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Studies on 1-(2-Phenethyl)-4-(*N*-propionylanilino)piperidine (Fentanyl) and Related Compounds. I. Spectrometric and Chromatographic Analyses of 3-Methylfentanyl and α-Methylfentanyl

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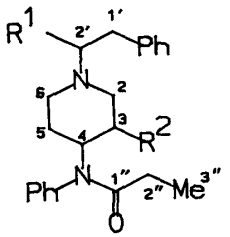
The structure of a new drug of abuse called China White was confirmed to be α-methylfentanyl, one of the compounds related to fentanyl, based on comparisons of their electron impact and chemical ionization mass, nuclear magnetic resonance and infrared spectra. 3-Methylfentanyl, which was previously assigned as a component of China White, and α-methylfentanyl could be discriminated from each other by not only spectrometric but also chromatographic analyses, such as thin layer chromatography and gas chromatography. The detection limits were 0.1 μg in both methods.

Keywords——α-methylfentanyl; 3-methylfentanyl; mass spectrometry; nuclear magnetic resonance spectrometry; infrared spectrometry

Since fentanyl [1-(2-phenethyl)-4-(*N*-propionylanilino)-piperidine, **1**] (Fig. 1A), an analgesic drug, was prepared in 1964,[1a] various related compounds, such as 3-methylfentanyl [3-methyl-1-(2-phenethyl)-4-(*N*-propionylanilino)piperidine, **2**] (Fig. 1B) and α-methylfentanyl [1-(1-methyl-2-phenethyl)-4-(*N*-propionylanilino)piperidine, **3**] (Fig. 1C) have been synthesized and their analgesic activity has been examined.[1b,c] Analyses of **1** and several related compounds by gas chromatography (GC)[2a-c] and high-pressure liquid chromatography[2d] have been reported.

In 1981, a powerful analgesic drug, called "China White," began to be abused. In several cases, overdoses of China White proved to be lethal.[3a,b] In 1981, Kram *et al.*[3a] proposed that the structure of China White was **2** on the bases of mass spectrometry (MS), nuclear magnetic resonance (NMR) spectrometry and infrared (IR) spectrometry. However, they obtained the spectral data of China White with the hydrochloride salt, while only the spectral data of 3-methylfentanyl oxalate (**2a**) were available in the literature.[1c] Therefore, it could not be expected that the spectra of both compounds would be superimposable in detail, especially the ^{1}H-NMR and IR spectra, and some doubt still remained concerning the structural confirmation of China White.



A: $R^1=R^2=H$ fentanyl
B: $R^1=H$, $R^2=Me$ 3-methylfentanyl
C: $R^1=Me$, $R^2=H$ α-methylfentanyl

Fig. 1. Structures of Fentanyl and Related Compounds

Recently, McLafferty *et al.*[4] proposed that the structure of China White was **3** based on a comparison of the electron impact (EI) mass spectra of **2** and **3**. However, this seems to be an insufficient basis for the structural confirmation of China White.

Thus, we prepared **2a**, 3-methylfentanyl hydrochloride (**2b**) and α-methylfentanyl hydrochloride (**3**), and compared their spectral data in detail. Furthermore, suitable analytical conditions for thin layer chromatography (TLC) and GC were developed to discriminate the 3-methyl and α-methyl derivatives.

Materials and Methods

Spectrometric Analysis——EI and chemical ionization (CI) mass spectra were measured with a Hitachi M-80 double focussing mass spectrometer having a direct inlet system. The conditions for EI-and CI-MS were as follows: ionization energy, 20 eV (EI), 100 eV (CI); ionization current, 110 μA; temperature of ion source, 180 °C; reactant gas for CI-MS, isobutane.

Measurement of ^{1}H- and ^{13}C-NMR spectra was conducted with a JEOL FX-100 NMR spectrometer, and samples were dissolved in deuteriochloroform with tetramethylsilane as an internal standard. IR spectra were obtained with a JASCO DS 701G instrument.

