*Donald Cooper,*[1] *B.S.; Michael Jacob;*[2] *and Andrew Allen,*[1] *B.S.*

# Identification of Fentanyl Derivatives

**REFERENCE:** Cooper, D., Jacob, M., and Allen, A., **"Identification of Fentanyl Derivatives,"** *Journal of Forensic Sciences*, JFSCA, Vol. 31, No. 2, April 1986, pp. 511-528.

**ABSTRACT:** An interpretative approach to the identification of fentanyl homologs and analogs is presented. The techniques employed are liquid/liquid extractions; capillary gas chromatography; and infrared, mass, and nuclear magnetic resonance spectral characterization. Spectral data are presented for eight fentanyl derivatives of clandestine origin.

**KEYWORDS:** toxicology, fentanyl, chemical analysis, spectroscopic analysis

Fentanyl, *N*-(1-phenethyl-4-piperidyl)propionanilide, is a narcotic analgesic of the 4-anilinopiperidine series. Clinically, fentanyl is known for fast onset, short duration, and a high therapeutic index [*1-5*]. Not surprisingly, it has become widely used as a surgical anesthesia in conjunction with nitrous oxide and positive ventilation. As with other narcotic analgesics, fentanyl is addictive [*6*], and in overdose situations, death occurs by respiratory depression [*7*].

Fortunately, the abuse of fentanyl has not been a serious problem in the past. However, starting in the late 1970s with $\alpha$-methylfentanyl [*8*], nine homologs and one analog (excluding enantiomers) of fentanyl have appeared in the illicit marketplace. One of the most recent of these homologs to appear has been ($\pm$) *cis* (S,R:R,S) and *trans* (S,S:R,R) 3-methylfentanyl. Interestingly, Van Bever et al [*9*] state that the analgesic activity of (+)-*cis*-3-methylfentanyl is 16 times that of fentanyl. Further, DeCastro et al [*10*] have provided a comparison between fentanyl and morphine where, for a 70-kg man, an effective analgesic intravenous dose was 0.1 and 10 mg, respectively, and "serious side effects" occurred at the 5- and 200-mg level (where ventilation was controlled and therefore respiratory depression was not considered a side effect). If the data presented by Van Bever and DeCastro is extrapolated, it would suggest that a fatal dose of (+)-*cis*-3-methylfentanyl would be approximately 300 $\mu$g for a 70-kg man under conditions of positive ventilation.

Obviously the use of (+)-*cis*-3-methylfentanyl without positive ventilation should result in fatal consequences at doses considerably below the 300-$\mu$g level for the hypothetical 70-kg man. The illicit fentanyl homologs and analog (derivatives) encountered to date most probably have potencies that range between the extremes of fentanyl and (+)-*cis*-3-methylfentanyl. However, even for fentanyl, potency is clinically 100 times that of morphine [*7*], and undoubtedly, this feature has been primal in producing several fatalities on the U.S. West Coast. In point of fact, the illicit samples encountered to date range between 0.1 and 0.3% by weight, and assuming a 100-mg packaging unit, that would provide between 100 and 300 $\mu$g of drug. Considering this data, it is surprising that fatalities are not more common.

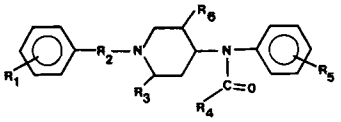
Received for publication 21 May 1985; accepted for publication 28 June 1985.

[1]Senior forensic chemists, Drug Enforcement Administration, Special Testing and Research Laboratory, McLean, VA.

[2]Summer Student, Rochester Institute of Technology, Rochester, NY.

When we first encountered the "fentanyls," in the form of α-methylfentanyl, it was decided that these compounds would provide good models for high performance liquid chromatography [*11,12*] and mass spectral [*13*] studies. Toward that end, some 29 homologs were synthesized (Table 1). The decision to make a certain homolog was based upon the usefulness to the envisioned studies and upon our perception of what might be a likely candidate for future illicit manufacture. Germane to this article is the fact that one of the next

TABLE 1—*Fentanyl homologs and analogs.*




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|
| 1. | . . . | $CH_2$ | . . . | $CH_3$ | . . . | . . . |
| 2. | . . . | $CH_2$ | . . . | $CH_2CH_3$ | . . . | . . . |
| 3.* | . . . | $CH_2CH_2$ | . . . | $CH_2CH_3$ | . . . | . . . |
| 3a.@ | . . . | $CH_2CH_2$ | . . . | $CH_3$ | . . . | . . . |
| 4. | . . . | $CH_2CH_2CH_2$ | . . . | $CH_3$ | . . . | . . . |
| 5. | . . . | $CH_2CH_2CH_2$ | . . . | $CH_2CH_3$ | . . . | . . . |
| 6.@ | . . . | $CH_2CH\ CH_3$ | . . . | $CH_2CH_3$ | . . . | . . . |
| 7. | . . . | $CH_2CH_2$ | . . . | $CH_3$ | o-$CH_3$ | . . . |
| 8. | . . . | $CH_2CH_2$ | . . . | $CH_3$ | m-$CH_3$ | . . . |
| 9. | . . . | $CH_2CH_2$ | . . . | $CH_3$ | p-$CH_3$ | . . . |
| 10. | . . . | $CH_2CH_2$ | . . . | $CH_2CH_3$ | o-$CH_3$ | . . . |
| 11. | . . . | $CH_2CH_2$ | . . . | $CH_2CH_3$ | m-$CH_3$ | . . . |
| 12. | . . . | $CH_2CH_2$ | . . . | $CH_2CH_3$ | p-$CH_3$ | . . . |
| 13. | o-$CH_3$ | $CH_2CH_2$ | . . . | $CH_3$ | . . . | . . . |
| 14. | m-$CH_3$ | $CH_2CH_2$ | . . . | $CH_3$ | . . . | . . . |
| 15. | p-$CH_3$ | $CH_2CH_2$ | . . . | $CH_3$ | . . . | . . . |
| 16. | o-$CH_3$ | $CH_2CH_2$ | . . . | $CH_2CH_3$ | . . . | . . . |
| 17.* | m-$CH_3$ | $CH_2CH_2$ | . . . | $CH_2CH_3$ | . . . | . . . |
| 18. | p-$CH_3$ | $CH_2CH_2$ | . . . | $CH_2CH_3$ | . . . | . . . |
| 19. | . . . | $CH_2CH_2$ | $CH_3$ | $CH_2CH_3$ | . . . | . . . |
| 20. | . . . | $CH_3CH\ CH_2$ | . . . | $CH_3$ | . . . | . . . |
| 21. | . . . | $CH_3CH\ CH_2$ | . . . | $CH_2CH_3$ | . . . | . . . |
| 22.@ | . . . | $CH_2CH_2$ | . . . | $CH_2CH_3$ | p-F | . . . |
| 23. | . . . | $CH_2CH_2$ | . . . | $CH_2CH_3$ | o-F | . . . |
| 24. | . . . | $CH_2CH_2$ | . . . | $CH_3$ | m-F | . . . |
| 25. | . . . | $CH_2CH_2$ | . . . | $CH_2CH_3$ | m-F | . . . |
| 26.@ | . . . | $CH_2CH_2$ | . . . | $CH_2CH_3$ | . . . | $CH_3$ (CIS) |
| 26a.@ | . . . | $CH_2CH_2$ | . . . | $CH_2CH_3$ | . . . | $CH_3$ (TRANS) |
| 27. | . . . | $CH_2CH_2$ | . . . | $CH_3$ | . . . | $CH_3$ (TRANS) |
| 28.@ | . . . | $CH_2CH\ CH_3$ | . . . | $CH_3$ | . . . | . . . |
| 29.@ | . . . | $CH_2CH\ CH_3$ | . . . | $CH{=}CH_2$ | . . . | . . . |
| 30.@1 | 2-Thiopene | $CH_2CH\ CH_3$ | . . . | $CH_2CH_3$ | . . . | . . . |

