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Isomeric Fluoro-methoxy-phenylalkylamines: a new series of controlled-substance analogues (designer drugs)

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Abstract

An impressively large number of clandestinely produced controlled-substance analogues (designer drugs) of amphetamine with high structural variety have been encountered in forensic samples in recent years. The continuous designer drug exploration and their widespread consumption results in an increasing number of reports regarding abuse and intoxication. This study presents the analytical properties of a series of new fluoro-methoxy-substituted controlled-substance analogues of amphetamine. Three ring positional isomeric fluoroamphetamines, two isomeric fluoromethoxyamphetamines, two *N*-alkyl 4-fluoroamphetamines, and one 4-fluorophenylbutan-2-amine were identified and differentiated by gas chromatography–mass spectrometry (GC–MS), ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR), and gas chromatography–infrared spectroscopy (GC–IR). The regioisomeric 2-, 3-, and 4-fluoroamphetamines and the regioisomeric fluoro-methoxyamphetamines show virtually identical mass spectra so that this method is insufficient to discriminate between these closely related compounds. The mass spectra of the acetylated compounds allowed a differentiation of the 4-fluoroamphetamine from its regioisomeric 2- and 3-fluoroamphetamines. The gas chromatographic properties of the three regioisomeric fluoroamphetamines and their acetylated and trifluoroacetylated derivatives are also so similar that a complete separation of these compounds could not be achieved under GC–MS conditions. The two isomeric compounds 5-fluoro-2-methoxyamphetamine and 3-fluoro-4-methoxyamphetamine on the other hand showed significant different gas chromatographic retention times so that a separation was uncomplicated. The trifluoroacetylation of these compounds proved to be an effective method for their mass spectral differentiation. Gas chromatography–infrared spectroscopy and ^{1}H- and ^{13}C-nuclear magnetic resonance allowed an unequivocal differentiation of all studied regioisomeric fluoroamphetamines and fluoro-methoxyamphetamines.

Keywords: Fluoroamphetamines; Fluoro-methoxyamphetamines; Designer drugs; Fluorophenylalkylamines; Mass spectra; NMR; Illicit synthesis; Drug abuse

1. Introduction

Amphetamine and its derivatives are widely abused central nervous system stimulants and are well documented in literature [1]. The large number of structurally closely related amphetamine variants seriously affects the ability to detect novel amphetamine controlled-substance analogues [2–4] and makes their identification an ardous task [5–10,32].

In January 2003, a series of clandestinely prepared fluoro-methoxy-substituted phenylalkylamines were seized in the federal state of Sachsen–Anhalt (Germany), which were so far unknown on the illicit market. The white powders consisted of nearly pure 2-fluoroamphetamine sulfate **1**, respectively hydrochloride salts of 3- and 4-fluoroamphetamine **2**–**3**, 5-fluoro-2-methoxyamphetamine **4**, 3-fluoro-4-methoxyamphetamine **5**, *N*-methyl-4-fluoroamphetamine **6**,

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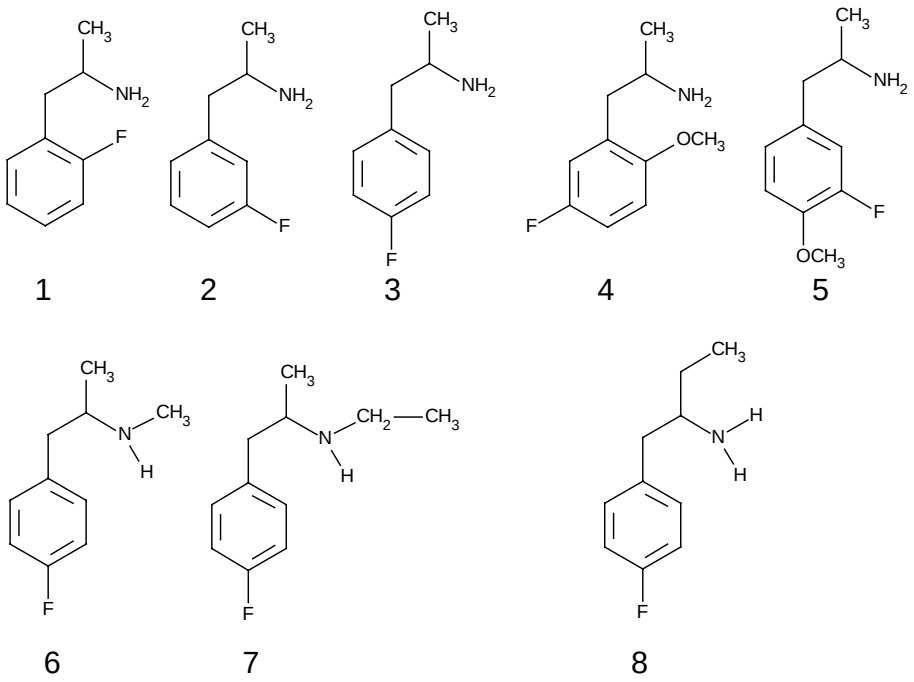


Fig. 1. Chemical structures of the analysed fluoro-methoxy-substituted phenylalkylamines **1–8**.