Chromatographic Analysis——TLC was carried out on 0.25 mm thick Silica Gel F_{254} plates (E. Merck, Darmstadt, FRG) and solvent systems used for development were (a) acetone–chloroform (1 : 2, v/v); (b) benzene–chloroform–methanol (2 : 10 : 1, v/v); (c) chloroform–*n*-hexane–methanol (10 : 2 : 1, v/v). The plates after development were examined under ultraviolet (UV) light (254 nm) and then sprayed with one of the following coloring reagents: (i) 1% iodine in methanol solution; (ii) Dragendorff reagent; (iii) iodoplatinate reagent.

For GC analysis, a Shimadzu GC 4CM gas chromatograph equipped with a flame ionization detector was used. A glass column (1 m × 3 mm i.d.) was packed with 1% OV-17 on 80—100 mesh Chromosorb W AW DMCS. The carrier gas was nitrogen (50 ml/min). The column temperature was 220 °C, and the injection port and detector temperatures were 240 °C.

Synthesis of Standard Samples——Samples of *cis*- and *trans*-**2** and **3** were prepared according to the method of Van Bever *et al.*[1c]; *cis*- and *trans*-**2** were purified as the oxalate (*cis*- and *trans*-**2a**) and the hydrochloride (*cis*- and *trans*-**2b**), and **3** was prepared as the hydrochloride.

cis-3-Methylfentanyl Oxalate (*cis*-**2a**): ^{1}H-NMR ($CDCl_3$)δ: 1.00 (3H, t, J=8 Hz, $COCH_2\underline{CH_3}$), 1.22 (3H, d, J=8 Hz, 3-$\underline{CH_3}$), 1.94 (2H, q, J=8 Hz, $COCH_2CH_3$), 4.59 (1H, m, C_4-H). EI-MS *m/z*: 259 ($M^+ - C_7H_7$), 203 ($M^+ - C_7H_7$, C_3H_4O), 202 ($M^+ - C_7H_7$, C_3H_7N), 160, 110 ($C_7H_{12}N^+$), 91 ($C_7H_7^+$), 58 ($C_3H_8N^+$), 57 ($C_3H_5O^+$). CI-MS *m/z*: 351 (QM^+), 259 ($M^+ - C_7H_7$), 203 ($M^+ - C_7H_7$, C_3H_4O), 202 ($M^+ - C_7H_7$, C_3H_7N), 160, 110 ($C_7H_{12}N^+$).

trans-3-Methylfentanyl Oxalate (*trans*-**2a**): ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=8 Hz, $COCH_2\underline{CH_3}$), 1.02 (3H, d, J=8 Hz, 3-$\underline{CH_3}$), 1.94 (2H, q, J=8 Hz, $COCH_2CH_3$), 4.59 (1H, m, C_4-H). The EI and CI mass spectra were identical with those of *cis*-**2a**. These analytical data were identical with those reported by Janssen *et al.*[1]

cis-3-Methylfentanyl Hydrochloride (*cis*-**2b**): ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7 Hz, $COCH_2\underline{CH_3}$), 1.44 (3H, d, J=7 Hz, 3-$\underline{CH_3}$), 1.93 (2H, q, J=7 Hz, $COCH_2CH_3$), 4.31 (1H, m, C_4-H). ^{13}C-NMR ($CDCl_3$) δ: 9.34 (q, 3-$\underline{CH_3}$), 13.27 (q, $C_{3''}$), 23.35 (t, C_5), 28.82 (t, $C_{2,6}$), 29.90 (d, C_3), 52.93 (t, $C_{2''}$), 54.88 (d, C_4), 57.10 (t, $C_{1'}$), 58.83 (t, $C_{2'}$), 127.09, 128.66, 128.83, 129.31, 130.07, 130.29 (d, aromatic carbons), 136.25, 139.07 (s, aromatic carbons), 174.93 (s, $C_{1''}$). The EI and CI mass spectra were identical with those of **2a**. IR ν_{max}^{KBr} cm^{-1}: 1660 (NCO).

