Synthesis and X-Ray Crystal Structures of Isonipecotinamide Derivatives as Reverse Amide Analogues of Fentanyl

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Several isonipecotinamide derivatives which represent reverse amide derivatives of the potent analgetic agent fentanyl were prepared and evaluated for analgetic activity. The synthetic approaches utilized and stereochemical assignments are discussed. The most potent compound, **3**, displayed much weaker analgetic activity than fentanyl itself.

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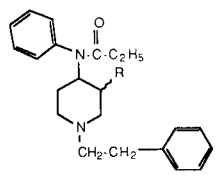
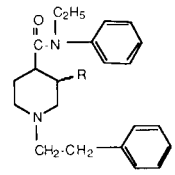
Introduction.

Fentanyl (**1**) is a potent, centrally-acting analgetic agent which is representative of the 4-anilidopiperidine class of narcotic analgetics. Several studies have been reported in which structural [1-10] and conformational [11-17] effects on analgetic activity have been examined. Of particular interest are the reports that a 3-methyl group enhances activity [7] and that the *cis*-3-methyl derivative **2a** is significantly more potent than the *trans*-isomer **2b** [6]. Substitution of a methyl group at the 2-position, on the other hand, significantly reduces analgetic activity. Based on these reports, and upon X-ray crystallographic studies, we suggested [18] that an axially-oriented *cis*-3-methyl group forces the *N*-phenyl substituent into the favorable conformation for interaction with analgetic receptor(s). In order to test this hypothesis the synthesis of reverse amide analogues of fentanyl **3-4** was carried out since the 3-methyl substituent in these derivatives in **4a** and **4b** is too far removed from the *N*-phenyl group to exert any effect on its conformation. Thus, little differences in activity would be expected in these reverse amides.



1 R = H
2a R = *cis*-CH_3
2b R = *trans*-CH_3

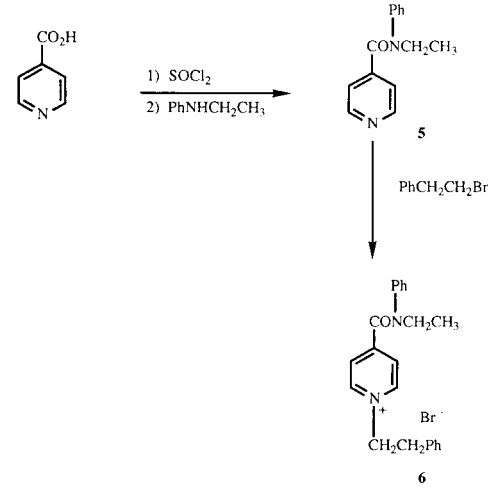


3 R = H
4a R = *cis*-CH_3
4b R = *trans*-CH_3

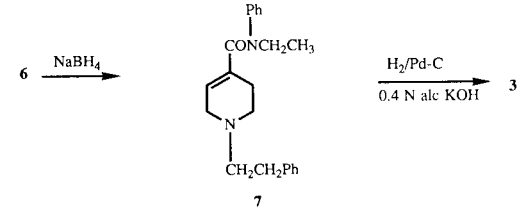
Discussion.

Isonicotinic acid was treated with thionyl chloride and *N*-ethylaniline (using *N*-ethyl aniline as solvent) to give the amide **5** as shown in Scheme I. Hamilton [19] reported that pyridinium salts are hydrogenated to the corresponding piperidines using platinum oxide catalyst in either absolute ethanol or glacial acetic acid. The quaternary salts are usually more readily reduced than the parent bases or hydrochlorides. Thus, the pyridinium bromide **6** was prepared and subjected to hydrogenation using platinum oxide as the catalyst. However, the major product obtained was the one in which one of the phenyl rings, along with the pyridine nucleus, were reduced as indicated by ^{1}H nmr and mass spectrometry. An alternative approach to the reduction of the pyridine nucleus involved the formation of a 1, 2, 5, 6-tetrahydropyridine from the pyridinium salt with sodium borohydride as reported by Lyle [23]. The 1, 2, 5, 6-tetrahydropyridine **7** was easily obtained using this approach (Scheme II).

Scheme I



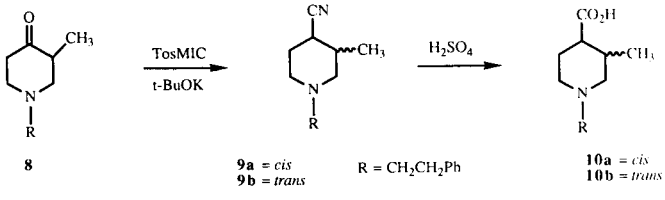
Scheme II



Reduction of the double bond in **7** by hydrogenation over palladium-on-carbon proved to be more difficult than expected as this olefin was not reduced after 24 hours. Platinum oxide was too reactive as one of the phenyl rings in addition to the olefin was reduced. However, hydrogenation of **7** in 0.4 *N* alcoholic potassium hydroxide gave **3** in moderate yields.

The synthesis of **4a** and **4b** from **8** (prepared by the method of Beckett, *et. al.*, [20]) as illustrated in Scheme III was explored. Addition of tosylmethyl isocyanide (TosMIC) to **8** produced a mixture of the two diastereomeric nitriles **9a** and **9b**. Column chromatography on silica gel 60 yielded the two isomers in a 3:4 ratio, which was determined in retrospect to be the *cis*- and *trans*-diastereomers, respectively, as will be discussed below. Relative stereochemistry could not be determined by ^{1}H nmr spectroscopy due to overlap of peaks.

