Carbon-13 Nuclear Magnetic Resonance Spectra of Fentanyl Analogs

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Natural abundance carbon-13 chemical shifts are reported for the hydrochloride salts of fentanyl (**1a**) and fifteen analogs. The signals are assigned on the basis of chemical shift theory, SFORD multiplicities, signal intensities, comparisons with model compounds, and thiophene carbon-proton coupling constants. In addition to its forensic value, the data suggest that the solution conformations of the analogs are similar to that of fentanyl hydrochloride.

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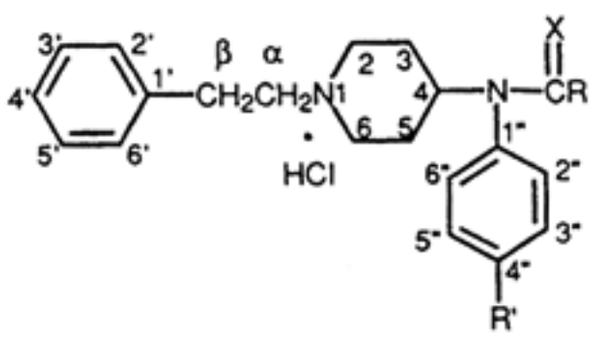
The high analgesic potency and relative ease of preparation of fentanyl (**1a**) and many of its analogs have made these compounds attractive candidates for illicit use [1]. Beginning with the identification of street samples of "China White" as α-methylfentanyl (**8**) [2], several fentanyl analogs have been identified as drugs of abuse [3]. As a consequence a number of reports on spectroscopic methods for the identification of fentanyl (**1a**) and its analogs have appeared [4-6]. In this paper we report the carbon-13 chemical shifts of fifteen fentanyl analogs. In addition to its forensic value, our data suggest that the solution conformations of these analogs are similar to that of fentanyl (**1a**) hydrochloride.

The compounds examined in the present study are summarized in Charts I and II. The ^{13}C nmr spectra were obtained on the hydrochloride salts under conditions described in the Experimental. Signal assignments were made on the basis of ^{13}C nmr chemical shift theory, multiplicities as obtained by single-frequency off-resonance decoupling (SFORD) experiments, signal intensities, and comparisons to the model compounds shown in Chart III. In addition, the thiophene carbon-proton primary coupling constants were used to verify the assignments of the thiophene C-5′ resonances. In the case of α-methylfentanyl (**8**), we also compared our assignments to previously reported values [6]. The chemical shift assignments are summarized in Tables I and II.

Chart I



1a ; R = CH_2CH_3, R′ = H, X = O

1b ; R = CH_3, R′ = H, X = O

1c ; R = $CH_2CH_2CH_3$, R′ = H, X = O

1d ; R = $CH(CH_3)_2$, R′ = H, X = O

1e ; R = $CH_2(CH_2)_2CH_3$, R′ = H, X = O

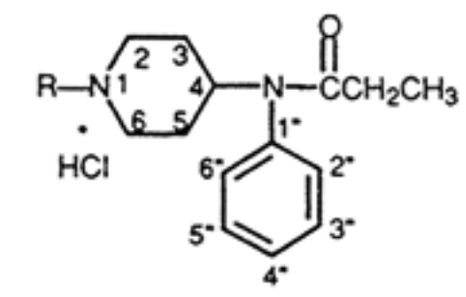
2 ; R = CH_2CH_3, R′ = H, X = S

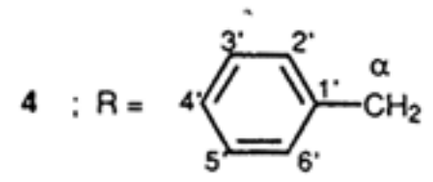
3a ; R = CH_2CH_3, R′ = CH_3, X = O

3b ; R = CH_2CH_3, R′ = OCH_3, X = O

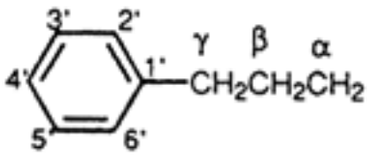
3c ; R = CH_2CH_3, R′ = F, X = O

Chart II

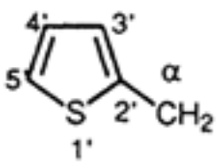




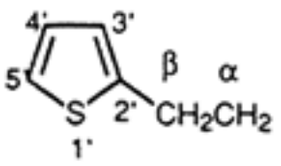
4 ; R =



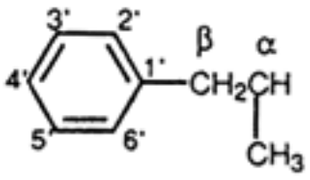
5 ; R =



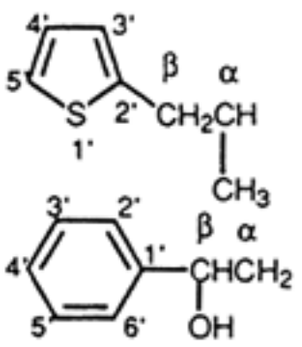
6 ; R =



7 ; R =



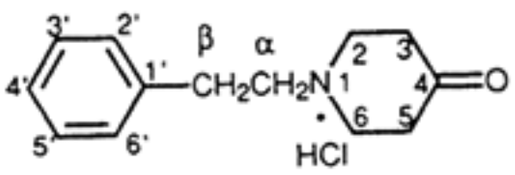
8 ; R =



9 ; R =

10 ; R =

Chart III



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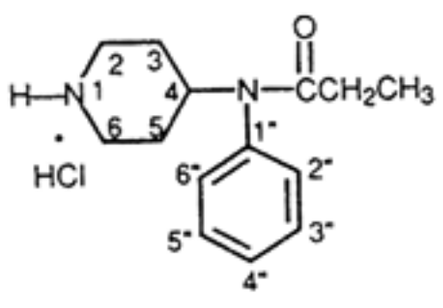

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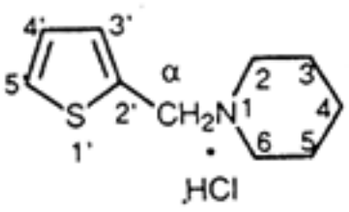

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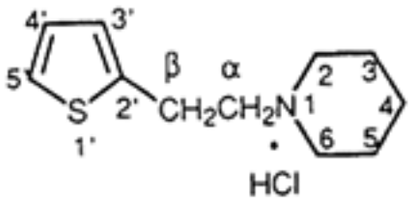