N-ethyl-4-fluoroamphetamine **7**, and 1-(4-fluorophenyl)butan-2-amine **8** (Fig. 1).

Little is known about the pharmacological properties of fluoroamphetamine derivatives, less for fluoro-methoxy-substituted amphetamines. The 2,5-dimethoxy-4-fluoroamphetamine (DOF) is known to have less psychoactivity than its well-known analogues 4-bromo-2,5-dimethoxyamphetamine (DOB), and 2,5-dimethoxy-4-iodoamphetamine (DOI) [1].

The mono-substituted fluoroamphetamine analogues, however, obviously have a potential for abuse. Drug discrimination studies in rats showed that **3**, a fluoro-substituted (+)-amphetamine, showed short-term serotonin-releasing effects [11]. The substitution of a hydrogen atom by a fluorine atom is commonly employed to increase the lipophilicity and to enhance the passing of the blood brain barrier of central nervous system (CNS) agents like amphetamine derivatives [12,13]. It is therefore likely that fluoroamphetamine and fluoro-methoxy amphetamines elicit pharmacological effects.

The detection and identification of unknown drugs is typically performed by gas chromatography–mass spectrometry (GC–MS) due to the high sensitivity and ability to separate organic compounds in complex mixtures. The usually performed electron impact (EI) ionization method is often insufficient to discriminate closely related amphetamine derivatives because of their often virtually identical mass spectra [4,6,7,9]. One of the major drawbacks of mass spectrometry is its inability to locate aromatic ring substituents so that the employment of NMR spectroscopy becomes unavoidable. ^{1}H- as well as ^{13}C-NMR spectroscopy has been a very helpful tool in the structure elucidation of substituted amphetamines and designer drugs [21,22], especially for those with one or more substituents, like a methoxy or an ethoxy group or one or more methyl groups in the aromatic ring [9,23–25]. These spectroscopic techniques allow the unambiguous determination of the position of substituents in the aromatic ring by analysis of the chemical shift and also the splitting of the signals and the corresponding coupling constants. Infrared (IR) spectroscopy and gas chromatography–infrared spectroscopy (GC–IR) have been successful in differentiating closely related amphetamine isomers [14,15]. In order to add a significant level of confidence in identifying the designer drugs **1–8** this technique was also applied. The synthesis [16] and some spectroscopic data of the three fluoro-amphetamines **1–3** have been published [17].

This paper describes the analytical techniques necessary for the differentiation and identification of regioisomeric fluoro-methoxy-phenyalkylamines **1–8** using GC, GC–MS coupling, IR- and NMR-spectroscopy.

2. Instrumentation

2.1. GC

For separation studies of compounds **1–3** a Varian 3400 CX gas chromatograph with a fused silica capillary column DB1 (30 m × 0.32 mm, thickness 0.25 μm) and flame

ionization detector was used. The measurements were made isothermally at 90 °C with open split (1/100). The injector and detector temperatures were 280 °C, the carrier gas was helium.

To gain additional information and a better gas chromatographic separation the acetylated and trifluoroacetylated compounds were also studied.

2.2. GC–MS

The electron impact mass spectra were obtained with a Finnigan TSQ 70 (Finnigan MAT, Bremen) with a DEC-Station 2100, coupled to a Varian 3400 CX gas chromatograph. A fused silica capillary column DB1 (30 m × 0.32 mm, thickness 0.25 μm) was used. The temperature program consisted of an initial temperature of 80 °C held for 1 min, followed by a linear ramp to 280 °C at 15 °C/min. The final temperature was held for 15 min. The split/splitless injector and detector temperatures were 280 °C, the carrier gas was helium. The following optimized detector parameters were used:

- EI-mode: ionization voltage, 70 eV; scan time, 1 s; and scan range, 40–600 Da.
- CI-mode: ionization voltage, 70 eV; source temperature, 150 °C; reactant gas, methane; source pressure, 0.2 Pa; scan time, 1 s; and scan range, 50–600 Da.