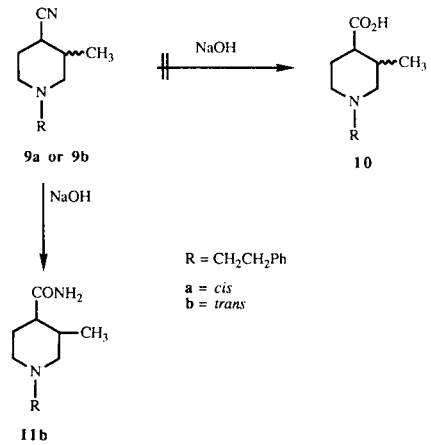
Scheme III



8 **9a** = *cis*, **9b** = *trans* **10a** = *cis*, **10b** = *trans*

Sodium hydroxide in aqueous ethanol was used initially to separately convert **9a** and **9b** to the carboxylic acids **10a** and **10b** respectively. The solid from each of the reaction mixture as the only isolated organic material, gave identical ^{1}H nmr spectra and melting points. All spectral data indicated that this product was the primary amide **11b** (Scheme IV). Based on the inference that the *trans* isomer of the 3-methyl and 4-cyano groups is more favorable than the *cis* isomer, **11b** must be the *trans*-isomer. Thus, these results indicated that **9a** is the *cis*-isomer and **9b** is the *trans*-isomer, and that epimerization of the *cis*-nitrile **9a** to the *trans*-amide **11b** had occurred under basic condit

Scheme IV



9a or **9b** **10** **11b**

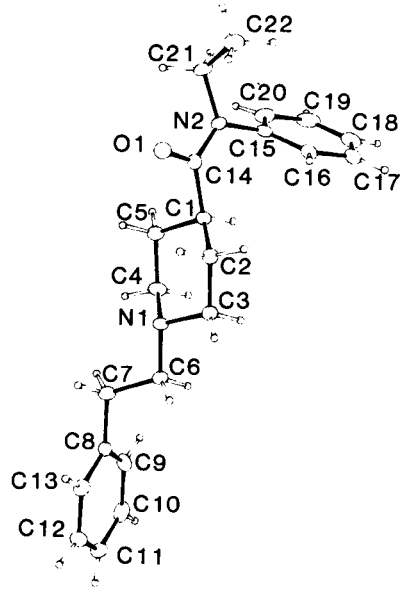


Figure 1. Compound 3

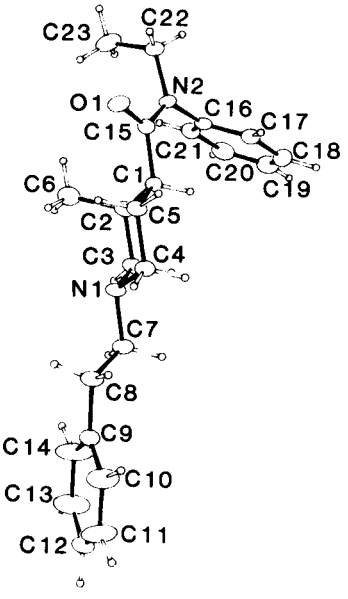


Figure 2. Compound 4a

The conversion of **9a** and **9b** to **10a** and **10b** was accomplished under acidic conditions. While hydrolysis of the *trans*-nitrile produced the *trans*- carboxylic acid, hydrolysis of the *cis*-nitrile gave a mixture of *cis* and *trans*-carboxylic acids. Proof for the existence of the latter diastereomeric mixture was based on the presence of two 3-proton doublets in the nmr spectrum due to the 3-methyl group in each isomer as well as the isolation of the two diastereomeric target fentanyl analogues **4a** and **4b** from this sample after subsequent reactions (see below). The *trans*-carboxylic acid **10b** was isolated as a white solid while the *cis*-

Table 1

Bond Lengths and Angles for **3**

Table of Bond Distances in Angstroms

Atom1	Atom2	Distance	Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C14	1.225(2)	Cl	Cl4	1.526(2)	C11	Cl2	1.385(2)
N1	C3	1.466(2)	C2	C3	1.524(2)	C12	C13	1.394(2)
N1	C4	1.471(2)	C4	C5	1.525(2)	C15	C16	1.388(2)
N1	C6	1.466(2)	C6	C7	1.530(2)	C15	C20	1.388(2)
N2	C14	1.371(2)	C7	C8	1.513(2)	C16	C17	1.393(2)
N2	C15	1.433(2)	C8	C9	1.393(2)	C17	C18	1.384(2)
N2	C21	1.478(2)	C8	C13	1.385(2)	C18	C19	1.380(2)
C1	C2	1.527(2)	C9	C10	1.393(2)	C19	C20	1.389(2)
C1	C5	1.539(2)	C10	C11	1.373(2)	C21	C22	1.507(2)

Table of Bond Angles in Degrees

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C3	N1	C4	109.1(1)	C1	C5	C4	111.0(1)	O1	C14	C1	120.9(1)
C3	N1	C6	110.0(1)	N1	C6	C7	112.1(1)	N2	C14	C1	117.9(1)
C4	N1	C6	111.1(1)	C6	C7	C8	112.5(1)	N2	C15	C16	120.2(1)
C14	N2	C15	124.5(1)	C7	C8	C9	120.1(1)	N2	C15	C20	120.1(1)
C14	N2	C21	117.0(1)	C7	C8	C13	121.2(1)	C16	C15	C20	119.7(1)
C15	N2	C21	116.8(1)	C9	C8	C13	118.7(1)	C15	C16	C17	120.3(1)
C2	C1	C5	109.4(1)	C8	C9	C10	120.2(1)	C16	C17	C18	119.9(1)
C2	C1	C14	111.2(1)	C9	C10	C11	120.4(1)	C17	C18	C19	119.5(2)
C5	C1	C14	106.9(1)	C10	C11	C12	120.2(1)	C18	C19	C20	121.1(1)
C1	C2	C3	110.7(1)	C11	C12	C13	119.4(1)	C15	C20	C19	119.5(2)
N1	C3	C2	111.0(1)	C8	C13	C12	121.1(1)	N2	C21	C22	112.5(1)
N1	C4	C5	110.9(1)	O1	C14	N2	120.9(1)				

Numbers in parentheses are estimated standard deviations in the least significant digits.

carboxylic acid **10a** was isolated initially as a viscous brown oil which turned to dry solid foams *in vacuo*. Attempts to purify **10a** which was hygroscopic, were unsuccessful. Thus, the crude mixture was used in subsequent reactions.