*Fentanyl

@Compounds encountered in case samples

1The Phenyl Ring has been replaced with a 2-thiophene

clandestine fentanyl derivatives encountered was not in that group and, in fact, before this article, does not appear in the open literature where over 220 derivatives are presently described [*1,9,11,14–16*]. Although through personal communications[3,4,5] within the forensic science community spectral data for the illicit fentanyl derivatives have been disseminated as they were encountered, that hardly meets the need of the forensic science community in identifying the "next" fentanyl derivative. We herein propose that a viable solution to this problem lies in spectral interpretation.

In general, spectral interpretation for molecules of the size and complexity of fentanyl are quite time-consuming and not necessarily assured of success. However, for the fentanyl derivatives, there are two attenuating reasons why interpretation of infrared (IR), mass spectrometric (MS), and nuclear magnetic resonance (NMR) spectral data are most likely to be successful and to be so within reasonable time frames. The first of these reasons is delineated by the work of Riley et al [*1*] and Maryanoff et al [*14*] where it is shown that connecting either end of the fentanyl molecule to form fused ring systems greatly reduces analgesic activity. The importance of these findings for this work resides in a decreased likelihood of clandestine manufacture, and in the event such fused ring compounds are made, they will be present in samples at relatively high concentrations. The second of these reasons is centered around the fact that the electron impact mass spectrum [*13*] and the H-1 NMR spectrum [*1,8,9,14,16,17*] have for the case of fentanyl been structurally elucidated. It is our intention in this article to describe the interpretative logic along with the separations schemes that have allowed unknown fentanyl derivatives to be identified in our laboratory.

## Experimental Procedure

Nuclear magnetic resonance spectra were obtained with a Nicolet NT-200WB Fourier transform spectrometer equipped with a model 293A programmable pulser. Spectra were obtained on the free bases in deuterochloroform with tetramethylsilane as the internal standard. The mass spectrometers employed used a quadrupole mass analyzer (Finnigan 4000 and 4600) and were operated under electron ionization conditions at 70 eV.

Infrared spectra were recorded in potassium bromide (KBr) with a Beckman model 4240 spectrometer.

Gas chromatograms were generated in the split mode (50/1) on a Hewlett-Packard 5710A gas chromatograph (GC) fitted with a 12-m by 0.20-mm inside diameter (ID) fused silica capillary column coated with SE-54 (Hewlett-Packard, Avondale, PA) at a film thickness of 0.24 $\mu$m. The GC was equipped with a flame ionization detector (FID) and interfaced with a Hewlett-Packard 3380A integrator. Injector and detector temperatures were maintained at 300°C. The oven temperature was programmed as follows: initial temperature, 210°C; initial hold, 2 min; temperature program rate, 2°C/min; final temperature, 280°C; and final hold, none. Hydrogen (ultrahigh purity) was used as the carrier gas at a flow rate of 50 cm/s. Nitrogen was used as the makeup gas at 30 mL/min. All chromatograms were recorded at an attenuation of 8 and at a chart speed of 1.0 cm/min. The internal standard was *n*-triacontane (C30).

## Results and Discussion

Few laboratories enjoy the use of chromatographically interfaced IR and NMR equipment. Most laboratories must therefore isolate the analyte from the sample matrix before analysis by IR and NMR. Several communications[3,4,5,6] have described a liquid/liquid ex-

[3]D. Cooper, A. Allen, and I. Lurie, personal communication, Nov. 1981.
[4]A. C. Allen and I. S. Lurie, personal communication, Jan. 1984.
[5]A. Allen, D. Cooper, and T. Kram, personal communication, March 1981.
[6]J. A. Heagy, personal communication, May 1981.

tracting scheme and two[3,4] provide high performance liquid chromatographic (HPLC) systems for the isolation of fentanyl derivatives. Each of the extraction schemes used an ion pairing step for the final separation of the fentanyl derivative. The extraction scheme shown in Fig. 1 is an amalgamation of these schemes, and perhaps represents the best compromise in terms of analyte recovery and final purity.

A sample containing *p*-fluorofentanyl (*p*-FF) and associated synthesis impurities was extracted according to the scheme shown in Fig. 1. The various compounds found in that sample and the fraction in which they were extracted is depicted in Fig. 2. *Para*-fluorofentanyl (Compound 7, Fig. 2) was isolated in fraction 'C' at an estimated 90% plus purity and a 70% recovery level. Although in our hands this extraction scheme is generally successful (when only one fentanyl derivative is present), it seldom delivers an analyte of near 100% purity. Recrystallization schemes [*9,15,18*] are available in the literature and perhaps they may provide high purity products; however, these procedures are generally too time-consuming for our purposes. A separations technique that offers a superior alternative to these schemes is provided by HPLC and several systems are described in the literature [*1,11,12*].

In our hands, infrared data is considerably less informative than it could be. However, even minor interpretative efforts can provide valuable structural insights. For instance, all fentanyl derivatives must show an amide absorption band at or near 1650 $cm^{-1}$ and evidence for the basic nitrogen such as the amine halogen absorption band (the so called ammonium band) centered at 3500 $cm^{-1}$ (see Figs. 3 to 7). In addition, those absorption bands normally ascribed to methylene are seen between 1200 and 1500 $cm^{-1}$ and the directly interpretable