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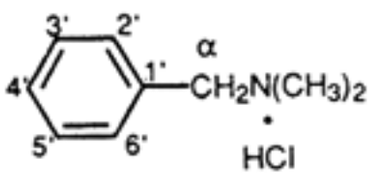

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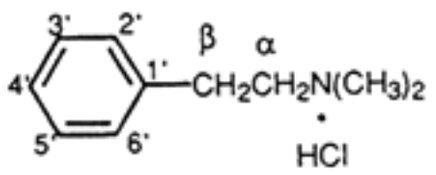

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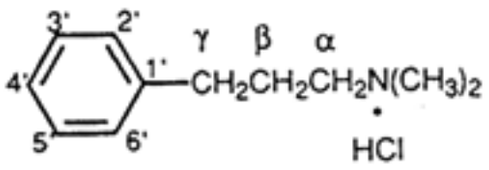

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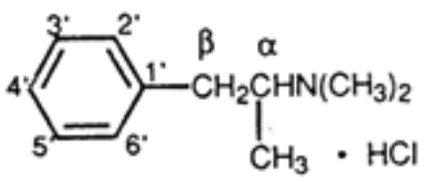

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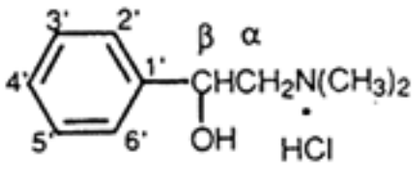

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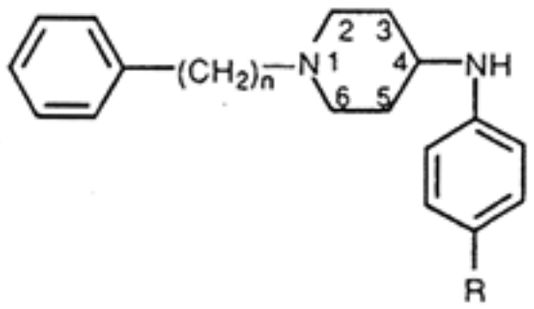
Chart IV



20a ; n = 2, R = H

20b ; n = 2, R = CH_3

20c ; n = 2, R = OCH_3

20d ; n = 2, R = F

20e ; n = 1, R = H

Discussion.

The piperidine C-4 resonance was distinguished by its chemical shift, its appearance as a doublet in the SFORD spectra, and its consistency throughout the entire series of analogs (*cf.* Table I). With three exceptions, the four remaining piperidine carbons gave rise to two two-carbon signals (SFORD triplets) which were differentiated from other methylene resonances on the basis of signal intensity. Of these, the upfield signal was assigned to the piperidine 3,5 carbons and the downfield signal to the piperidine 2,6 carbons. With the exception of analogs **8**, **9** and **10**, both of these resonances also had consistent chemical shifts. The γ-effect of the α-methyl group in analogs **8** and **9** was expected to cause a small upfield shift of the piperidine C-2,6 signal and the δ-effect of the β-hydroxyl group in analog **10** was expected to cause a smaller downfield shift [7]. As shown in Table I, both of the expected shifts were observed. In addition, the piperidine 2,6-carbons in analogs **8**, **9** and **10** appeared as separate resonances due to the molecular asymmetry introduced into the 1-(β-phenylethyl) substituent by the α-methyl and β-hydroxyl groups. Both we [8] and others [9] have observed a similar molecular asymmetry effect in the ^{13}C nmr spectra of barbiturates.

The propanamide carbon resonances were easily distinguished on the basis of chemical shift theory, signal intensities, SFORD multiplicities and their consistency in all the analogs which had this particular amide group. Variation of the amide group (**1b-1e**, **2**) had no discernible effect on resonances in the remainder of the molecule. The chemical shift assignments for the carbons in the other amide groups paralleled known assignments in simpler amides or the corresponding carboxylic acids [10,11]. The one anomaly was that the thioamide carbonyl carbon resonance was shifted downfield only slightly from that of the fentanyl amide carbonyl carbon [12].

The consistency of the propanamide methyl resonance at 9.3-9.4 ppm helped distinguish it from the α-methyl resonance at 12.5-12.6 ppm in analogs **8** and **9**. In the case of α-methylfentanyl (**8**), our assignment of these resonances was reversed from the previously reported [6] assignment. The methyl signals in the spectra of analogs **3a** and **3b** were distinguished by their appearance as quartets in the SFORD spectra and their downfield position relative to the propanamide methyl resonance.

The α and β carbons of the phenylethyl moiety of the analogs shown in Chart I gave rise to two one-carbon resonances (SFORD triplets) of which the more downfield signal was assigned to the carbon bonded to the nitrogen. These signals were differentiated from other methylene resonances on the basis of signal intensity, the consistency of the propanamide methylene resonance in analogs **4-10**,

Table I

Carbon-13 Nuclear Magnetic Resonance Chemical Shifts of Fentanyl Hydrochloride and Its Analogs in Dimethyl Sulfoxide-d_6 Solution

Compound Carbon	**1a**	**1b**	**1c**	**1d**	**1e**	**2**	**3a**	**3b**
2,6 [a]	50.96	50.68	50.75	50.88	50.68	50.88	50.75	50.75
3,5 [a]	27.36	27.16	27.24	27.26	27.16	27.21	27.24	27.16
4	49.13	49.01	49.01	49.09	49.09	49.06	49.01	49.01
α	56.49	56.29	56.29	56.35	56.29	56.34	56.37	56.35
β	29.56	29.28	29.28	29.48	29.28	29.41	29.36	29.28
γ								
α-CH_3								
C=O (S)	172.19	168.88	171.15	175.64	171.31	175.53	172.22	172.49
CH_2CH_3	27.74		18.06		21.55	31.08	27.62	27.50
$CH_2CH_2CH_3$			36.04		26.86			
$CH_2(CH_2)_2CH_3$					33.76			
CH_3		22.99						
CH_2CH_3	9.38		13.50		13.50	19.32	9.33	9.30
$CH(CH_3)_2$				31.16				
$CH(CH_3)_2$ [a]				19.40				
ArCH_3							20.56	
ArOCH_3								55.26
1′ (2′) [b]	137.06	137.09	137.01	137.07	137.09	136.99	137.09	137.10
2′,6′ [a] (3′)	128.64 [c]	128.52 [c]	128.52 [c]	128.62 [c]	128.52 [c]	128.57 [c]	128.52 [d]	128.51 [d]
3′,5′ [a] (4′)	128.64 [c]	128.52 [c]	128.52 [c]	128.62 [c]	128.52 [c]	128.57 [c]	128.52 [d]	128.51 [d]
4′ (5′)	126.75	126.62	126.62	126.78	126.62	126.67	126.62	126.61
1″	138.20	138.53	138.08	138.10	138.08	138.05	135.42	130.53
2″,6″ [a]	130.39	130.03	130.19	130.13	130.19	130.08	129.96 [d]	131.22
3″,5″ [a]	129.48	129.35	129.35	129.48	129.35	129.40	129.96 [d]	114.42
4″	128.64 [c]	128.52 [c]	128.52 [c]	128.62 [c]	128.52 [c]	128.57 [c]	137.85	158.82