The target fentanyl analogues **4a** and **4b** were obtained from **10a** and **10b** respectively. Conversion of **10b** to the acid chloride with thionyl chloride, followed by acylation with *N*-ethylaniline, as previously mentioned, gave the *trans*-isomer **4b**. The product was purified first by removal of excess *N*-ethylaniline by distillation, followed by recrystallization to give white crystals. Similarly, the mixture of **10a** and **10b** was converted to the acid chlorides followed by acylation with *N*-ethylaniline to produce a mixture of the two diastereomeric products **4a** and **4b**. The two isomers were isolated in a 1:1.7 ratio, which was determined to be the *cis*- and *trans*-diastereomers **4a** and **4b**, respectively. The *cis*-isomer was isolated initially as an oil which

Table 2

Bond Lengths and Angles for **4a**

Table of Bond Distances in Angstroms

Atom1	Atom2	Distance	Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C15	1.228(2)	C2	C3	1.523(2)	C13	Cl4	1.393(2)
N1	C3	1.461(2)	C2	C6	1.520(2)	C16	C17	1.386(2)
N1	C4	1.463(2)	C4	C5	1.523(2)	C16	C21	1.391(2)
N1	C7	1.465(2)	C7	C8	1.520(2)	C17	C18	1.386(2)
N2	C15	1.368(2)	C8	C9	1.518(2)	C18	C19	1.379(3)
N2	C16	1.438(2)	C9	C10	1.364(2)	C19	C20	1.383(3)
N2	C22	1.476(2)	C9	C14	1.383(2)	C20	C21	1.389(2)
C1	C2	1.541(2)	C10	C11	1.398(2)	C22	C23	1.510(2)
C1	C5	1.527(2)	C11	C12	1.361(3)			
C1	C15	1.524(2)	C12	C13	1.366(3)			

Table of Bond Angles in Degrees

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C3	N1	C4	109.7(1)	N1	C4	C5	111.1(1)	O1	C15	C1	121.6(1)
C3	N1	C7	109.0(1)	C1	C5	C4	110.1(1)	N2	C15	C1	117.4(1)
C4	N1	C7	111.9(1)	N1	C7	C8	112.6(1)	N2	C16	C17	120.4(1)
C15	N2	C16	123.1(1)	C7	C8	C9	112.7(1)	N2	C16	C21	119.9(1)
C15	N2	C22	118.7(1)	C8	C9	C10	121.5(2)	C17	C16	C21	119.7(1)
C16	N2	C22	118.1(1)	C8	C9	C14	120.9(1)	C16	C17	C18	120.3(2)
C2	C1	C5	109.6(1)	C10	C9	C14	117.6(2)	C17	C18	C19	120.0(2)
C2	C1	C15	111.7(1)	C9	C10	C11	121.2(2)	C18	C19	C20	120.1(2)
C5	C1	C15	111.4(1)	C10	C11	C12	120.8(2)	C19	C20	C21	120.3(2)
C1	C2	C3	108.2(1)	C11	C12	C13	118.8(2)	C16	C21	C20	119.6(2)
C1	C2	C6	113.2(1)	C12	C13	C14	120.5(2)	N2	C22	C23	113.3(1)
C3	C2	C6	112.2(1)	C9	C14	C13	121.1(2)				
N1	C3	C2	112.3(1)	O1	C15	N2	120.9(1)				

Numbers in parentheses are estimated standard deviations in the least significant digits.

slowly solidified on standing and was ultimately obtained as white crystals after recrystallization. It is interesting to note that the hydrochloride and oxalate salts of **4b** are solids while those of **4a** are oils.

In ^{1}H nmr spectra, the chemical shifts of the protons of the 3-methyl group of **4a** and **4b** are quite different. The *trans*-isomer showed a doublet at δ 0.82 while the *cis* isomer exhibited a doublet at δ 1.03. Thus, the protons of a 3-methyl group are shifted upfield by shielding from the anilido phenyl group in **4b** whereas this is not possible in **4a**. This observation is supportive of the assigned stereochemistry.

Stereochemical assignments were supported by x-ray crystallographic studies of **3**, **4a**, and **4b** which are shown in Figures 1, 2, and 3, respectively. Bond lengths and angles for these structures are given in Tables 1, 2, and 3.

Table 3

Bond Lengths and Angles for **4b**

Table of Bond Distances in Angstroms

Atom1	Atom2	Distance	Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C15	1.219(3)	C2	C3	1.510(4)	C13	Cl4	1.393(4)
N1	C3	1.458(3)	C2	C6	1.505(4)	C16	C17	1.362(4)
N1	C4	1.459(3)	C4	C5	1.504(4)	C16	C21	1.382(4)
N1	C7	1.460(3)	C7	C8	1.513(4)	C17	C18	1.395(4)
N2	C15	1.359(3)	C8	C9	1.500(4)	C18	C19	1.367(5)
N2	C16	1.432(4)	C9	C10	1.384(4)	C19	C20	1.345(5)
N2	C22	1.472(4)	C9	C14	1.380(4)	C20	C21	1.379(5)
C1	C2	1.533(4)	C10	C11	1.383(4)	C22	C23	1.450(5)
C1	C5	1.543(4)	C11	C12	1.359(4)			
C1	C15	1.512(4)	C12	C13	1.388(4)			

Table of Bond Angles in Degrees

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C3	N1	C4	108.3(2)	N1	C4	C5	112.3(2)	O1	C15	C1	121.3(3)
C3	N1	C7	111.0(2)	C1	C5	C4	111.1(2)	N2	C15	C1	118.3(2)
C4	N1	C7	109.9(2)	N1	C7	C8	113.3(2)	N2	C16	C17	121.0(3)
C15	N2	C16	125.0(2)	C7	C8	C9	113.3(2)	N2	C16	C21	119.6(3)
C15	N2	C22	118.1(2)	C8	C9	C10	120.1(3)	C17	C16	C21	119.3(3)
C16	N2	C22	116.7(2)	C8	C9	C14	121.8(3)	C16	C17	C18	120.6(3)
C2	C1	C5	109.4(2)	C10	C9	C14	118.1(3)	C17	C18	C19	118.5(3)
C2	C1	C15	109.5(2)	C9	C10	C11	121.1(3)	C18	C19	C20	121.6(3)
C5	C1	C15	109.7(2)	C10	C11	C12	120.4(3)	C19	C20	C21	119.9(3)
C1	C2	C3	109.8(2)	C11	C12	C13	120.0(3)	C16	C21	C20	120.0(3)
C1	C2	C6	110.4(2)	C12	C13	C14	119.3(3)	N2	C22	C23	111.0(3)
C3	C2	C6	111.6(2)	C9	C14	C13	121.1(3)				
N1	C3	C2	112.9(2)	O1	C15	N2	120.9(3)				

Numbers in parentheses are estimated standard deviations in the least significant digits.

All three compounds crystallize with the piperidine rings in chair conformations and the phenethyl groups bonded in antiperiplanar conformations to the nitrogen atoms.