2.3. NMR spectroscopy

The spectra were recorded with a Bruker ARX 300 NMR spectrometer, at a resonance frequency of 300.13 MHz for ^{1}H-NMR spectra and 75.47 MHz for ^{13}C-NMR spectra at 300 K. The ^{1}H-NMR spectra were recorded using standard pulse programs. The ^{13}C-NMR spectra are recorded with ^{1}H decoupling using composite pulse decoupling.

Five to ten milligrams of the compounds were dissolved in 100 μl of DMSO-d_6 and 500 μl of $CDCl_3$ were added (compounds **2**–**8**), compound **1** was dissolved in 300 μl of D_2O, then 300 μl of acetone-d_6 were added. Tetramethylsilane (TMS) was used as an internal standard for both ^{1}H- and ^{13}C-NMR spectra.

For the determination of the (HH) and (HF) coupling constants two-dimensional *J*-resolved spectra were recorded using the manufacturer's pulse program with an optimized sweep width for the aromatic region (corresponding to 0.3–0.7 ppm) using 256 data points in the F2 region and 128 data points in the F1 region, which was set to 60 Hz.

2.4. IR, GC–IR

The infrared spectra were acquired using a Bruker IFS 66 Fourier Transform Infrared (FT-IR) spectrometer with a resolution of 2 cm^{-1}. In cases of vapor-phase spectra, a resolution of 8 cm^{-1} was used and the sample was introduced by an interfaced Carlo Erba 6000 gas chromatograph equipped with a SE 30 capillary column.

In cases of solid-phase spectra the compounds were prepared as potassium bromide (KBr) pellets.

3. Results and discussion

3.1. GC

The retention times of 3- and 4-fluoroamphetamine **2** and **3** are so similar that a separation of these compounds was not possible under standard GC–MS operating conditions. Only the 2-fluoroamphetamine **1**, having an calculated Kovats retention index [18] of 1103, could be separated partially from co-eluting **2** and **3** with an index of 1109. The acetylated and trifluoroacetylated compounds **1**–**3** showed no better results under these circumstances.

The isothermal measurements on a separately operated GC showed a somewhat better separation (Fig. 2). 2-Fluoroamphetamine **1** could be baseline separated from its isomeric compounds **2** and **3** under these optimized conditions but the co-eluting compounds **2** and **3** showed still overlapping peaks with only partial separation. The calculated Kovats indices were 1106 for **1**, 1112 for **2**, and 1114 for **3**.

The fluoro-methoxyamphetamines **4** and **5**, having calculated Kovats retention indices of 1318 and 1363, respectively, could be separated under standard GC–MS operating conditions without difficulties.

3.2. Mass spectrometry

3.2.1. Mass spectrometry of the pure compounds

The electron impact mass spectra of the phenalkylamines **1**–**8** (Fig. 3) show intense immonium ions [7] and molecular ions with very low intensities [19]. The nominal molecular weights were, therefore, established by chemical ionization (CI) using methane as reagent gas for all compounds [20].

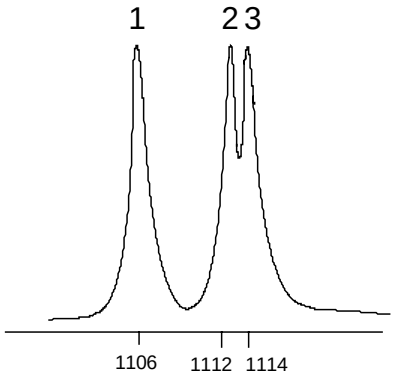


Fig. 2. Gas chromatogram of the mixture of the fluoroamphetamines **1–3** with Kovats indices (separately operated GC).