Compound Carbon	**3c**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
2,6 [a]	50.75	50.66	50.82	50.17	51.04	46.70	46.35	50.66
						48.09	48.13	52.56
3,5 [a]	27.08	27.09	27.69	27.09	27.69	27.65	27.18	27.69
4	49.01	49.25	49.14	49.20	49.09	49.24	49.07	48.98
α	56.37	58.84	55.37	52.29	56.24	62.03	61.76	62.36
β	29.36		32.02		23.90	36.37	30.53	66.70
γ			24.87					
α-CH_3						12.50	12.51	
C=O (S)	172.14	174.12	172.17	172.17	172.17	172.27	172.12	172.12
CH_2CH_3	27.62	27.74	27.26	27.69	27.31	27.44	27.63	27.09
$CH_2CH_2CH_3$								
$CH_2(CH_2)_2CH_3$								
CH_3								
CH_2CH_3	9.26	9.43	9.38	9.38	9.38	9.33	9.33	9.43
$CH(CH_3)_2$								
$CH(CH_3)_2$ [a]								
ArCH_3								
ArOCH_3								

Table I (continued)

1′ (2′) [b]	137.09	129.97	140.54	130.30	138.75	136.98	138.55	141.73
2′,6′ [a] (3′)	128.52 [d]	131.33	128.18	132.30	125.91	129.13 [e]	126.62	125.96
3′,5′ [a] (4′)	128.52 [d]	128.73	128.40 [e]	127.48	127.21	128.51	127.14	128.29
4′ (5′)	126.70	129.48 [e]	126.07	129.10	124.77	126.71	125.02	127.70
1″	134.28	138.15	138.15	138.10	138.15	138.25	138.16	138.15
2″,6″ [a]	132.61	130.30	130.30	130.30	130.35	130.31	130.28	130.41
	132.23							
3″,5″ [a]	116.68	129.48 [e]	129.43	129.43	129.48	129.41	129.34	129.43
	115.70							
4″	156.13	128.51	128.40 [e]	128.45	128.51	129.13 [e]	128.37	128.46

[a] Unless otherwise indicated, the resonances for these carbons were twice as intense as other similar resonances. [b] The numbers in parenthesis are for the thiophene carbons. [c] These resonances were five times as intense as other similar resonances. [d] These resonances were four times as intense as other similar resonances. [e] These resonances were three times as intense as other similar resonances.

Table II

Carbon-13 Nuclear Magnetic Resonance Chemical Shifts of the Model Compounds in Dimethyl Sulfoxide-d_6 Solution

Compound Carbon	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
2,6 [a]	49.61	42.59	50.77	51.85					
3,5 [a]	36.80	26.99	21.95	22.24					
4	202.76	49.31	21.35	21.41					
α	55.27		52.11	56.27	59.11	57.04	55.94	61.56	62.67
β	29.58			23.59		29.65	31.89	35.96	66.89
γ							25.15		
α-CH_3								11.97	
$C=O$		172.07							
CH_2CH_3		27.69							
CH_2CH_3		9.38							
$N(CH_3)_2$					41.23	41.77	41.74	37.53	42.70 [g]
1′(2′) [b]	136.95		130.37	138.93	130.45	137.01	140.48	136.89	141.71
2′,6′ [a] (3′)	128.56 [d]		132.29	125.72	130.98	128.57 [f]	128.17 [f]	129.15	125.90
3′,5′ [a] (4′)	128.56 [d]		127.31	127.13	128.62	128.52 [f]	128.31 [f]	128.48	128.19
4′ (5″)	126.67		128.93	124.63	129.22	126.65	125.99	126.66	127.57
1″		138.26							
2″,6″ [a]		130.35							
3″,5″ [a]		129.43							
4″		128.45							

[a], [b] and [d]: see notes to Table I. [f] Assignments in any one column may be interchanged. [g] At room temperature (*ca.* 298° K), this resonance appeared as a broad hump. At 360° K, it appeared as a sharp singlet at 42.58 ppm.

and comparison to model compound **16** [13]. The modifications of the phenylethyl moiety expressed in analogs **4-10** (*cf.* Chart II) had the expected effects on the chemical shifts and SFORD multiplicties of these carbons. For six analogs (**4-8,10**) the assignments summarized in Table I were confirmed by comparison to a simpler model compound (*cf.* Chart III and Table II). The α carbon resonance (SFORD doublet) of analog **9** appeared at essentially the same position as the α carbon resonance of α-methylfentanyl (**8**) while the β carbon signal was shifted upfield about 5.8 ppm. An upfield shift of the same magnitude was observed for the β carbon signal when the 2-(2-thienyl)ethyl analog **7** was compared to fentanyl (**1a**).

In the ^{13}C nmr spectrum of fentanyl (**1a**) hydrochloride, the phenyl C-1′ and C-1″ resonances were distinguished from the other aromatic resonances by their appearance as singlets in the SFORD spectrum. Assignment of all the aromatic resonances in the fentanyl spectrum (*cf.* Table I)

was made possible by comparison to the spectra of model compounds **11**, **12** and **16** (*cf.* Chart III and Table II). In addition to the C-1′ and C-1″ signals, the resonances due to C-4′, C-2″,6″ and C-3″,5″ were easily differentiated. The remaining five aromatic carbons appeared as a five-carbon resonance at 128.64 ppm. Similar aromatic carbon signals were observed in the spectra of analogs **1b-e** and **2**. Thus, the assignments were similar (*cf.* Table I).