The conformation of the *N*-phenyl groups is dependent on the rotation about the C15-N2 (or C14-N2 for **3**) bonds as well as the rotation about the C1-C15 (or C1-C14 for **3**) bonds. The torsion angles (C1-C15-N2-C16) that describe the variation in the structures around the C15-N2 (or C14-N2 for **3**) bond are very similar in magnitude (**3**, −169.8°; **4a**, −172.5°; and **4b**, −177.4°). However, there is a significant difference in the torsion angles (C2-C1-C15-N2) that describe the rotation around the C1-C15 (or C1-C14 for **3**) bond (**3**, 140.0°; **41**, −69.0°; and **4b**, 130.9°). Using **3** (with no methyl group on the piperidine ring) as a reference structure, addition of a *trans*-methyl substituent to the piperidine ring at C2 (**4b**) apparently has little effect on the conformation of the *N*-phenyl ring. The closest contact between the methyl hydrogens and the

Table 4

Summary of Crystal Data, Data collection and Refinement Parameters for **3**, **4a**, and **4b**

	3	**4a** (*cis*)	**4b** (*trans*)
Chemical formula	$C_{22}H_{28}N_2O$	$C_{23}H_{30}N_2O$	$C_{23}H_{30}N_2O$
Formula weight	336	350	350
Space group	$P2_1/C$	$P2_1/C$	$P2_1/C$
Unit cell dimensions (at 100 K) a, Å	20.376(3)	13.013(4)	19.250(3)
b, Å	8.115(5)	11.025(3)	8.422(2)
c, Å	11.917(3)	15.338(5)	12.546(2)
β, °	102.91(2)	116.07(2)	98.20(1)
V, $Å^3$	1920.8	1976.5	2013.2
Number of Molecules per unit cell	4	4	4
Density calculated g cm^{-3}	1.162	1.177	1.155
Absorbtion coefficient, Mo Kα, cm^{-1}	0.77	0.78	0.76
2θ limit, degrees	50	50	46
hkl range	$0 \le h \le 24$ $0 \le k \le 9$ $-13 \le l \le 13$	$-15 \le h \le 15$ $0 \le h \le 13$ $0 \le l \le 18$	$-21 \le h \le 21$ $0 \le k \le 9$ $0 \le l \le 13$
Number of unique data measured	3689	4302	2795
Number of data used in refinement, $I>3\sigma(I)$	2492	2704	1698
Number of parameters	338	339	261
R* [a]	0.041	0.043	0.059
R_w** [b]	0.044	0.054	0.076
S*** [c]	2.74	1.73	2.41

[a] $R = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$. [b] $R_w = (\Sigma w(|F_o| - |F_c|)^2 / \Sigma w F_o^2)^{1/2}$. [c] $S = [\Sigma w(|F_o| - |F_c|)^2 / n_o n_v)]^{1/2}$.

Table **5a**

Fractional Atomic Coordinates for **3**

Table of Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	B($Å^2$)
O1	0.31546(7)	0.3192(2)	1.1946(1)	1.91(3)
N1	0.09928(8)	0.2284(2)	0.9830(2)	1.18(3)
N2	0.36565(8)	0.1262(2)	1.1049(2)	1.50(4)
C1	0.2413(1)	0.1400(3)	1.0617(2)	1.30(4)
C2	0.1922(1)	0.1307(3)	1.1416(2)	1.44(4)
C3	0.1212(1)	0.0981(3)	1.0703(2)	1.39(4)
C4	0.1434(1)	0.2292(3)	0.9002(2)	1.45(4)
C5	0.2156(1)	0.2662(3)	0.9634(2)	1.49(4)
C6	0.0292(1)	0.2012(3)	0.9217(2)	1.37(4)
C7	-0.0007(1)	0.3508(3)	0.8482(2)	2.00(5)
C8	-0.0743(1)	0.3287(3)	0.7914(2)	1.45(4)
C9	-0.1228(1)	0.4015(3)	0.8412(2)	1.49(4)
C10	-0.1905(1)	0.3847(3)	0.7876(2)	1.69(4)
C11	-0.2103(1)	0.2959(3)	0.6856(2)	1.74(4)
C12	-0.1628(1)	0.2225(3)	0.6350(2)	1.87(5)
C13	-0.0950(1)	0.2403(3)	0.6882(2)	1.78(4)
C14	0.3101(1)	0.1999(3)	1.1288(2)	1.44(4)
C15	0.3669(1)	-0.0378(3)	1.0594(2)	1.46(4)
C16	0.3439(1)	-0.1698(3)	1.1147(2)	1.53(4)
C17	0.3482(1)	-0.3304(3)	1.0742(2)	1.87(5)
C18	0.3759(1)	-0.3586(3)	0.9788(2)	2.16(5)
C19	0.3990(1)	-0.2270(3)	0.9246(2)	2.28(5)
C20	0.3942(1)	-0.0662(3)	0.9632(2)	1.94(5)
C21	0.4312(1)	0.2040(3)	1.1552(2)	1.95(5)
C22	0.4614(1)	0.1458(3)	1.2782(2)	2.67(6)

Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as: (4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) + ac(cos beta)*B(1,3) + bc(cos alpha)*B(2,3)].

N-phenyl hydrogens is between H6 on the methyl group and H21 on the phenyl group (H6---H21, 2.86 Å). However, the addition of a *cis*-methyl substituent to the piperidine ring at C2 (**4a**) causes rotation of the *N*-phenyl and *N*-ethyl groups around the C1-C15 bond in order to minimize the contacts between the methyl hydrogen atoms and the C23 hydrogen atoms on the *N*-ethyl substituent (H6---H23", 2.78 Å). In any case, the conformation of the *N*-phenyl rings in these reverse amide analogues of fentanyl is not conductive to enhanced analgetic activity.

Pharmacological testing for analgetic activity was conducted utilizing the mouse tail flick method previously described [22] and Swiss male albino mice. At a dose of 30 mg/kg a 50% increase in activity was observed for **3** with a maximal effect noted at 60 mg/kg indicating a considerable loss in activity relative to fentanyl which possesses an AD_{50} of 0.01 mg/kg.