trans-3-Methylfentanyl Hydrochloride (*trans*-**2b**): ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz, $COCH_2\underline{CH_3}$), 1.19 (3H, d, J=7 Hz, 3-$\underline{CH_3}$), 1.90 (2H, q, J=7 Hz, $COCH_2CH_3$), 4.50 (1H, m, C_4-H). ^{13}C-NMR ($CDCl_3$), δ: 9.70 (q, 3-$\underline{CH_3}$), 15.11 (q, $C_{3''}$), 27.57 (t, C_5), 30.18 (t, $C_{2,6}$), 32.02 (d, C_3), 48.59 (t, $C_{2''}$), 54.07 (t, $C_{1'}$), 54.55 (d, C_4), 58.56 (t, $C_{2'}$), 127.09, 128.66, 128.83, 129.31, 130.07, 130.29 (d, aromatic carbons), 136.14, 139.07 (s, aromatic carbons), 174.93 (s, $C_{1''}$). The EI and CI mass spectra and IR spectrum were identical with those of *cis*-**2b**.

α-Methylfentanyl Hydrochloride (**3**): ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=8 Hz, $COCH_2\underline{CH_3}$), 1.22 (3H, d, J=7 Hz, >CH-$\underline{CH_3}$), 1.98 (2H, q, J=8 Hz, $COCH_2CH_3$), 2.56 (1H, m, CH_2-$\underline{CH}$-CH_3), 4.74 (1H, m, C_4-H). ^{13}C-NMR ($CDCl_3$) δ: 10.22 (q, α-$\underline{CH_3}$), 13.44 (q, $C_{3''}$), 29.06 (t, $C_{3,5}$), 29.53 (t, $C_{2,6}$), 48.79 (t, $C_{2''}$), 50.49 (t, $C_{1'}$), 51.49 (d, C_4) 64.93 (d, $C_{2'}$), 128.40, 129.99, 130.28, 130.46, 131.04, 131.30 (d, aromatic carbons), 137.44, 139.26 (s, aromatic carbons), 176.07 (s, $C_{1''}$). EI-MS *m/z*: 259 ($M^+ - C_7H_7$), 203 ($M^+ - C_7H_7$, C_3H_4O), 202 ($M^+ - C_7H_7$, C_3H_7N), 146, 110 ($C_7H_{12}N^+$), 91 ($C_7H_7^+$), 58 ($C_3H_8N^+$), 57 ($C_3H_5O^+$). CI-MS *m/z*: 351 (QM^+), 259 ($M^+ - C_7H_7$), 203 ($M^+ - C_7H_7$, C_3H_4O), 202 ($M^+ - C_7H_7$, C_3H_7N), 146, 110 ($C_7H_{12}N^+$). IR ν_{max}^{KBr} cm^{-1}: 1655 (NCO).

Results and Discussion

Spectrometric Analysis of 3-Methylfentanyl and α-Methylfentanyl

In the EI mass spectra of **2** and **3**, molecular ion (M^+) peaks were not observed, and the

highest mass ion peaks were observed at *m/z* 259 as the base ion peaks. These ions arose from the elimination of $C_7H_7^+$. In a comparison of other diagnostic ions, almost all the fragment ions were identical in the two spectra, except the fragment ions at *m/z* 160 (**2**) and *m/z* 146 (**3**) with weak intensity. According to the EI mass spectral analysis of these compounds,[4] these ions arose from the 2–3 and 1–6 bond cleavage of the piperidine ring and the elimination of the propionyl group. These fragment ions were also observed in the CI mass spectra of these compounds, and the relative intensities of these peaks were increased by 10—20%. The comparison of these ion peaks made it possible to discriminate between **2** and **3**. In the EI-mass spectrum of China White reported by Kram *et al.*,[3a] diagnostic ion peaks were observed at *m/z* 259, 203, 202, 146, 110, 91, 58 and 57, and these peaks were all observed in the EI mass spectrum of **3**.