Some support for the above aromatic carbon assignments was obtained from the spectra of analogs **3a-c**, which had substituents in the para position of the anilide ring. The aromatic carbons of the phenylethyl moiety gave rise to signals at 137.1 (C-1′), 126.6 (C-4′) and 128.5 ppm (C-2′, 3′, 5′, 6′), in good agreement with the signals observed in the spectra of compounds **1a-e** and **2**. The remaining aromatic carbon resonances in each spectrum were attributed to the anilide ring. In each case, the observed chemical shifts were compared with values calculated from the corresponding carbons of fentanyl (**1a**) hydrochloride using the appropriate aromatic substituent parameters [14]. The excellent agreement between the observed and calculated values resulted in the assignments shown in Table I. In addition, the C-4″ carbon was distinguished by its appearance as a singlet in the SFORD spectrum. As depicted in Table I, very small chemical shift differences between C-2″ and C-6″ and between C-3″ and C-5″ were observed in the spectrum of analog **3c**.

In the spectra of analogs **4-10**, the chemical shifts of the anilide ring aromatic carbons were essentially identical to those observed in the spectra of compounds **1a-e** and **2**. The anilide carbon resonances were easily differentiated from the thiophene carbon signals (**6**, **7** and **9**) on the basis of signal intensity, chemical shift, and comparison to model compounds **13** and **14** (*cf.* Chart III and Table II). For the rest of the analogs (**4**, **5**, **8** and **10**), the chemical shifts of the remaining aromatic carbons varied due to the different alkyl groups linking the aromatic ring to the piperidine nitrogen. Assignment of these latter aromatic carbon resonances was facilitated by comparison of the analog spectra to the spectra of model compounds **15**, **17**, **18** and **19**. For the most part distinguishing these latter resonances from the anilide carbon resonances was straightforward, although in three instances some overlap did occur (*cf.* Table I). In the case of analogs **4** and **6**, the phenyl C-1′ signal and thiophene C-2′ signal were observed more easily in the SFORD spectra.

The thiophene C-2′ signal in the spectra of analogs **6**, **7** and **9** was also distinguished by its appearance as a singlet in the SFORD spectra. The other easily differentiated thiophene resonance was that of C-4′, whose chemical shift was only slightly affected by the subsitution at C-2′ [15]. The C-3′ and C-5′ resonances were assigned on the basis that C-3′ appeared further downfield in the spectrum of thiophene and that alkyl substitution at C-2′ caused similar shifts of the C-3′ and C-5′ signals [15]. Confirmation of the assignment of the thiophene C-5′ signal was provided by obtaining the proton coupled ^{13}C nmr spectra of model compounds **13** and **14** (*cf.* Chart III) and elucidating the thiophene carbon-proton primary coupling constants ($^1J_{CH}$). For compound **13** the following coupling constant values were observed for the protonated carbon resonances: 127.31 ($^1J_{CH}$ 169 hertz), 128.93 ($^1J_{CH}$ 188 hertz), and 132.29 ppm ($^1J_{CH}$ 168 hertz). For compound **14** the values were as follows: 124.63 ($^1J_{CH}$ 188 hertz), 125.74 ($^1J_{CH}$ 173 hertz), and 127.18 ppm ($^1J_{CH}$ 165 hertz). As C-5′ was bonded directly to the sulfur, its expected $^1J_{CH}$ value was 189 hertz whereas the expected value for C-3′ and C-4′ was 168 hertz [16]. Consequently, the observed $^1J_{CH}$ coupling constants verified the assignment of the thiophene C-5′ resonance in both of the model compounds (*cf.* Table II) and in analogs **6**, **7** and **9** (*cf.* Table I).

An X-ray crystallographic analysis of fentanyl citrate indicated a solid state conformation in which the piperidine ring was in a chair conformation and the bulky 1-(β-phenylethyl) and 4-propionanilide substituents occupied equatorial positions [17]. Previous ^1H nmr data had implied a similar conformation in solution [1]. The present ^{13}C nmr data (*cf.* Table I) not only were compatible with the same solution conformation but also suggested that all of the analogs examined in the present study had a solution conformation similar to that of fentanyl (**1a**) hydrochloride. A key observation was the consistency of the piperidine carbon resonances over the entire series of analogs. Moreover, in the spectra of analogs **8**, **9** and **10**, it was possible to rationalize the observed shifts in the piperidine C-2,6 resonances in terms of substituent effects without invoking conformational changes. The implication of a similar solution conformation for both fentanyl hydrochloride and the various analogs was in agreement with earlier ^1H nmr data obtained on the free bases [5].

It is apparent from the present study that the fentanyl analogs are easily differentiated from each other by ^{13}C nmr. A similar differentiation using ^1H nmr is often more difficult. Consequently, it is anticipated that ^{13}C nmr will become increasingly useful for the identification of forensic samples.

EXPERIMENTAL

Melting points were determined on a Hoover capillary apparatus and are uncorrected. The optical rotation of compound **18** was obtained in methanol solution on a Rudolph Research Autopol III Polarimeter. Anhydrous sodium sulfate was routinely used to dry organic solutions. Elemental analyses were carried out by Atlantic Microlab Inc., Atlanta, GA, and Galbraith Laboratories, Inc., Knoxville, TN. A sample of α-methylfentanyl hydrochloride (**8**) was obtained from the Drug Enforcement Administration through the courtesy of the National Institute on Drug Abuse.

The natural abundance ^{13}C nmr spectra were run on either a JEOL FX-90Q nmr spectrometer or a Bruker WM-250 nmr spectrometer. The latter instrument was interfaced with a 80K Aspect 3000 data system with an Array processor and a 32M CDC disk. Generally the spectra were obtained on 0.5 mole of analog and 0.10 mole of model compound in 0.3 ml of solvent. Samples were run at ambient temperature in 5 mm o.d. tubes, using the deuterium resonance of the solvent as an internal lock. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are believed to be precise to within ±0.05 ppm. The proton coupled ^{13}C nmr spectra were obtained on the Bruker instument using 80-100 mg samples in 0.3 ml of solvent. Routine ^{1}H nmr spectra were also run on the Bruker instrument.

1-(β-Phenylethyl)-4-anilinopiperidine (**20a**) (*cf.* Chart IV).