Table 5b

Fractional Atomic Coordinates for **4a**

Table of Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	B(Å^2)
O1	0.95842(9)	0.1717(1)	0.51262(8)	2.18(3)
N1	0.8141(1)	0.1590(1)	0.16236(9)	1.69(3)
N2	1.1368(1)	0.1836(1)	0.52299(9)	1.60(3)
C1	0.9759(1)	0.1306(2)	0.3656(1)	1.51(3)
C2	0.9802(1)	0.2409(2)	0.3057(1)	1.82(4)
C3	0.9317(1)	0.2028(2)	0.1996(1)	1.94(4)
C4	0.8099(1)	0.0524(2)	0.2175(1)	1.80(4)
C5	0.8536(1)	0.0823(2)	0.3248(1)	1.70(3)
C6	0.9201(2)	0.3521(2)	0.3199(1)	2.71(5)
C7	0.7710(1)	0.1324(2)	0.0587(1)	2.04(4)
C8	0.6417(2)	0.1185(2)	0.0081(1)	2.28(4)
C9	0.5944(1)	0.1165(2)	-0.1017(1)	2.03(4)
C10	0.5222(2)	0.0271(2)	-0.1560(1)	3.10(5)
C11	0.4760(2)	0.0281(2)	-0.2573(1)	3.63(5)
C12	0.5034(2)	0.1174(2)	-0.3046(1)	2.50(4)
C13	0.5785(2)	0.2056(2)	-0.2512(2)	4.50(6)
C14	0.6227(2)	0.2063(2)	-0.1504(2)	4.61(6)
C15	1.0221(1)	0.1612(2)	0.4731(1)	1.58(3)
C16	1.2173(1)	0.1564(2)	0.4849(1)	1.64(3)
C17	1.2751(1)	0.2491(2)	0.4641(1)	2.07(4)
C18	1.3521(2)	0.2228(2)	0.4268(1)	2.62(4)
C19	1.3711(2)	0.1041(2)	0.4097(1)	2.86(4)
C20	1.3145(2)	0.0110(2)	0.4310(1)	2.60(4)
C21	1.2384(1)	0.0365(2)	0.4697(1)	1.96(4)
C22	1.1814(1)	0.2322(2)	0.6226(1)	2.02(4)
C23	1.1760(2)	0.3688(2)	0.6261(1)	3.08(5)

Table 5c

Fractional Atomic Coordinates for **4b**

Table of Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	B(Å^2)
O1	0.8050(1)	0.1497(3)	0.9430(2)	3.30(6)
N1	0.5913(2)	0.2433(4)	1.0586(2)	2.39(6)
N2	0.8562(2)	0.3798(4)	0.9975(3)	3.21(7)
C1	0.7377(2)	0.3213(4)	1.0397(3)	2.43(8)
C2	0.7176(2)	0.1850(5)	1.1104(3)	2.42(8)
C3	0.6480(2)	0.2206(5)	1.1476(3)	2.63(8)
C4	0.6087(2)	0.3794(5)	0.9956(3)	2.90(9)
C5	0.6761(2)	0.3554(5)	0.9498(3)	2.65(8)
C6	0.7745(2)	0.1583(6)	1.2040(3)	4.4(1)
C7	0.5247(2)	0.2710(5)	1.0984(3)	2.79(8)
C8	0.4960(2)	0.1247(5)	1.1470(3)	3.29(9)
C9	0.4296(2)	0.1552(4)	1.1932(3)	2.48(8)
C10	0.4313(2)	0.2424(5)	1.2870(3)	2.84(9)
C11	0.3706(2)	0.2728(5)	1.3307(3)	3.48(9)
C12	0.3079(2)	0.2147(5)	1.2831(4)	3.9(1)
C13	0.3045(3)	0.1250(5)	1.1896(4)	4.1(1)
C14	0.3657(2)	0.0968(5)	1.1452(3)	3.19(9)
C15	0.8020(2)	0.2753(5)	0.9904(3)	2.70(8)
C16	0.8616(2)	0.5223(5)	1.0604(3)	3.03(9)
C17	0.8440(2)	0.6657(5)	1.0141(3)	3.50(9)
C18	0.8524(2)	0.8048(5)	1.0750(4)	4.3(1)
C19	0.8801(2)	0.7940(6)	1.1814(4)	4.9(1)
C20	0.8984(3)	0.6535(6)	1.2280(4)	6.0(1)
C21	0.8892(3)	0.5157(6)	1.1682(4)	5.3(1)
C22	0.9175(2)	0.3374(6)	0.9454(4)	4.5(1)
C23	0.9654(3)	0.2360(7)	1.0144(5)	5.8(1)

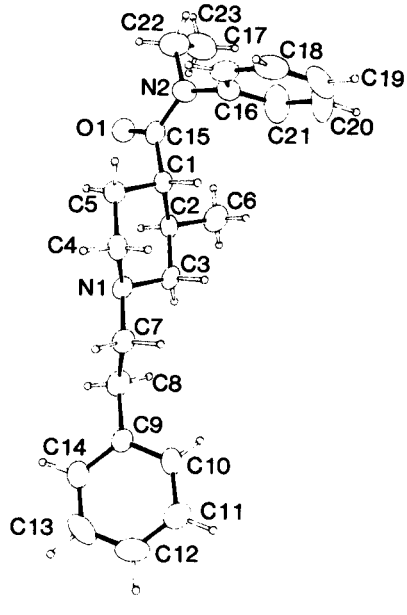


Figure 3. Compound 4b

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover Unimelt (uncorrected) or on a Mel-Temp apparatus. Infrared spectra were determined with a Perkin-Elmer Model 281B spectrometer. Solution ir spectra were taken in matched sodium chloride cells of 0.197 mm (reference) and 0.214 mm (sample) widths. All ^{1}H nmr spectra were obtained on a Varian Model EM 390 and all values are reported in ppm (δ) downfield from either TMS or DSS. Thin-layer chromatography was performed on Macherey-Nagel silica gel G (0.25 mm) with fluorescent indicator. Column chromatography was performed on Macherey-Nagel silica gel 60 (0.05-0.2 mm), and flash chromatography was performed on Merck silica gel 60 (0.040-0.063 mm). Mass spectra and gc/ms were recorded at an electron energy of 70 eV on a Finnigan 3200, MS/DS system. The term "*in vacuo*" refers to water aspirator vacuum (15-30 mm). All solvents were AR grade except those used for extraction. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

N-Phenyl-*N*-ethylisonicotinamide (**5**).

To a mixture of 23.0 g (0.187 mole) of isonicotinic acid in 275 ml of anhydrous benzene was added 57 g (0.48 mole) of thionyl chloride and the mixture was refluxed for 24 hours. Removal of benzene and excess thionyl chloride *in vacuo* gave isonicotinoyl chloride as an off-white solid which was used without further purification.

