P. A. J. Janssen, *J. Med. Chem.*, **29**, 2290 (1986).
- [7] P. M. Carabateas and L. Grumbach, *J. Med. Pharm. Chem.*, **5**, 913 (1962).
- [8] P. L. Feldman and M. F. Brackeen, *J. Org. Chem.*, **55**, 4207 (1990).
- [9] C. K. Johnson, ORTEP II, Oak Ridge National Laboratory Report ORNL-5138 (1976).
- [10] D. F. Taber and M. Rahimizadeh, *J. Org. Chem.*, **57**, 4037 (1992).
- [11] J. A. Colapret, G. Diamantidis, H. K. Spencer, T. C. Spaulding and F. G. Rudo, *J. Med. Chem.*, **32**, 968 (1989).
- [12] G. A. Brine and P. A. Stark, unpublished results.
- [13] R. A. Sparks, Computing Methods and the Phase Problem in X-ray Crystal Analysis, R. A. Pepinsky, J. M. Robertson and J. C. Speakman, eds, Pergaman Press, New York, New York, 1961, p 170.
- [14] International Tables for X-ray Crystallography, Vol IV, Kynoch Press, Birmingham, 1974, p 71.
- [15] G. M. Sheldrick, SHELXTL User's Manual, Revision 5.1, Siemens Analytical Instruments, Madison, Wisconsin, 1985.