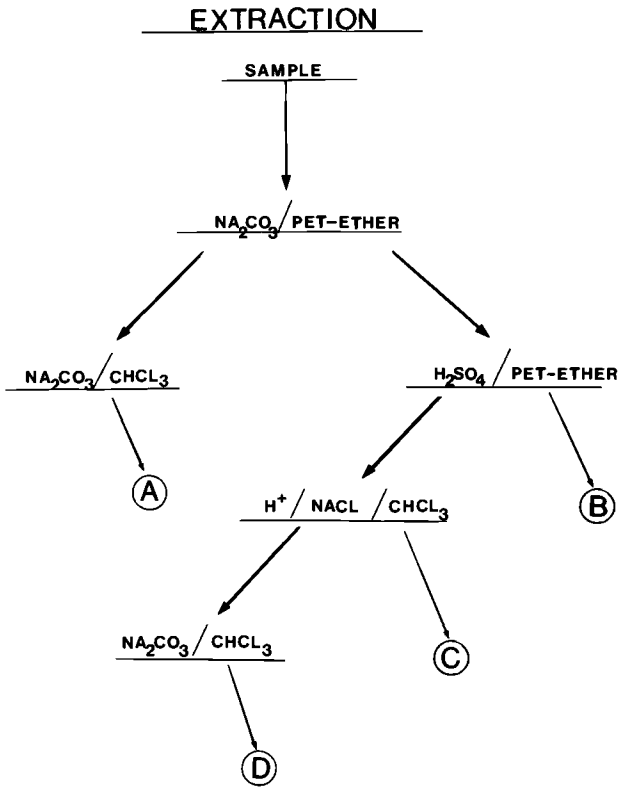



FIG. 1—*Liquid-liquid extraction scheme for fentanyl derivatives.*

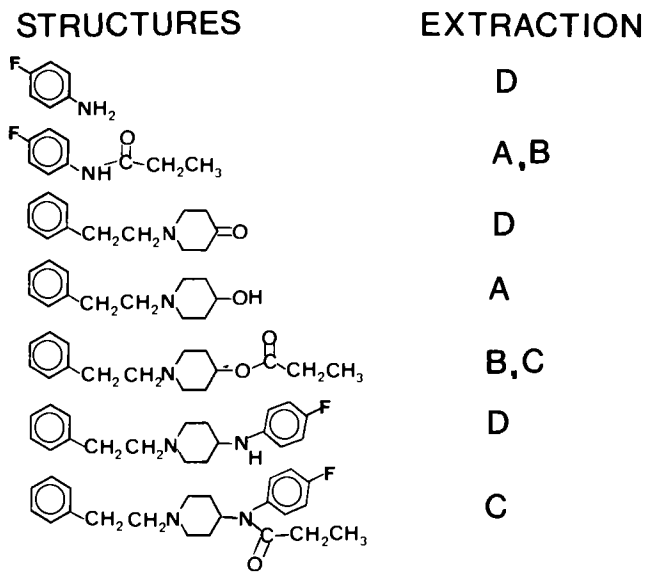



FIG. 2—*Compounds isolated from a* p*-fluorofentanyl sample via the extraction scheme, Fig. 1.*

bands at 708 and 740 $cm^{-1}$ provide definitive proof for the monosubstituted phenyl rings. The comparison of the fentanyl IR spectrum to that of *p*-fluorofentanyl (*p*-FF) (Fig. 3) graphically demonstrates the fact that the two compounds are quite structurally similar. Differences between the fentanyl IR spectrum and the *p*-FF spectrum are observed in those bands related to phenyl ring absorptions (695, 732, 744, and 847 $cm^{-1}$) and in the presence of the medium intensity band at 1218 $cm^{-1}$ caused by the presence of the aryl fluorine. At this point, one can see that this interpretation for *p*-FF has provided evidence for the presence of a *p*-fluoro substituent on one of the aromatic rings in what would likely be a fentanyl derivative.

Although H-1 NMR analysis requires a not inconsiderable amount of sample, it can provide structural information of commensurate value. The ease with which structural information can be extracted from NMR data is further enhanced when a model compound spectrum can be assigned as has been accomplished by this laboratory for fentanyl (Fig. 8). The assignments shown for fentanyl were obtained via the deductive use of decoupling experiments and coupling constants. Specifically, the isolated H-4 resonance (4.6 ppm) was employed as a decoupling probe. This allows the identification of those resonances which are due to the vicinally coupled hydrogens at C-3 and C-5 as 1.4 and 1.8 ppm. The resonance at 1.4 ppm was assigned to the axial hydrogens as they would be expected to be upfield of equatorial hydrogens and the observed coupling satisfies the Karplus equation. In turn, the decoupling of the axial C-3, C-5 hydrogens allows assignment of the C-2 and C-6 hydrogens at 2.2 and 3.0 ppm. The resonance at 2.2 ppm was again assigned to the axial hydrogens for the reasons given previously. It then follows that the methylene resonances from the phenethyl portion of the molecule must be at 2.6 and 2.7 ppm. The resonances due to the ethyl of the propionyl moiety are obvious assignments of the multiplet signals at 1.1 and 1.9 ppm.

In most instances, we have found that the simple comparison of the NMR spectrum of fentanyl to that obtained from a homolog allows elucidation of the homolog structure. Further, it is noted that this approach can in some cases also be successful for analogs. An example is provided by the comparison of the fentanyl NMR spectrum to that of *p*-fluorofen-

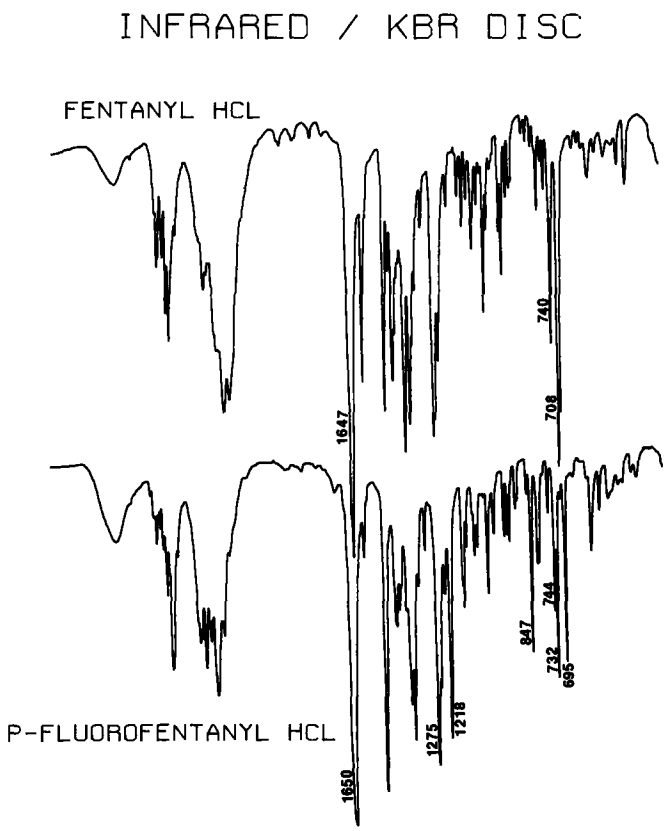



FIG. 3—*Infrared spectra for fentanyl and* p*-fluorofentanyl as hydrochloride salts, in KBr. Compounds 3 and 22, Table 1.*

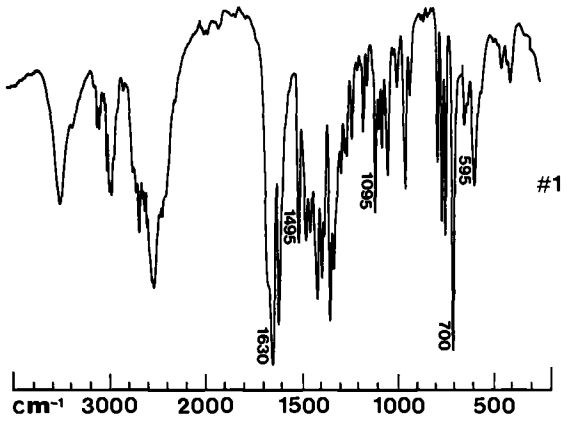



FIG. 4—*Infrared spectrum of* N*-(1-benzyl-4-piperidyl)-*N*-phenylacetamide hydrochloride in KBr, Compound 1, Table 1.*