To a stirred solution of 1-(β-phenylethyl)-4-piperidone (50.28 g, 0.25 mole) and *p*-toluenesulfonic acid monohydrate (0.10 g) in toluene (500 ml) was added aniline (23.05 g, 0.25 mole). The resultant mixture was refluxed 22 hours using a Dean-Stark trap to separate the water. Afterwards, the mixture was cooled to room temperature and diluted with absolute ethanol (500 ml). Solid sodium borohydride (9.40 g, 0.25 mole) was added in portions to the stirred mixture, causing evolution of gas and a lightening in color. Following the addition, the mixture was stirred 3 hours at room temperature. Afterwards, water (200 ml) was added dropwise and the resultant mixture was stirred overnight at room temperature. The mixture was then adjusted to *p*H 3 by addition of 10% hydrochloric acid (600 ml). The layers were separated, and the aqueous layer was washed with toluene (600 ml). The aqueous layer was then made basic by addition of 50% sodium hydroxide solution and extracted with methylene chloride (3 x 450 ml). The combined methylene chloride layers were dried and evaporated to give 61.37 g of crude solid. This was dissolved in diethyl ether (1700 ml). The solution was filtered, concentrated to 600 ml and diluted with petroleum ether (600 ml). The resultant solution was filtered, concentrated until crystallization began, and cooled. Subsequent collection of the product yielded 49.43 g (71%) of yellow crystals, mp 95-99° (lit 96-97° [18]).

1-(β-Phenylethyl)-4-(*p*-toluidino)piperidine (**20b**).

The procedure described for the preparation of **20a** was followed except that *p*-toluidine was used in place of aniline. Compound **20b** was obtained in 58% yield as a tan solid, mp 60-63° (lit 59-60° [19]).

1-(β-Phenylethyl)-4-(*p*-anisidino)piperidine (**20c**).

The procedure described for the preparation of **20a** was followed except that *p*-anisidine was used in place of aniline. Compound **20c** was obtained in 58% yield as a yellow solid, mp 93-95.5°, which was used with no further characterization.

1-(β-Phenylethyl)-4-(*p*-fluoroanilino)piperidine (**20d**).

The procedure described for the preparation of **20a** was followed except that *p*-fluoroaniline was used in place of aniline. Compound **20d** was obtained in quantitative yield as an oil which was utilized with no further purification or characterization.

1-Benzyl-4-anilinopiperidine (**20e**).

The procedure described for the preparation of **20a** was followed except that 1-benzyl-4-piperidone was used in place of 1-(β-phenylethyl)-4-piperidone. Compound **20e** obtained in 62% yield as an off-white solid, mp 87-89° (lit 85-86° [20]).

Fentanyl Hydrochloride (**1a**).

To a stirred solution of **20a** (8.4 g, 0.030 mole) in toluene (80 ml) was added propionic anhydride (4.8 g, 0.037 mole). The resultant mixture was refluxed 2 hours, cooled to room temperature and diluted with diethyl ether (250 ml). Subsequent introduction of hydrogen chloride gas into the mixture caused precipitation of the hydrochloride salt, which was collected by filtration and washed with diethyl ether. Recrystallization from ethanol/ethyl acetate provided 6.24 g (56%) of the title compound as a white solid, mp 253-254.5° (lit 254-255° [20]).

Anal. Calcd. for $C_{22}H_{29}ClN_2O$: C, 70.86; H, 7.84; Cl, 9.51; N, 7.51. Found: C, 70.65; H, 7.94; Cl, 9.64; N, 7.43.

Workup of the reaction mixture as described below for the preparation of compound **1b** provided fentanyl base. Following recrystallization from diethyl ether/diisopropyl ether, the base was obtained as a white solid, mp 82.5-83.5° (lit 82-84° [20]).

N-[1-(2-Phenylethyl)-4-piperidyl]-*N*-phenylacetamide Hydrochloride (**1b**).

To a stirred solution of **20a** (10.0 g, 0.036 mole) in toluene (60 ml) was added acetic anhydride (4.8 g, 0.047 mole). The resultant mixture was refluxed 3 hours under a nitrogen atmoshere, then cooled to room temperature and poured over ice (47 g). The aqueous mixture was adjusted to *p*H 12 by addition of 10% sodium hydroxide. Stirring was continued for 15 minutes after the addition of base was complete. The layers were separated and the aqueous layer was extracted with toluene (2 x 100 ml). The combined toluene extracts were dried and evaporated to obtain a brown oil which solidified on standing. Recrystallization from diisopropyl ether gave 10.04 g of the free base as tan crystals, mp 98-98.5° (lit 96-97° [21]). The crystals were dissolved in diethyl ether (300 ml) and the solution was treated with hydrogen chloride gas until no additional solid precipitated. The solid was collected and recrystallized from methanol/ethyl acetate to obtain 9.72 g (75%) of the title compound as white crystals, mp 245-247°.

Anal. Calcd. for $C_{21}H_{27}ClN_2O$: C, 70.28; H, 7.58; Cl, 9.88; N, 7.80. Found: C, 70.42; H, 7.40; Cl, 10.18; N, 7.85.

N-[1-(2-Phenylethyl)-4-piperidyl]-*N*-phenylbutyramide Hydrochloride (**1c**).

The procedure described for the preparation of **1b** was followed except that butyric anhydride was used in place of acetic anhydride. Compound **1c** was obtained in 70% yield as an off-white solid, mp 211-213° (lit 210-211° [21]).

Anal. Calcd. for $C_{23}H_{31}ClN_2O$: C, 71.39; H, 8.07; Cl, 9.16; N, 7.24. Found: C, 71.48; H, 7.93; Cl, 9.00; N, 7.27.

N-[1-(2-Phenylethyl)-4-piperidyl]-*N*-phenylisobutyramide Hydrochloride (**1d**).

The procedure described for the preparation of **1b** was followed except that isobutyric anhydride was used in place of acetic anhydride. Compound **1d** was obtained in 27% yield as off-white crystals, mp 232-234°.

Anal. Calcd. for $C_{23}H_{31}ClN_2O$: C, 71.39; H, 8.07; Cl, 9.16; N, 7.24. Found: C, 71.06; H, 8.23; Cl, 9.25; N, 7.16.

N-[1-(2-Phenylethyl)-4-piperidyl]-*N*-phenylvaleramide Hydrochloride (**1e**).

The procedure described for the preparation of **1b** was followed except that valeric anhydride was used in place of acetic anhy-

dride . Compound **1e** was obtained in 61% yield as a white solid, mp 205-207°.

Anal. Calcd. for $C_{24}H_{33}ClN_2O$: C, 71.89; H, 8.29; Cl, 8.84; N, 6.99. Found: C, 71.80; H, 8.41; Cl, 8.88; N, 7.09.

N-[1-(2-Phenylethyl)-4-piperidyl]-*N*-phenylthiopropanamide Hydrochloride (**2**).