A mixture of the acid chloride and 130 g (1.07 moles) of *N*-ethylaniline was heated at 140° with stirring under nitrogen for 24 hours. Upon cooling, the dark solid material was dissolved in 200 ml of saturated sodium carbonate and extracted with ether (2 × 200 ml). After removal of ether *in vacuo*, excess aniline was distilled to leave a red oil which crystallized on standing. Recrystallization from ethyl acetate gave 12.3 g (29% based on isonicotinic acid) of white crystals, mp 112-114°; ir (chloroform): 3000 cm^{-1} (-CH_2-), 1636 cm^{-1} (C=O, amide), 1592 cm^{-1} (Ar), 1492 cm^{-1} (Ar); ^{1}H nmr (deuteriochloroform): δ 1.21 (t, 3, -CH_2CH_3), 3.97 (q, 2, -CH_2CH_3), 7.10 (m, 7, pyridine-H and ArH), 8.43 (m, 2, pyridine-H); ms: m/e 226.2 (m+), 106 (base).

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.23; N, 12.38. Found: C, 74.23; H, 6.27; N, 12.28.

1-(2-Phenylethyl)-*N*-phenyl-*N*-ethylisonicotinamide Bromide (**6**).

To a solution of 12.3 g (54.5 mmoles) of **5** in 100 ml of acetonitrile was added 12.2 g (65.9 mmoles) of phenethyl bromide and the mixture was refluxed for 24 hours. Removal of the solvent *in vacuo* gave a yellow oil which crystallized on standing. Recrystallization from ethanol/ether gave 15.8 g (71%) of white crystals; mp 216-218°; ir (potassium bromide): 2987 cm^{-1} (-CH_2-), 1645 cm^{-1} (C=O, amide); ^{1}H nmr (deuteriochloroform): δ 1.21 (t, 3, -CH_2CH_3), 3.27 (t, 2, -CH_2CH_2Ar), 3.97 (q, 2, -CH_2CH_3), 5.26 (t, 2, -CH_2CH_2Ar), 6.90-7.40 (m, 10, ArH), 7.65 (d, 2, pyridine-H), 9.23 (d, 2, pyridine-H); ms: m/e 329 (m+).

Anal. Calcd. for $C_{22}H_{23}BrN_2O$: C, 64.23; H, 5.63; N, 6.81. Found: C, 64.32; H, 5.69; N, 6.81.

N-(2-Phenylethyl)-*N'*-phenyl-*N'*-ethyl-1,2,5,6-tetrahydroisonicotinamide (**7**).

A modified procedure of Lyle, *et. al.*, [23] was followed. A solution of 15.0 g (36.6 mmoles) of **6** in 500 ml of absolute ethanol was placed in a 1-liter 3-necked round-bottomed flask equipped with a thermometer and stir bar under nitrogen. After cooling the mixture to below 10°, 5.53 g (146.2 mmoles) of sodium borohydride was added in portions while keeping the temperature below 20°. Upon completing addition of the hydride the mixture was stirred at room temperature for 20 hours. The solvent was removed *in vacuo* and the residue was dissolved in 200 ml of water. The aqueous solution was saturated with sodium chloride and extracted with chloroform (2 × 200 ml). The combined organic extracts were dried over sodium sulfate and the solvent removed *in vacuo* to give a yellow oil. Further purification was achieved by flash chromatography on silica gel 60 (ether/benzene, 1:1) to give a yellow oil which solidified on standing. Recrystallization from hexane gave 10.4 g (85%) of white crystals, mp 53-55°; ^{1}H nmr (deuteriochloroform): δ 1.13 (t, 3, -CH_2CH_3-), 2.0-2.27 (m), 2.40-2.77 (m), 2.87-2.97 (m), 3.83 (q, 2, CH_2CH_3), 5.80 (m, 1, olefinic-H), 7.0-7.43 (m, 10, ArH); ms: m/e 334.1 (m+), 243 (base).

N-(2-Phenylethyl)-*N'*-phenyl-*N'*-ethylisonipecotinamide (**3**).

A solution of 5.1 g (15 mmoles) of **7** and 150 ml of 0.4 *N* potassium hydroxide in ethanol and 275 mg of 10% palladium on charcoal was hydrogenated (50 psi) at room temperature for 3 weeks. After filtering over Celite, the filtrate was transferred to a separatory funnel and 100 ml of water was added and extracted with ether (2 × 100 ml). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to yield a yellow solid which was recrystallized from ethyl acetate and washed with hexane to give 2.8 g (27%) of white crystals, mp 106-107°; ir (chloroform): 3000 cm^{-1} (-CH_2-), 2945 cm^{-1} (-CH_2-), 1636 cm^{-1} (C=O, amide), 1592 cm^{-1} (Ar), 1492 cm^{-1} (Ar); ir (potassium bromide): 1640 cm^{-1} (C=O, amide); ^{1}H nmr (deuteriochloroform): δ 1.13 (t, 3, -CH_2CH_3), 1.53-2.23 (m), 2.37-3.1 (m), 3.83 (q, 2, -CH_2CH_3), 7.13-7.58 (m, 10, ArH); ms: m/e 336.9 (m+) 96 (base).

Anal. Calcd. for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.33; H, 8.38; N, 8.29.

1-(2-Phenylethyl)-3-methyl-4-cyanopiperidine (**9a-b**).

A 2-ℓ 3-necked round-bottomed flask equipped with a thermometer and 2 dropping funnels was charged with 12.24 g (56 mmoles) of **8** [20] and 340 ml of anhydrous 1,2-dimethoxyethane under nitrogen. One dropping funnel was charged with a solution of 19.0 g (170 mmoles) of potassium *t*-butoxide in 135 ml of warm *t*-butyl alcohol (freshly distilled and stored over potassium carbonate) while the other funnel contained a solution of 17.0 g (87 mmoles of tosylmethyl isocyanide in 190 ml of anhydrous 1,2-dimethoxyethane. The flask was cooled to −10° and stirred magnetically with simultaneous dropwise addition of the contents of the dropping funnels. The rate of addition was monitored such that the temperature did not exceed 0°. The mixture was stirred at room temperature for 2.5 hours and then concentrated *in vacuo*, diluted with 500 ml of water and extracted with ether (2 × 500 ml). The combined ether extracts were dried over sodium sulfate. Evaporation of ether *in vacuo* yielded an orange oil which gave two spots by thin-layer chromatography.