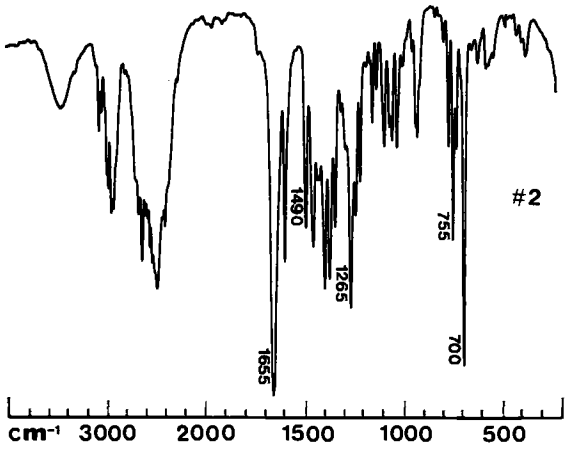



FIG. 5—*Infrared spectrum of* N-*(1-benzyl-4-piperidyl)*-N-*phenyl propanamide hydrochloride in KBr, Compound 2, Table 1.*

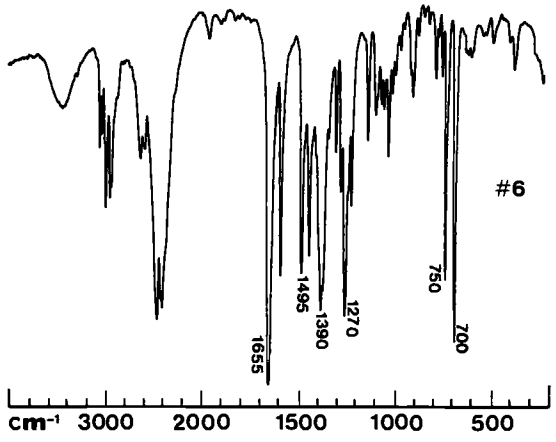



FIG. 6—*Infrared spectrum of α-methylfentanyl hydrochloride in KBr, Compound 6, Table 1.*

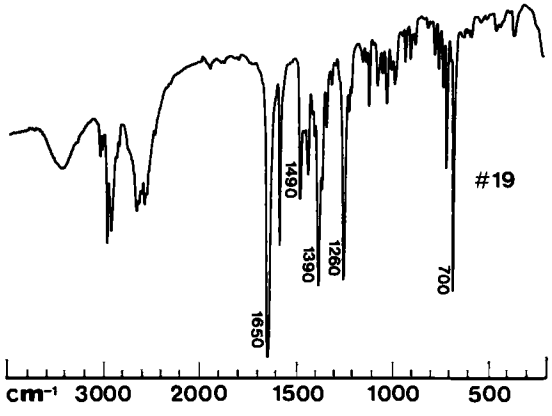



FIG. 7—*Infrared spectrum of 2-methylfentanyl hydrochloride in KBr, Compound 19, Table 1.*

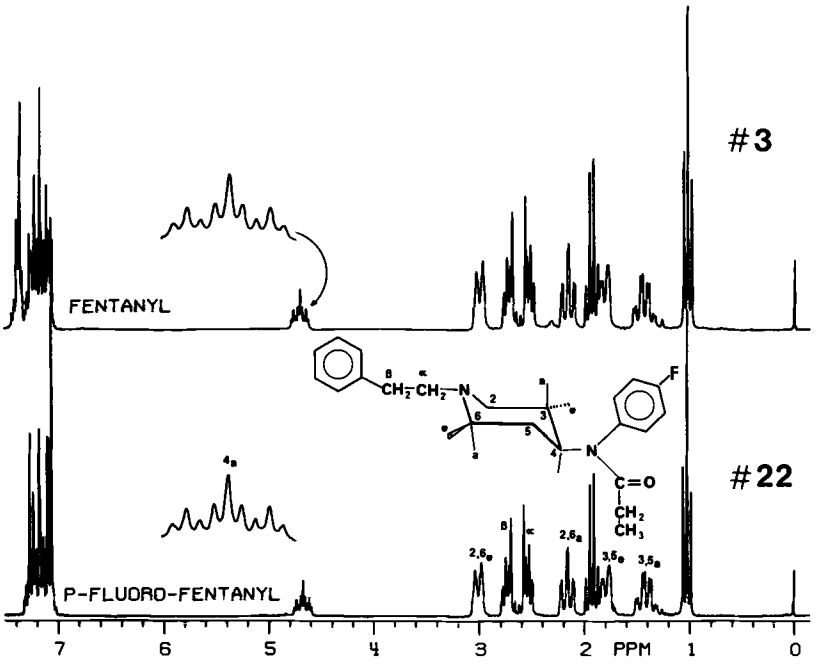



FIG. 8—*H-1 NMR spectra of fentanyl and* p*-fluorofentanyl.*

tanyl (Fig. 8). Examination of the other NMR spectra provided in this work (Figs. 9 to 13), further demonstrates the facility with which homolog structural assignments can be made using this comparative approach. For instance, in the case of 3-methylfentanyl (Compound 26 in Fig. 10), changes are observed in the high field resonances as compared to fentanyl. The presence of a strong doublet at 1.5 ppm supports a methyl substitution whereas the appearance of the H-4 resonance at 4.4 ppm reveals its location. The H-4 resonance in fentanyl appears as a triplet of triplets, the result of the axial C-4 hydrogen being coupled by two large axial couplings ($J_{4A\text{-}3A,5A}$) and two small equatorial couplings ($J_{4A\text{-}3E,5E}$). In the spec-

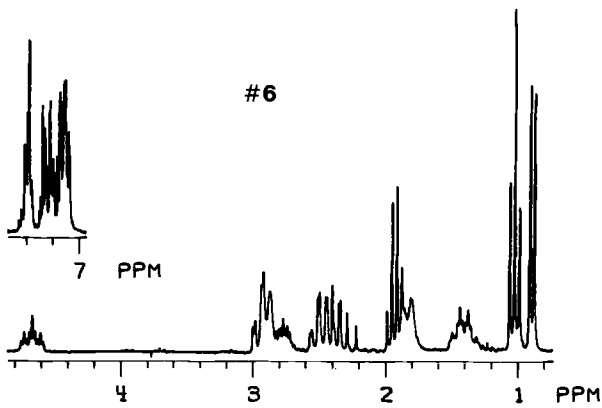



FIG. 9—*H-1 NMR spectrum of* $\alpha$*-methylfentanyl in* $CDCl_3$*, Compound 6, Table 1.*

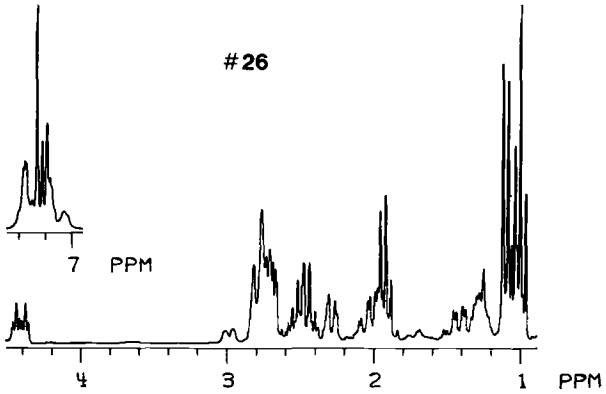



FIG. 10—*H-1 NMR spectrum of* cis*-3-methylfentanyl in* $CDCl_3$*, Compound 26, Table 1.*