Under a nitrogen atmosphere a mixture of fentanyl base (4.20 g, 0.0125 mole) and *p*-methoxyphenylthionophosphine sulfide dimer (Lawesson's reagent) [22] (3.03 g, 0.0075 mole) in toluene (45 ml) was refluxed 5 hours. After cooling, the mixture was slowly poured into diethyl ether (200 ml), causing precipitation of a solid. After further cooling at −4°, the solid was collected by filtration, washed with additional ether, and vacuum dried. The dried solid was resuspended in diethyl ether, stirred and again collected. Subsequent addition of ethanol and then methanol to the solid (in an attempt to dissolve it) resulted in a sticky mass. This was added to the ether filtrates saved from the above steps. After stirring, the precipitated solid was collected by filtration and put aside. The filtrate was treated with hydrogen chloride gas to generate the desired hydrochloride. Recrystallization from ethyl acetate/ethanol provided 3.04 g (63%) of the title compound as a white solid, mp 232-234°.

Anal. Calcd. for $C_{22}H_{29}ClN_2S$: C, 67.93; H, 7.51; Cl, 9.11; N, 7.20; S, 8.24. Found: C, 68.03; H, 7.53; Cl, 9.06; N, 7.18; S, 8.18.

N-(4-Methylphenyl)-*N*-[1-(2-phenylethyl)-4-piperidyl]propanamide Hydrochloride (**3a**).

Propionylation of **20b** using propionic anhydride was accomplished using the same procedure described for the preparation of **1b**. The intermediate free base was crystallized from diisopropyl ether as tan crystals, mp 136-138° (lit 136-138° [21]). Following recrystallization from methanol/diethyl ether, the hydrochloride salt was obtained in 63% yield as a white solid, mp 237-239°.

Anal. Calcd. for $C_{23}H_{31}ClN_2O$: C, 71.39; H, 8.07; Cl, 9.16; N, 7.24. Found: C, 70.96; H, 7.87; Cl, 9.00; N, 7.13.

N-(4-Methoxyphenyl)-*N*-[1-(2-phenylethyl)-4-piperidyl]propanamide Hydrochloride (**3b**).

Propionylation of **20c** using propionic anhydride was accomplished using the same procedure described for the preparation of **1b**. The intermediate free base was crystallized from diisopropyl ether as a tan solid, mp 132.5-134° (lit 131.5-132.5° [23]). Following recrystallization from methanol/ethyl acetate, the hydrochloride salt was obtained in 51% yield as an off-white solid, mp 230-232° (lit 210-211.5° [21]).

Anal. Calcd. for $C_{23}H_{31}ClN_2O_2 \cdot 0.25H_2O$: C, 67.80; H, 7.79; Cl, 8.70; N, 6.87. Found: C, 68.04; H, 7.78; Cl, 8.70; N, 6.83.

N-(4-Fluorophenyl)-*N*-[1-(2-phenylethyl)-4-piperidyl]propanamide Hydrochloride (**3c**).

Propionylation of crude **20d** using propionic anhydride was accomplished using the same procedure described for the preparation of **1b**. The intermediate free base was crystallized from diisopropyl ether as white flakes, mp 108-110°. Following recrystallization from methanol/ethyl acetate, the hydrochloride salt was obtained in 25% yield as white crystals, mp 247-249°.

Anal. Calcd. for $C_{22}H_{28}ClFN_2O$: C, 67.59; H, 7.22; Cl, 9.07; N, 7.16. Found: C, 67.59; H, 7.25; Cl, 9.43; N, 7.13.

N-(1-Benzyl-4-piperidyl)-*N*-phenylpropanamide Hydrochloride (**4**).

Propionylation of **20e** using propionic anhydride was accomplished using the same procedure described for the preparation of **1b**. The intermediate free base was isolated as a yellow oil, which was converted to the hydrochloride salt by treatment of a diethyl ether solution with hydrogen chloride gas. Recrystallization from methanol/ethyl acetate provided an 86% yield of the title compound as a white solid, mp 238-240° (lit 235-237° [20]).

Anal. Calcd. for $C_{21}H_{27}ClN_2O$: C, 70.28; H, 7.58; Cl, 9.88; N, 7.80. Found: C, 70.44; H, 7.52; Cl, 10.12; N, 7.77.

If the material was to be used for the preparation of intermediate **12**, the free base was regenerated by dissolving the salt in water, adding concentrated ammonium hydroxide until *p*H 10, and extracting with several portions of methylene chloride. The pooled organic extracts were dried and evporated to give the free base as a pale yellow oil.

N-(4-Piperidyl)-*N*-phenylpropanamide Hydrochloride (**12**).

Using a Parr apparatus, a mixture of compound **4** (64.0 g, 0.20 mole), 10% palladium/carbon (4.5 g), concentrated hydrochloric acid (16 ml) and absolute ethanol (300 ml) was hydrogenated at 40 psi and 50° until no starting material was detectable by tlc. The mixture was filtered through Celite and the clear filtrate evaporated to a white foam (55.03 g). The foam was dissolved in water (500 ml) and the solution treated with concentrated ammonium hydroxide until *p*H 10. Extraction with methylene chloride (3 x 500 ml) followed by combining, drying and evaporating the organic extracts gave 43.87 g (95%) of white solid. Recrystallization from diethyl ether/petroleum ether provided *N*-(4-piperidyl)-*N*-phenylpropanamide base as a white crystalline solid, mp 92-94° (lit 84-85° [20]). This material was used as the starting material for the preparation of analogs **5-10**.

A solution of the free base (1.01 g) in diethyl ether (80 ml) was treated with hydrogen chloride gas to generate the hydrochloride salt. The somewhat sticky salt was crystallized from methanol/ethyl acetate and recrystallized from absolute ethanol to obtain a white solid which was vacuum dried at 84° for 48 hours, after which time it had mp 180-181°.

Anal. Calcd. for $C_{14}H_{21}ClN_2O_2$: C, 62.56; H, 7.88; Cl, 13.19; N, 10.42. Found: C, 62.21; H, 7.84; Cl, 13.02; N, 10.34.

N-[1-(3-Phenylpropyl)-4-piperidyl]-*N*-phenylpropanamide Hydrochloride (**5**).