Column chromatography of the crude oil on silica gel 60 ethyl acetate/petroleum ether, 1:1), gave a white solid with R_f = 0.57, which contained a mixture of the *trans*-isomer (**9b**) and a tosylmethyl isocyanide derivative. This was taken up in hot petroleum ether and filtered to remove the insoluble tosylmethyl isocyanide derivative, and **9b** crystallized out in the filtrate to give 4.56 g (60% of the recovered product) of the *trans*-isomer **9b**, mp 76-78°; ir (chloroform): 2950 cm^{-1} (-CH_2-), 2800 cm^{-1} (CH_2-), 2237

cm^{-1} (-CN); ^1H nmr (deuteriochloroform): δ 0.97 (d, 3, -CHCH_3), 1.43-2.02 (m), 2.30-3.05 (m), 7:12 (s, 5, ArH); ms: m/e 228 (m+), 137 (base).

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.83; H, 8.86; N, 12.19.

In addition to a fraction containing both isomers a fraction containing 3.05 g (40% of the recovered pure product) of the *cis*-isomer (**9a**) with R_f = 0.24 was obtained as a yellow oil; ir (neat): 2952 cm^{-1} (-CH_2-), 28.05 cm^{-1} (-CH_2-), 2237 cm^{-1} (-CN), ^1H nmr (deuteriochloroform): δ 0.97 (d, 3, -CHCH_3), 1.78-2.83 (m), 7.13 (s, 5, ArH); ms: m/e 228 (m+), 137 (base). The hydrochloride salt was prepared and recrystallized from ethanol/ethyl acetate to give white crystals, mp 219-221°.

Anal. Calcd. for $C_{15}H_{21}N_2Cl$: C, 68.03; H, 7.99; N, 10.58. Found: C, 68.11; H, 8.03; N, 10.56.

trans-1-(2-Phenylethyl)-3-methylisonipecotinamide (**11b**).

A solution of 1.57 g (6.9 mmoles) of **9b** in 25 ml of 10% sodium hydroxide and 40 ml of ethanol was refluxed for 6 hours. After removing ethanol *in vacuo*, the resulting precipitate was filtered and the filter cake dissolved in 50 ml of chloroform, washed with 50 ml of water and dried over sodium sulfate. Concentration *in vacuo* yielded a white solid which was recrystallized from ethyl acetate to give 286 mg (17%) of white crystals, mp 168-170°; ir (chloroform): 3520 cm^{-1} (NH_2, amide), 3405 cm^{-1} (NH_2, amide), 2946 cm^{-1} (-CH_2-), 2807 cm^{-1} (-CH_2-), 1674 cm^{-1} (C=O, amide); ^1H nmr (deuteriochloroform): δ 0.90 (d, 3, -CHCH_3), 1.50-2.10 (m), 2.40-3.13 (m), 5.87 (bd, 2, NH_2, exchange with deuterium oxide), 7.22 (s, 5, ArH); ms: m/e 246 (m+), 155 (base).

Attempted Synthesis of *cis*-1-(2-Phenylethyl)-3-methylisonipecotinamide (**11a**).

A procedure analogous to that for the synthesis of **11b** was used. A solution of 1.0 g (4.4 mmoles) of **9a** in 15 ml of 10% sodium hydroxide and 25 ml of ethanol was refluxed for 6 hours. After removing ethanol *in vacuo*, the resulting precipitate was filtered and the filter cake dissolved in 50 ml of chloroform, washed with 50 ml of water and dried over sodium sulfate. Concentration *in vacuo* yielded a white solid which was recrystallized from ethyl acetate to give 195 mg (19%) of white crystals, mp 168-170°; ^1H nmr data were identical to that of **11b**, thus the product was the *trans*-isomer.

trans-1-(2-Phenylethyl)-3-methylisonipecotic acid (**10b**).

A solution of 31 ml of water and 26 ml of concentrated sulfuric acid was cooled and added to 6.3 g (27.6 mmoles) of **9b**. The resulting solution was refluxed with stirring for 6 hours. After cooling in an ice bath, the solution was neutralized with 35% sodium hydroxide and the precipitate was filtered. The filter cake was added to boiling ethanol and the inorganic salts were filtered. The product **10b** crystallized out in the filtrate and was filtered and dried at 40° *in vacuo* in a drying oven overnight. After filtering the remaining inorganic salts, the dried crystals were recrystallized from absolute ethanol to give 1.8 g (26%) of white crystals, mp 140-141°; ir (potassium bromide): 1665 cm^{-1} (CO_2-, amino acid), 1580 cm^{-1} (CO_2-, amino acid); ^1H nmr (deuterium oxide): δ 0.88 (d, 3, -CHCH_3), 1.97 (bs, 4), 2.48-3.70 (m, 9), 4.67 (s, H_2O), 7.40 (s, 5, ArH); ms: m/e 246 (m+ −1), 156 (base).

Anal. Calcd. for $C_{15}H_{21}NO_2 \cdot H_2O$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.91; H, 8.73; N, 5.26.

cis-1-(2-Phenylethyl)-3-methylisonipecotic Acid (**10a**).

A procedure analogous to that for the synthesis of **10b** was used. A solution of 15 ml of water and 12 ml of concentrated sulfuric acid was cooled and added to 3.1 g (12.8 mmoles) of **9a**. The resulting solution was refluxed with stirring for 6 hours. After cooling in an ice bath, the solution was neutralized with 35% sodium hydroxide and the precipitate was filtered. The residual brown oil from the precipitate-aqueous phase mixture was dried *in vacuo* to give solid foams, which were added to boiling ethanol. After filtering the inorganic salts, the ethanol was removed *in vacuo* to afford a brown oil which foamed to give brown crystals *in vacuo*. The aqueous filtrate was removed *in vacuo* and the resulting solid was heated in ethanol and filtered. The filtrate was evaporated *in vacuo* to give a brown oil which foamed *in vacuo* to give brown crystals. All the brown crystals were combined and dried *in vacuo* in a drying oven overnight. The crystals were then dissolved in boiling absolute ethanol and filtered to remove remaining inorganic salts. The ethanol was evaporated *in vacuo* to yield a brown oil which foamed *in vacuo* to give brown crystals. Drying *in vacuo* overnight gave 3.14 g (99%) of brown crystals which resisted attempts to recrystallize, mp 85-95°; ^1H nmr (deuterium oxide): δ 0.81 (d, 3, -CHCH_3 for *trans*- (**10b**)), 1.07 (d, 3, -CHCH_3 for *cis*-(**10b**)), 1.80-2.35 (m), 2.5-5.8 (m), 4.70 (s, H_2O), 7.40 (s, 5, ArH).

trans-*N*-(2-Phenylethyl)-3-methyl-*N'*-phenyl-*N'*-ethylisonipecotinamide (**4b**).