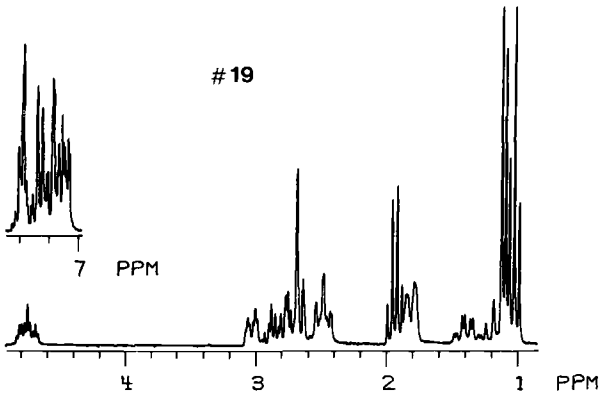



FIG. 11—*H-1 NMR spectrum of 2-methylfentanyl in* $CDCl_3$*, Compound 19, Table 1.*

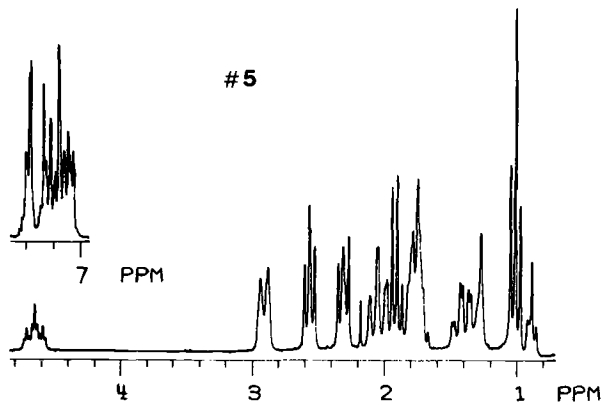



FIG. 12—*H-1 NMR spectrum of* N*-[1-(3-phenylpropyl)-4-piperidyl]-*N*-phenylpropanamide in* $CDCl_3$*, Compound 5, Table 1.*

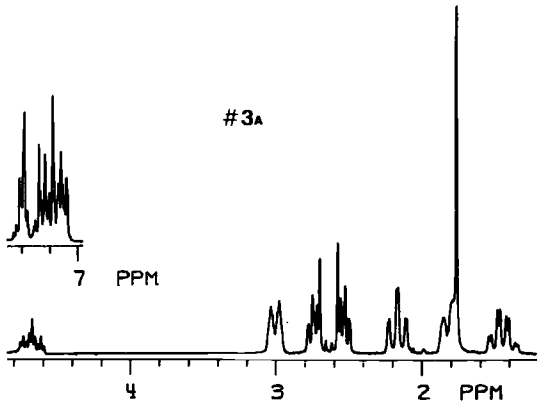



FIG. 13—*H-1 NMR spectrum of* N-*[1-(2-phenylethyl)-4-piperidyl]*-N-*phenylacetamide in* $CDCl_3$, *Compound 3a, Table 1.*

trum of 3-methylfentanyl, one large axial coupling is no longer present, hence the methyl substituent must be C-3 axial. As the remainder of the spectrum is essentially identical to fentanyl, one could then propose the structure of *cis*-3-methylfentanyl. Similar logic can be applied to α-methylfentanyl (Compound 6 in Fig. 9), for once again a high field doublet, 0.9 ppm, indicates the presence of a methyl substituent on a methine. However, the appearance of the H-4 resonances as a triplet of triplets has not changed, and further, all of the resonances resulting from the piperidine ring hydrogens are essentially the same as observed for fentanyl. Also, note that the resonances due to the ethyl of the propionyl moiety are present, hence the methyl substitution must be in the ethyl portion of the phenethyl group.

Although H-1 NMR is one of the more powerful structure elucidation tools available, it of course does have limitations. In the case of α-methylfentanyl, the precise location of the methyl substitution, α or β to the piperidine nitrogen, is not easily determined, and via the H-1 NMR of *p*-FF we were not able to assign the position of the fluorine substitution within the aromatic rings nor determine which of the two rings contained that substitution. As noted previously, infrared can provide data on the position of the fluorine and it will be shown that MS can determine whether the phenyl or the anilino ring actually contains the fluorine substituent.

Combining data from IR, NMR, and MS can, with some diligence, assure identification of virtually any organic molecule less than 500 molecule weight. However, with fentanyl and fentanyl derivatives, one quite often does not have sufficient sample for non-Fourier transform IR and NMR instrumentation. It is in these cases where the superior sensitivity of the mass spectrometer might provide the only spectral data.

For molecules of a size comparable to fentanyl (MW 336), mass spectral data will nearly always reflect minor structural modifications, but frequently it does not allow for easy interpretation. This is not the case for the fentanyl derivatives as we have found that these compounds can in almost all cases be easily and fully determined via the technique. To demonstrate the MS interpretation sequence that has been successful for us, the interpretation of *p*-fluorofentanyl and 3-methylfentanyl spectra are given in the following section.

All of the data used in the forthcoming discussion were obtained under electron ionization (EI). What is particularly germane to the identification of fentanyl derivatives via MS is the fact that EI for most of these derivatives does not provide molecular weight information. Therefore, if molecular weight data can be obtained via an alternate method it would be highly desirable. For that purpose, we have found methane chemical ionization (CI-MS) to be suitable. However, it will be shown that the molecular weight can normally be deduced from EI data alone by summing the masses of the appropriate complementary ion pairs [*13*].

### *p*-Fluorofentanyl Mass Spectral Interpretation

In the EI mass spectrum of fentanyl, the ion observed at highest mass is due to the loss of the benzyl radical from the molecule ion and it occurs at the mass to charge ($m/z$) value of 245 (Fig. 14, ion *A*; ion structure *A*, Table 2). Ion *I* at $m/z$ 91 is due to the benzyl ion and, for fentanyl, constitutes the complementary ion of *A*, that is, the sum of the masses of ions *A* and *I* is equal to the mass of the intact molecule (MW 336). Almost all fentanyl derivatives presently known share the structural feature where a 2-phenylethyl moiety is attached to the piperidine nitrogen (the most notable exception is the substitution of a thiophene for the phenyl ring). Therefore, the molecular weight can be determined by observing the ion at highest mass (Ion *A*), noting the presence of Ion *I* and summing the respective masses. For the case of *p*-FF (Fig. 14), Ion *A* occurs at the $m/z$ value of 263 and Ion *I* is at $m/z$ 91, therefore 263 + 91 = 354, the molecular weight of *p*-FF. The presence of the 2-phenethyl moiety in *p*-FF is given further support by the ion at $m/z$ 105 (Table 2, ion *G*). Note that substitution on the phenyl ring or the carbon alpha to the phenyl ring would result in an appropriate mass shift for the Ions *I* and *G*, and of course, there would be noted a reduced abundance for the ion at $m/z$ 91.