A mixture of 1-bromo-3-phenylpropane (25.68 g, 0.13 mole), *N*-(4-piperidyl)-*N*-phenylpropanamide (15.00 g, 0.065 mole) and sodium bicarbonate (33.15 g, 0.39 mole) in dimethylformamide (100 ml) was stirred 2.5 hours at 90-100°. Afterwards, the mixture was cooled and filtered. The filtrate was evaporated to a yellow oil which was taken up in methylene chloride (100 ml) and washed with water (3 x 150 ml). The organic layer was dried and evaporated to obtain another yellow oil. This oil was dissolved in diethyl ether and again washed with water to remove the last traces of dimethylformamide. The organic layer was again dried and evaporated. The recovered yellow oil was redissolved in a mixture of diethyl ether (490 ml) and methanol (24 ml) and the solution was treated with hydrogen chloride gas. Subsequent evaporation of the solvents afforded a yellow oil which crystallized from methanol/ethyl acetate to give 12.66 g (50%) of white solid. This was combined with crude product (4.68 g) from a smaller scale reaction. The combined solids were recrystallized several times from methanol/ethyl acetate to obtain 13.22 g of compound **5** as a white, crystalline solid, mp 157-158°.

Anal. Calcd. for $C_{23}H_{31}ClN_2O$: C, 71.39; H, 8.07; Cl, 9.16; N, 7.24. Found: C, 70.98; H, 7.82; Cl, 9.08; N, 7.15.

N-Phenyl-*N*-[1-(2-thienyl)methyl-4-piperidyl]propanamide Hydrochloride (**6**).

A solution of 2-thiophenemethanol (3.35 g, 0.029 mole) in diethyl ether (20 ml) was cooled in an ice bath. A solution of thionyl chloride (5.14 g, 0.043 mole) in diethyl ether (20 ml) was gradually added. Following the addition, the mixture was stirred 3 hours at ice bath temperature. After evaporation of the solvent and excess reagent, the crude (2-thienyl)methyl chloride was taken up in methylene chloride (25 ml). This solution was added dropwise to a cold solution of *N*-(4-piperidyl)-*N*-phenylpropanamide (14.03 g, 0.060 mole) in methylene chloride (30 ml). The resultant mixture was stirred overnight during which time the temperature was allowed to rise from ice bath temperature to room temperature. Afterwards, the mixture was concentrated, then added gradually to diethyl ether. After stirring *N*-(4-piperidyl)-*N*-phenylpropanamide hydrochloride separated from the mixture. It was recovered by filtration and washed with diethyl ether. The filtrate was treated with hydrogen chloride gas to generate the product hydrochloride. The crude salt was collected by filtration, washed with diethyl ether and dried. Recrystallization from ethyl acetate/ethanol afforded 6.97 g (65%) of an off-white solid, mp 235°. This material was combined with similar material from a probe reaction and again recrystallized from ethyl acetate/ethanol to provide 7.37 g of compound **6** as white crystals, mp 241-242°.

Anal. Calcd. for $C_{19}H_{25}ClN_2OS$: C, 62.53; H, 6.91; Cl, 9.72; N, 7.68; S, 8.79. Found: C, 62.44; H, 6.92; Cl, 9.80; N, 7.64; S, 8.70.

N-Phenyl-*N*-[1-[2-(2-thienyl)ethyl]-4-piperidyl]propanamide Hydrochloride (**7**).

To an ice cold solution of 2-(2-thienyl)ethanol (4.22 g, 0.033 mole) in dry pyridine (6 ml) was added in portions solid *p*-toluenesulfonyl chloride (6.90 g, 0.036 mole). The resultant mixture was stirred 2 hours at ice bath temperature, then poured into crushed ice/water (*ca.* 100 ml). Concentrated hydrochloric acid was added until the mixture was acidic. The acidic solution was extracted with several portions of diethyl ether. The combined ether extracts were washed with water and saturated sodium chloride solution, then dried. Subsequent evaporation of the ether afforded a quantitative yield of crude 2-(2-thienyl)ethyl tosylate which was used with no further purification.

A solution of the crude ester (9.10 g, 0.032 mole) in toluene (30 ml) was added to a stirred mixture of *N*-(4-piperidyl)-*N*-phenylpropanamide (8.04 g, 0.035 mole) and sodium carbonate (17.51 g, 0.165 mole) in toluene (30 ml). The resultant mixture was refluxed 3.5 hours, cooled and filtered. The filtrate was evaporated, and the residue was treated with diethyl ether. After overnight refrigeration at −4°, the precipitated solid was removed by filtration. The filtrate was treated with hydrogen chloride gas. The crude hydrochloride salt was collected and recrystallized from ethyl acetate/ethanol. The recrystallized product was combined with product from an earlier run and recrystallized again from ethyl acetate/ethanol to provide 8.52 g of compound **7** as a white solid, mp 249-251°.

Anal. Calcd. for $C_{20}H_{27}ClN_2OS$: C, 63.39; H, 7.18; Cl, 9.36; N, 7.39; S, 8.46. Found: C, 63.46; H, 7.22; Cl, 9.30; N, 7.36; S, 8.42.

N-[1-[1-Methyl-2-(2-thienyl)ethyl]-4-piperidyl]-*N*-phenylpropanamide Hydrochloride (**9**).

2-Thiophenecarboxaldehyde was converted *via* 1-(2-thienyl)-2-nitropropene to 1-(2-thienyl)-2-propanone using procedures reported by Hass and co-workers [24]. The 1-(2-thienyl)-2-propanone was obtained in 29% overall yield as a yellow-orange oil; ir (methylene chloride): 1730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.20 (3H, s, CH_3), 3.89 (2H, s, ArCH_2), 6.88-7.32 (3H, m, Ar*H*).

To a stirred solution of 1-(2-thienyl)-2-propanone (4.2 g, 0.031 mole) in methanolic hydrogen chloride (128 ml, *p*H 3) was added solid *N*-(4-piperidyl)-*N*-phenylpropanamide (7.09 g, 0.031 mole). Upon addition of the amine the mixture color changed from yellow to orange. The mixture was stirred 24 hours at room temperature, then solid sodium cyanoborohydride (8.13 g, 0.13 mole) was added. The resultant mixture was stirred 50 hours at room temperature, then diluted with water (8.6 ml). The reaction mixture (*p*H 10) was asjusted to *p*H 2 with concentrated hydrochloric acid and filtered. Evaporation of the filtrate left an oily residue which was suspended in water (100 ml). The suspension was adjusted to *p*H 10 using concentrated ammonium hydroxide and extracted with chloroform (3 x 100 ml). The organic extracts were dried and evaporated to obtain a dark orange oil (11.07 g). This was combined with a similar product (2.47 g) from a probe reaction, and the combined sample was chromatographed on silica gel (667 g) using 5% acetone/chloroform as the eluting solvent. The chromatography yielded 2.71 g of product base contaminated with 1-(2-thienyl)-2-propanol and 1.37 g of pure product base. This latter sample was combined with a similar sample (0.39 g) from another probe reaction. The two fractions were dissolved in diethyl ether and treated with hydrogen chloride gas. Each of the resultant hydrochloride salts was chromatographically pure (tlc). The two solids were therfore combined and recrystallized from ethyl acetate/methanol to give, after vacuum drying 24 hours at 60°, 2.63 g of compound **9** as colorless crystals, mp 243-245°.