To a mixture of 1.45 g (5.9 mmoles) of **10b** in 25 ml of anhydrous benzene was added 3.26 g (27 mmoles) of thionyl chloride and the resulting solution was refluxed with stirring under nitrogen for 24 hours. Removal of benzene and excess thionyl chloride *in vacuo* gave the acid chloride as a solid which was used without further purification.

A mixture of the acid chloride and 9.6 g (79.3 mmoles) of *N*-ethylaniline was heated at 130° for 48 hours with stirring under nitrogen. Upon cooling, the mixture was dissolved in 25 ml of chloroform and 25 ml of 20% sodium carbonate was added. The mixture was extracted with chloroform (2 × 25 ml) and the combined extracts were dried over sodium sulfate. Removal of the solvent *in vacuo* and distillation of excess *N*-ethylaniline yielded a brown oil which solidified on standing. Recrystallization from ethyl acetate/hexane gave 305 mg (15% based on **10b**) of white crystals, mp 94-95°; ir (potassium bromide): 2930 cm^{-1} (-CH_2-), 2801 cm^{-1} (-CH_2-), 1637 cm^{-1} (C=O, amide), 1585 cm^{-1} (Ar), 1488 cm^{-1} (Ar); ^1H nmr (deuteriochloroform): δ 0.82 (d, 3, -CHCH_3), 1.12 (t, 3, -CH_2CH_3), 1.42-1.90 (m), 2.30-3.03 (m), 3.77 (q, 2, -C$H_2$$CH_3$), 7.07-7.47 (m, 10, ArH); ms: m/e 350 (m+), 259 (base). The oxalate salt was prepared and recrystallized from ethanol, mp 209-210°. The hydrochloride salt was also prepared, mp 249-250°.

Anal. Calcd. for $C_{23}H_{30}N_2O \cdot C_2H_2O_4$: C, 68.15; H, 7.32; N, 6.36. Found; C, 67.96; H, 7.35; N, 6.32.

cis-*N*-(2-Phenylethyl)-3-methyl-*N*-phenyl-*N'*-ethylisonipecotinamide (**4a**).

A procedure analogous to that for the synthesis of **4b** was used. To a mixture of 3.14 g (12.5 mmoles) of **10a-b** in 40 ml of anhydrous benzene was added 7.3 g (61.9 mmoles) of thionyl chloride and the resulting solution was refluxed with stirring under nitrogen for 24 hours. Removal of benzene and excess thionyl chloride *in vacuo* gave a mixture of acid chlorides as a dark oil which was used without further purification.

This mixture and 9.6 g (79.3 mmoles) of *N*-ethylaniline was heated at 130° with stirring under nitrogen for 48 hours. After

cooling, the mixture was dissolved in 50 ml of chloroform and 50 ml of 20% sodium carbonate was added. The mixture was extracted with chloroform (2 × 50 ml) and the combined extracts were dried over sodium sulfate. Concentration *in vacuo* and distillation of excess *N*-ethylaniline gave a dark oil **4** which gave two spots with R_f = 0.37 and 0.25 by thin-layer chromatography.

Column chromatography of the mixture on silica gel 60 (ethyl acetate/pet ether, 1:1) gave an orange oil with R_f = 0.37 (ethyl acetate with 1% ammonium hydroxide) which was determined to be the *cis*-isomer (**4a**). This oil solidified on standing and was recrystallized from ethyl acetate/hexane to give 34 mg (37% of the recovered pure product) of white crystals, mp 88-90°; ir (neat): 2925 cm^{-1} (-CH_2-), 2800 cm^{-1} (-CH_2-), 1645 cm^{-1} (C=O, amide), 1592 cm^{-1} (Ar), 1492 cm^{-1} (Ar); ^1H nmr (deuteriochloroform): δ 1.00-1.22 (t centered at 1.13 overlapping a doublet centered at 1.03, 6, -CH_2CH_3 and -$CHCH_3$), 1.43-2.233 (m), 2.37-3.03 (m), 3.75 (q, 2, -CH_2CH_3), 7.10-7.47 (m, 10, ArH); ms: m/e 350 (m+), 259 (base). A solid salt could not be obtained.

Anal. Calcd. for $C_{23}H_{30}N_2O$: C, 78.81; H, 8.62; N, 7.99. Found: C, 78.71; H, 8.63; N, 7.90.

X-Ray Structure Determination of **3**, **4a**, and **4b**.

Single crystals of **3**, **4a** and **4b** were mounted separately for low temperature data collection on an Enraf-Nonius CAD-4 diffractometer with graphite crystal monochromator and a molybdenum target X-ray tube. The setting angles for 25 accurately centered reflections were used to refine the unit cell parameters given in Table 4. Table 4 also includes a summary of data collection and refinement parameters. All three-dimensional intensity data were collected at 100 K in the ω:2θ scan mode. Three standard reflections were measured every two hours to check crystal and electronic stability. Only **4b** showed a significant change in intensity (9%). The data were corrected using a linear decay model. Absorption scans of each crystal were measured as a function of psi and only **3** showed a loss in intensity due to absorption (minimum transmission = 82.3%). The data were corrected empirically.

All three structures were solved by direct methods using MULTAN 11/82 [24]. Non-hydrogen atoms were located on the E-maps. Hydrogen atoms for **3** and **4a** were located on the difference fourier maps. Most of the hydrogen atoms for **4b** were located on the difference Fourier maps but the remaining hydrogen atoms were calculated on the basis of sp^2 or sp^3 geometry and a C-H bond length of 0.95 Å.

Refinement was by full-matrix least-squares. All non-hydrogen atoms were refined with anisotropic temperature factors. The positions and isotropic temperature factors for the hydrogen atoms from **3** and **4a** were refined. The hydrogen atom positions in **4b** were held fixed while the isotropic temperature factors were allowed to refine. The weighting scheme used was $w = 1/\sigma(F)^2$ where $\sigma(F)^2 = [\sigma(I)_{cs}^2 + (0.04)^2(F^2)^2]$ and $\sigma(I)_{cs}$ represents the contribution from counting statistics.

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