The molecule weight that was just calculated for *p*-FF (354) is 18 greater than fentanyl (336) and a fluorine substitution accounts nicely for that difference. Also the Ions *A*, *B*, *C*, and *D* are shifted by 18 daltons (Fig. 14), which in turn provides further proof for the presence of the fluorine atom. Examination of the ion structures *A*, *B*, *C*, and *D* also shows that the fluorine is *not* substituted in the benzyl portion of the molecule. The 18 mass shift of Ions *B* and *D* also provides proof that the fluorine is not present in the carbons alpha to the basic nitrogen nor in the "R" group attached to the amide carbonyl (if the fluorine was substituted at C-2 of the piperidine ring, ion current for Ion *D* would be split between $m/z$ 146 and 164). The presence of the dimethylammonium ion at $m/z$ 42 (*M*) and the propionyl ion at $m/z$ 57 (*L*), and the absence of ions shifted 18 mass units to $m/z$ 60 and 75, respectively, confirms the absence of the fluorine at those sites and the presence of the propionyl moiety. At this juncture, the presence of the fluorine has been limited to either the C-3, C-4 position in the piperidine ring or to the anilino ring. In fentanyl, the piperidine ring produces an ion at $m/z$

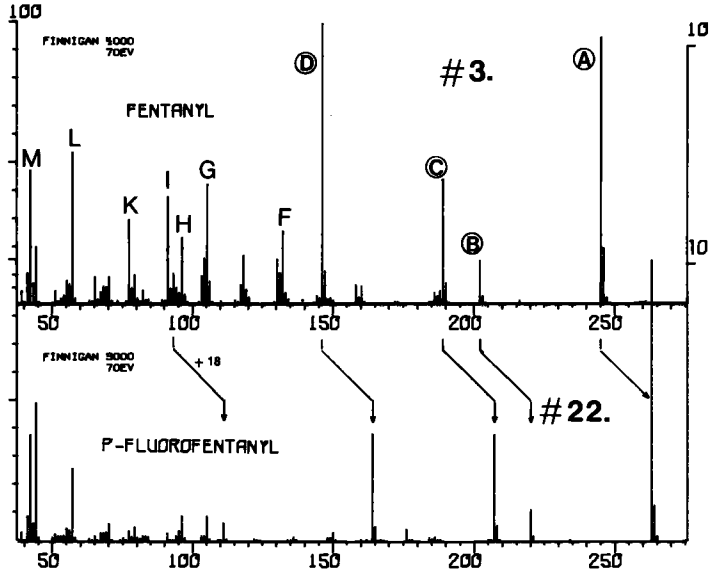
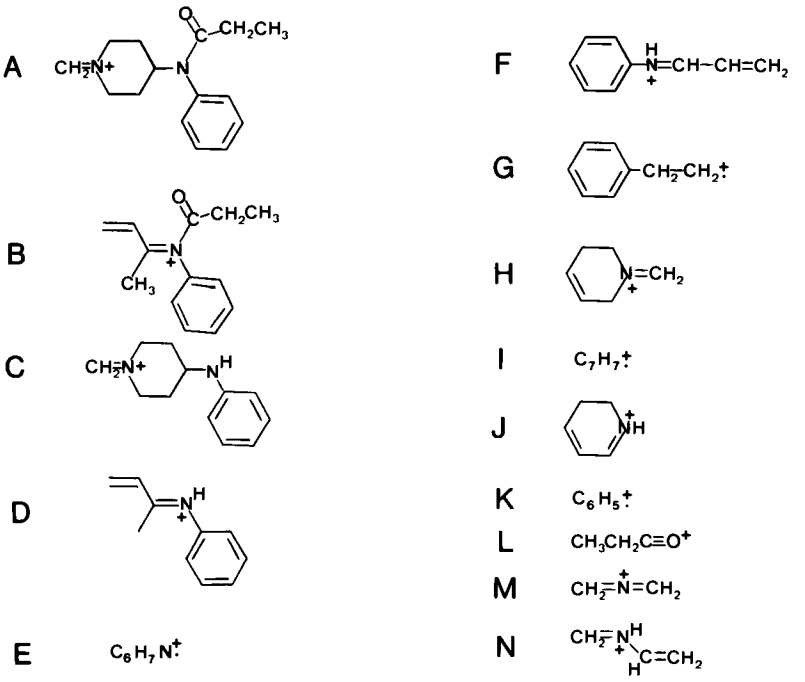



FIG. 14—*Electron ionization mass spectra for fentanyl and* p*-fluorofentanyl.*

TABLE 2—*Structures for the electron ionization produced ions of fentanyl.*




96 (*H*) and the anilino group an ion at *m/z* 93 (*E*). In *p*-FF, an ion is present at *m/z* 96 and the *m/z* 93 ion is not present; however, an ion is observed at 93 plus a fluorine (*m/z* 111). At this point, there can be little doubt as to the structure of *p*-FF; however, the position of the fluorine atom on the anilino ring cannot be assigned via this approach.

### 3-Methylfentanyl

As demonstrated with *p*-FF, the molecular weight for 3-methylfentanyl (3-MF) can be assessed by summing the Ions *A* and *I* ( 259 + 91), to give the molecular weight of 350 (Figs. 15 and 16). The difference in the molecular weights of fentanyl and 3-MF is 14 mass units, obviously a methylene addition. The position of the methyl substitution is determined, again as in the case of *p*-FF, by noting that the Ions *A*, *B*, *C*, and *D*, are each shifted to a value 14 daltons higher than observed for fentanyl, and that the Ions *L* and *M* do not shift (note that Ion *M* is shifted to *m/z* 56 in α-methylfentanyl and 2-methylfentanyl). At this point, the methyl substitution has been limited to the anilino ring and the C-3 and C-4 carbons of the piperidine ring. If C-4 was the substitution site, the Ions *A* and *C* would be shifted 14 daltons higher than the corresponding ions in fentanyl and the Ions *B* and *D* would remain at values *m/z* 202 and 146, respectively. Also, a weak Ion *E* is present at *m/z* 93, which indicates that the anilino moiety is not the site of substitution. Finally, the presence of the methyl group at C-3 of the piperidine ring is confirmed by the 14 mass shift of Ion *H* from *m/z* 96 for fentanyl to *m/z* 110 for 3-MF.

The structure of 3-MF is now defined except for the stereochemical relationship of the C-3 and C-4 carbons of the piperidine ring. Assuming isolated analyte is available, $H^1$-NMR can definitively allow that determination through the interpretation of those resonances, caused by the C-4 hydrogen.[4] However, in the case of 3-MF, the situation is such that the spatial

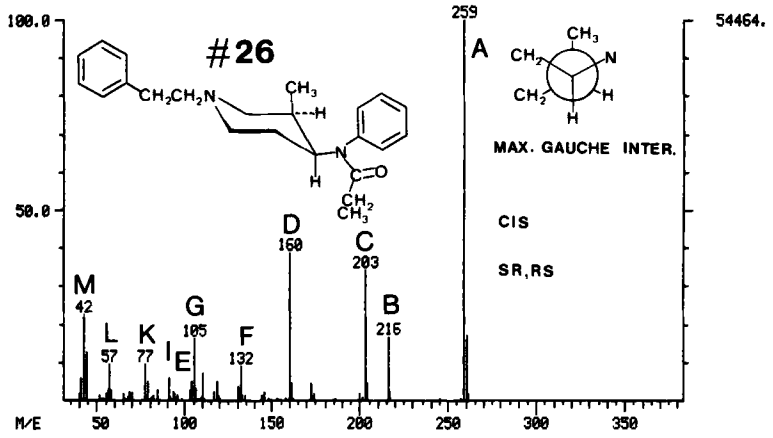



FIG. 15—*Electron ionization mass spectrum of* cis*-3-methylfentanyl, Compound 26, Table 1.*