The ^{1}H-NMR spectra of *cis*- and *trans*-**2a** prepared here were identical to those reported by Van Bever *et al.*[1c] Since the ^{1}H-NMR spectrum of China White reported by Kram *et al.*[3a] was measured with the hydrochloride, *cis*- and *trans*-**2a** were converted into the hydrochloride salts (**2b**), and the ^{1}H-NMR spectra were measured. Furthermore, the ^{1}H-NMR spectra of *cis*- and *trans*-**2b** and **3** were compared with that of China White shown by Kram *et al.*[3a] Although there was no difference in the ^{1}H-NMR signals between the 3- and α-methyl groups, the discrimination between *cis*- and *trans*-**2b** and **3** was accomplished by comparison of the chemical shifts of the protons at the 4-position of the piperidine ring. These signals appeared at δ 4.74 as a multiplet in the spectrum of **3**, while they appeared at δ 4.31 and 4.50 in the spectra of *cis*- and *trans*-**2b**, respectively. Further, a characteristic multiplet signal was observed at δ 2.56 only in the ^{1}H-NMR spectrum of **3**. A comparison of these spectra with the reported spectrum of China White indicated that the ^{1}H-NMR spectrum of **3** was identical with that of China White.

Compouds **2b** and **3** gave quite similar IR spectra, except in the regions of 1000—1200 and 1300—1500 cm^{-1}. Thus the discrimination of these two compounds was possible by the comparison of these regions in the IR spectra. The IR spectrum of China White reported by Kram *et al.*[3a] was identical with that of **3** even in the region of 1000—1500 cm^{-1}.

From the results mentioned above, China White was identified as **3**. This conclusion is in agreement with the result of McLafferty *et al.* based on EI-MS analysis.[4]

Chromatographic Analysis of 3-Methylfentanyl and α-Methylfentanyl

For the TLC analysis of **2** and **3**, various developing solvent systems were examined. However, the *Rf* values of the two compounds were very close to each other because of the similarity of structure and polarity. Finally, these two compounds were separated, as shown in Table I, by using several solvent systems as described in Materials and Method. The detection limits of these two compounds were 1 μg based on 254 nm UV absorption, 0.1 μg by using 1% iodine–methanol solution, 0.1 μg by using Dragendorff reagent and 0.2 μg by using iodoplatinate reagent. GC analysis with several liquid phases such as OV-1, OV-17 and SE-30 was also examined. These two compounds, **2** and **3**, were clearly separated by the use of 1% OV-17 as liquid phase with retention times of 17.1 and 20.2 min, respectively. The detection

TABLE I. *Rf* Values of 3- and α-Methylfentanyl

	Rf values		
	System (a)	System (b)	System (c)
3-Methylfentanyl	0.35	0.69	0.68
α-Methylfentanyl	0.25	0.62	0.60

Solvent systems (a), (b), and (c) are described in the text.

limit of these compounds with the flame ionization detector was 0.1 μg. Thus, **2** and **3** could be discriminated clearly by both TLC and GC analysis.

References

1) *a*) P. A. J. Janssen and J. F. Gardocki, U. S. Patent 3141823 (1964) [*Chem. Abstr.*, **61**, 10689*a* (1964)]; *b*) P. A. J. Janssen, U. S. Patent 3164600 (1965) [*Chem. Abstr.*, **62**, 14635*c* (1965)]; *c*) W. F. M. Van Bever, C. J. E. Niemegeers, and P. A. J. Janssen, *J. Med. Chem.*, **17**, 1047 (1974).
2) *a*) H. H. Van Rooy, N. P. E. Vermeulen, and J. G. Bovill, *J. Chromatogr.*, **223**, 85 (1981); *b*) J. A. Phipps, M. A. Sabourin, W. Buckingham, and L. Strunin, *ibid.*, **272**, 392 (1983); *c*) R. Woestenborghs, L. Michielsen, and J. Heykants, *ibid.*, **224**, 122 (1981); *d*) I. S. Lurie and A. C. Allen, *ibid.*, **292**, 283 (1984).
3) *a*) T. C. Kram, D. A. Cooper, and A. C. Allen, *Anal. Chem.*, **53**, 1379A (1981); *b*) S. Stinson, *Chem. Eng. News*, Jan. 19, 71 (1981).
4) M. T. Cheng, G. H. Kruppa, F. W. McLafferty, and D. A. Cooper, *Anal. Chem.*, **54**, 2204 (1982).