Anal. Calcd. for $C_{21}H_{29}ClN_2OS$: C, 64.18; H, 7.44; Cl, 9.02; N, 7.13; S, 8.16. Found: C, 64.17; H, 7.43; Cl, 8.94; N, 7.11; S, 8.65.

N-[1-(2-Hydroxy-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide Hydrochloride (**10**).

A next mixture of styrene oxide (3.31 g, 0.028 mole) and *N*-(4-piperidyl)-*N*-phenylpropanamide (5.80 g, 0.025 mole) was stirred 7 hours at 100°. Subsequent cooling gave a sticky residue which was dissolved in diethyl ether. The solution was treated with hydrogen chloride gas. The precipitated solid was collected and washed with additional ether. Recrystallization from ethanol/ethyl acetate afforded 6.83 g (70%) of white solid. This was combined with a similar solid from a probe run. The combined solids were recrystallized a second time to obtain 6.54 g of compound **10** as a white solid, mp 226-228°.

Anal. Calcd. for $C_{22}H_{29}ClN_2O_2$: C, 67.94; H, 7.52; Cl, 9.12; N, 7.20. Found: C, 68.03; H, 7.56; Cl, 9.15; N, 7.20.

1-(β-Phenylethyl)-4-piperidone Hydrochloride (**11**).

A solution of 1-(β-phenylethyl)-4-piperidone (1.5 g) in diethyl ether (50 ml) was treated with hydrogen chloride gas to generate the hydrochloride salt. After collection, the crude salt was recrystallized first from methanol/ethyl acetate and then from absolute ethanol to obtain a powdery white solid which was vaccum dried at 84° for 48 hours, after which time it had mp 181-182°.

Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.57; Cl, 14.79; N, 5.84. Found: C, 64.85; H, 7.53; Cl, 14.48; N, 5.67.

1-[(2-Thienyl)methyl]piperidine Hydrochloride (**13**).

Using the procedure described above, 2-thiophenemethanol (2.35 g, 0.021 mole) was converted in quantitative yield to (2-thienyl)methyl chloride. A solution of the chloride in diethyl ether (20 ml) was cooled in an ice bath. A solution of piperidine (3.55 g, 0.042 mole) in diethyl ether (20 ml) was added portionwise with stirring. Following the addition, the mixture was stirred 2 hours at ice bath temperature and then overnight at ambient temperature. Afterwards, the precipitated piperidine hydrochloride was removed by filtration and the filtrate was evaporated. The residue was treated with hexanes. The insoluble material was again separated by filtration and the filtrate evaporated. Any residual piperidine was then removed by azeotroping with toluene. The toluene treatment left a residual orange oil (1.73 g). This was dissolved in diethyl ether and the solution treated with hydrogen chloride gas. The solid was collected and recrystallized from methanol/diethyl ether to obtain 1.12 g (25%) of compound **13** as a white solid, mp 165.5-167.5°. An analytical sample was recrystallized first from methanol/diethyl ether and then from methylene chloride/hexanes. After vacuum drying 24 hours at 80°, the sample had mp 168.5-170.5°.

Anal. Calcd. for $C_{10}H_{16}ClNS$: C, 55.16; H, 7.41; Cl, 16.28; N, 6.43. Found: C, 55.02; H, 7.42; Cl, 15.97; N, 6.29.

1-[2-(2-Thienyl)ethyl]piperidine Hydrochloride (**14**).

Compound **14** was prepared from 1-(2-thienyl)ethyl tosylate and piperidine using the same procedure described above for compound **7**. Following recrystallization from ethanol/ethyl acetate, the product had mp 241-243°.

Anal. Calcd. for $C_{11}H_{18}ClNS$: C, 57.00; H, 7.83; Cl, 15.30; N, 6.04. Found: C, 56.97; H, 7.86; Cl, 14.91; N, 5.63.

General Procedure for the Preparation of Model Compounds **15-19** by Eschweiler-Clarke Methylation [25].

A mixture of the primary amine (3.0 g), 90% formic acid (12.0 ml) and 37% formaldehyde (24.0 ml) was refluxed overnight. After cooling, the mixture was acidified to *p*H 2 with concentrated hydrochloric acid, then extracted with three portions of diethyl ether. The aqueous layer was made basic (*p*H 10) by addition of concentrated ammonium hydroxide, then extracted three times with methylene chloride. The combined organic extracts were dried and evaporated to obtain the *N,N*-dimethylamino product as the free base. This was dissolved in methanol and treated with an equivalent amount of concentrated hydrochloric acid. Subsequent solvent evaporation provided the crude hydrochloride salt, which was purified by recrystallization from ethanol/diethyl ether. *N,N*-Dimethylbenzylamine hydrochloride (**15**) was obtained as white crystals, mp 172.5-174.5° (lit 175° [26]). *N,N*-Dimethyl-β-phenethylamine hydrochloride (**16**) was obtained as fluffy white crystals, mp 163.5-164.5° (lit 165° [27]). *N,N*-Dimethyl-*N*-(3-phenylpropyl)amine hydrochloride (**17**) was obtained as shiny white plates, mp 146-147° (lit 146° [28]).

(+)-*N,N*-Dimethylamphetamine Hydrochloride (**18**).

The starting material for this compound was (+)-amphetamine, which was isolated from the sulfate salt by neutralization and extraction. Following recrystallization, the product was obtained as white crystals, mp 184.5-186.5° (lit 182-183° [29]); $[\alpha]_D$ + 3.9° (c 1).

Anal. Calcd. for $C_{11}H_{18}ClN$: C, 66.15; H, 9.08; Cl, 17.75; N, 7.01. Found: C, 66.40; H, 9.04; Cl, 17.74; N, 6.96.

2-(*N,N*-Dimethylamino)-1-phenylethanol Hydrochloride (**19**).

This product was isolated as large white crystals which were broken with a spatula and vacuum dried at 84° for 48 hours. Afterwards, the powdery white solid had mp 147.5-148.5°.

Anal. Calcd. for $C_{10}H_{16}ClNO$: C, 59.55; H, 8.00; Cl, 17.58; N, 6.94. Found: C, 59.53; H, 8.00; Cl, 17.60; N, 6.71.

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