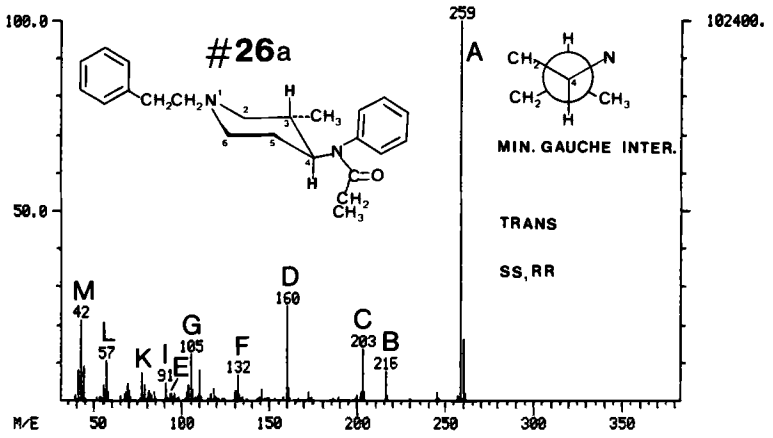



FIG. 16—*Electron ionization mass spectrum of* trans*-3-methylfentanyl, Compound 26a, Table 1.*

relationships between C-3 and C-4 are also easily assigned via MS. Meyerson and Weitkamp [*19*] have pointed out that after ionization the most stable isomer will have the least amount of energy available for further fragmentation of the molecule. Therefore, they argued, a fragment ion that occurs as a result of a simple cleavage reaction from the molecule ion of a isomer pair will also share this stability determined relationship. In the fentanyl derivatives, Ion *A* represents the principle simple cleavage product obtained from the molecule ion, and therefore, the two diastereoisomers of 3-MF provide a case in point. As such, in 3-MF, Ion *A* of the most stable isomer will undergo fewer additional fragmentations, and therefore, Ion *A* in that isomer will be the most abundant, hence other fragment ions will appear to be less abundant. Examination of EI-MS spectra for the 3-MF isomers (Figs. 15 and 16), shows clearly that the Isomer *26a* where the substituents at C-3 and C-4 are both equatorial, assuming the chair conformation, have fragment ions of lowered abundance relative to Ion *A*. Since the 3-MF isomers are encountered as a mixture of the two isomers, this feature, after separation has been accomplished, can be used to assign the stereochemistry.

All of the ions depicted in Table 2 have been discussed except those labeled *F, J, K,* and *N.* The Ions *J* and *K* are due to the presence of the piperidine and phenyl rings, respectively. The Ion *K* is useful in confirming the presence of a monosubstitution phenyl ring, but of course, it can arise from either end of the molecule. Ion *J,* in all cases examined, is present in low abundance for those derivatives where the piperidine ring is not substituted at C-2, 3, or 4. For those compounds where a substituent is present at C-2 or C-3, Ion *J* can still be observed at $m/z$ 82, however, the abundance is reduced to the point where it can become difficult to detect. Ion *F* incorporates the carbons from C-2, C-3 (or C-5, C-6), and C-4 of the piperidine ring and can be very useful in diagnosing a substitution at C-4. Ion *N* is interesting in that it apparently is of little importance except in the case of 2-methylfentanyl where an abundant $m/z$ 70 ion is present.

Figures 17 through 20 and Table 3 are provided so that the reader may verify the process just discussed. Note that three of the mass spectra (Figs. 18 to 20) are of fentanyl derivatives that have previously been encountered in "real" samples.

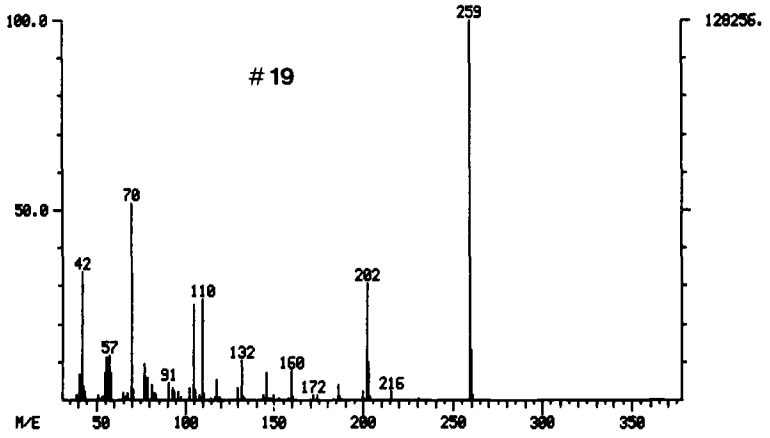



FIG. 17—*Electron ionization mass spectrum for 2-methylfentanyl, Compound 19, Table 1.*

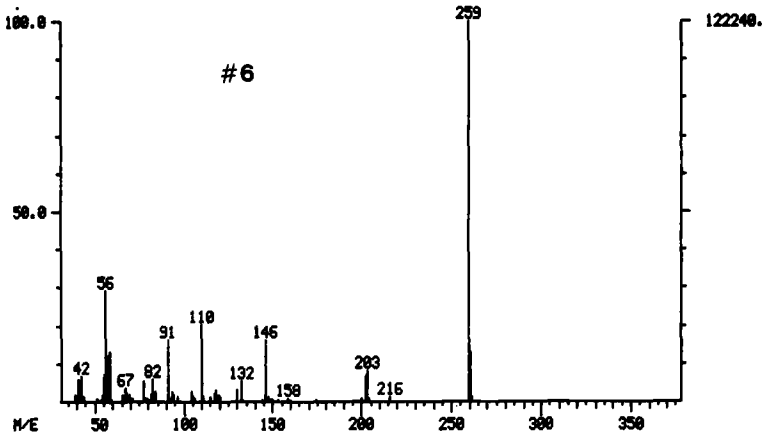



FIG. 18—*Electron ionization mass spectrum for α-methylfentanyl, Compound 6, Table 1.*

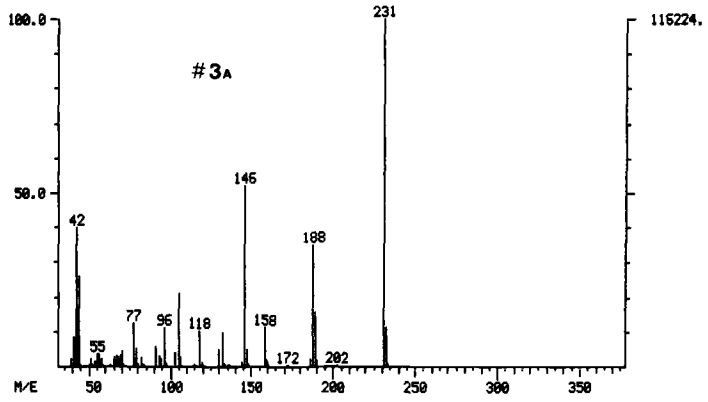



FIG. 19—*Electron ionization mass spectrum for* N-*[1-(2-phenylethyl)-4-piperidyl]*-N-*phenylacetamide, Compound 3a, Table 1.*

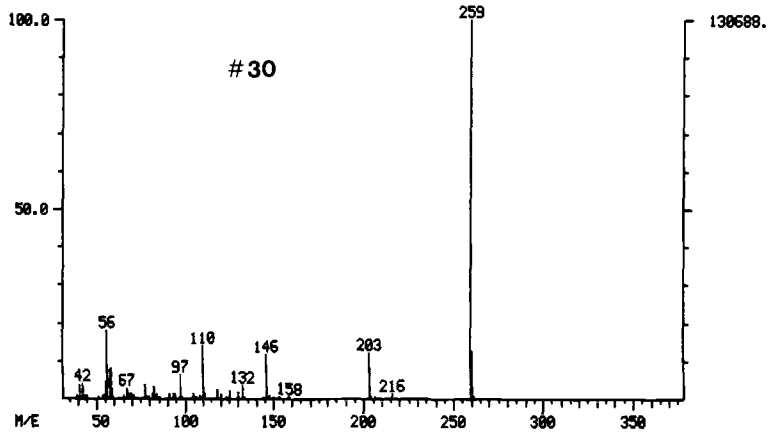



FIG. 20—*Electron ionization mass spectrum for α-methylthiofentanyl, Compound 30, Table 1.*

## Chromatographic Data

When the analysis of an unknown organic compound is attempted, it often is the case that data obtained from sources other than spectra are useful in supporting or, more importantly, negating a proposed structural feature. For instance, in the case at hand, a compound that *does not* extract from hydrochloric acid into chloroform as an ion pair is not likely to be a fentanyl derivative. In much the same manner, chromatographic data can be used to either add or subtract support for a given proposed structure. An obvious example for gas chromatography would be an expected increase in retention time for homologs with increasing molecular weight. In the main, the fentanyl homologs adhere to this generalization, however, there is at least one notable and useful exception. Compounds *20* and *21*, molecular weights of 336 and 350, respectively, were found to elute well before fentanyl under the conditions used in this work (Table 4). Where fentanyl (MW 336) is assigned a relative retention time (RRT) of 1.00, the compounds *20* and *21* had a RRT of 0.882 and 0.976, respectively. These compounds have a methyl substituted at the carbon beta to the piperi-

TABLE 3—*Mass to charge values for ion structures* A *through* N *for fentanyl and six derivatives.*

| Ion[a] | Fentanyl (3) | 3-MF (26, 26a) | 2-MF (19) | alpha-MF (6) | *p*-FF (22, 23, 25) | Acrylate (29) | Acetamide (28) |
|---|---|---|---|---|---|---|---|
| *A* | 245 | 259 | 259 | 259 | 263 | 257 | 245 |
| *B* | 202 | 216 | 202, 216 | 202 | 220 | 200 | 188 |
| *C* | 189 | 203 | 203 | 203 | 207 | 203 | 189 |
| *D* | 146 | 160 | 146, 160 | 146 | 164 | 146 | 146 |
| *E* | 93 | 93 | 93 | 93 | 111 | 93 | 93 |
| *F* | 132 | 132, 146 | 132, 146 | 132 | 150 | 132 | 132 |
| *G* | 105 | 105 | 105 | 119 | 105 | 119[b] | 119[b] |
| *H* | 96 | 110 | 110 | 110 | 96 | 110 | 110 |
| *I* | 91 | 91 | 91 | 91 | 91 | 91 | 91 |
| *J* | 82 | 82, 96 | 82, 96 | 82 | 82 | 82 | 82 |
| *K* | 77 | 77 | 77 | 77 | 77,95 | 77 | 77 |
| *L* | 57 | 57 | 57 | 57 | 57 | 55 | 43 |
| *M* | 42 | 42 | 42, 56 | 56 | 42 | 56 | 56 |
| *N* | 56 | 56 | 70[c] | 56 | 56 | 56 | 56 |

[a]See Tables 1 and 2 for structures.

[b]The formation of this ion for these compounds is not a favored process and therefore it is seen at quite low abundances; however, the absence of the $m/z$ 105 ion for these isomers stands out prominently.

[c]Ion *N* is of low abundance except in the case of 2-MF, Compound 19, Table 1.

TABLE 4—*Retention time data from capillary GC for fentanyl and derivatives.*

| Fentanyl Retention Times 16.68 min[a]<br>Tricontane Retention Times 23.499 min | |
|---|---|
| Compound No. (Table 1) | Relative Retention Time Referenced to Fentanyl |
| 1 | 0.732 |
| 2 | 0.817 |
| 3 | 1.000 |
| 3a | 0.907 |
| 4 | 1.076 |
| 5 | 1.176 |
| 6 | 1.082 |
| 7 | 1.010 |
| 8 | 1.006 |
| 9 | 1.062 |
| 10 | 1.099 |
| 11 | 1.094 |
| 12 | 1.152 |
| 13 | 1.086 |
| 14 | 1.049 |
| 15 | 1.078 |
| 16 | 1.181 |
| 17 | 1.142 |
| 18 | 1.171 |
| 19 | 1.056 |
| 20 | 0.882 |
| 21 | 0.976 |
| 22 | 0.951 |
| 23 | 0.866 |
| 24 | 0.834 |
| 25 | 0.920 |
| 26 | 1.065 |
| 27 | 0.965 |
| 28 | 1.003 |

[a]See Experimental Procedure for details.

dine nitrogen and alpha to the phenyl ring, a structural feature that could be supported by GC retention time data. Another situation when GC retention time data can be used to advantage is for that frequent occurrence when aromatic rings are substituted to yield a sample where both ortho and para positional isomers are present. With the fentanyl derivatives, it was found that for the anilino ring the para isomer eluted at longest RT, whereas for phenyl ring substitutions the ortho isomer was at longest RT.

Without doubt, other chromatographic techniques other than GC can offer complementary structural information in much the same manner. In point of fact, Lurie et al [*12*] have published HPLC results wherein fentanyl derivatives are related to retention volumn versus structural modifications. In that work a topological index is utilized to represent molecular surface areas, a concept that could provide structural information.

## Conclusion

The fentanyl derivatives can most conclusively be identified via the combined techniques of IR, NMR, and MS. However, the superior sensitivity of the mass spectrometer makes it the instrument of choice for a fentanyl derivative analysis. Further, it has been shown that most fentanyl derivatives can be fully determined via MS with electron ionization data only.

In the normal sequence of unknown compound identification the final step is to compare data from the unknown to that of a standard. For nearly all cases involving fentanyl derivatives that will require synthesis. For that work a number of authors have published the details of synthesis [*1,9,14-17,20-25*].

As a cautionary note the authors would like to point out that isolation or synthesis of fentanyl derivatives is not without risk. The magnitude of the danger involved in the inhalation or skin absorption of these compounds is not accurately known, but when one is handling compounds of such potency as (+)-*cis*-3-methylfentanyl it must be considerable.

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Address requests for reprints or additional information to
D. Cooper
Drug Enforcement Administration
Special Testing and Research Laboratory
7704 Old Springhouse Rd.
McLean, VA 22102