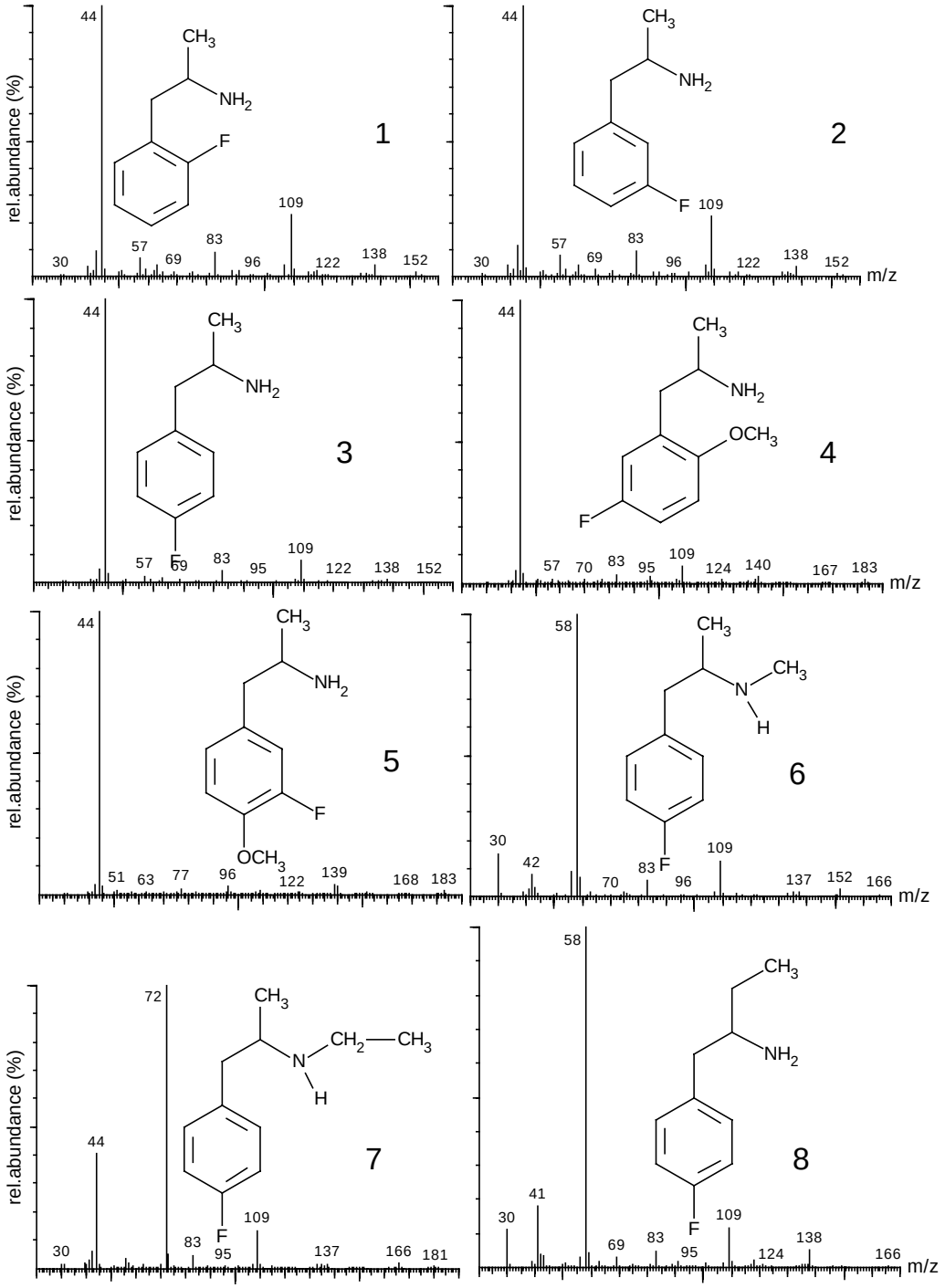
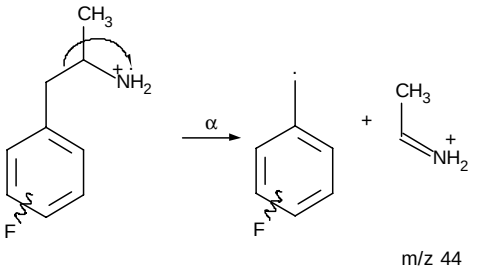
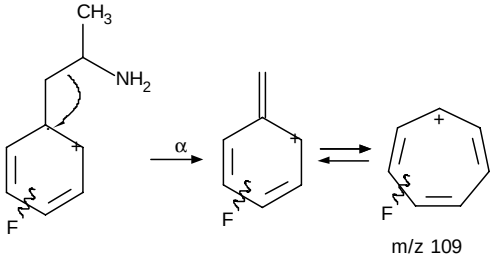


Fig. 3. EI mass spectra for the fluoro-methoxy-substituted phenylalkylamines **1**–**8**.

The electron-donating ability of the nitrogen atom in the isomeric fluoroamphetamines **1**–**3** induces a fast α-cleavage reaction (α) and produces intense immonium ions at *m*/*z* 44 and molecular ions of low intensities at *m*/*z* 153 (Scheme 1). The significant fragment at *m*/*z* 109 corresponds to a fluorobenzyl cation or a fluoro-substituted tropylium cation generated by an α-cleavage of the benzyl bond (Scheme 2). There is no observable *ortho* effect reaction [19], which could give any information for the aromatic fluoro position so that the isomeric fluoro-amphe-



Scheme 1. α-Cleavage reaction of fluoro phenethylamine derivatives.



Scheme 2. Benzyl bond cleavage reaction in fluoro phenethylamine derivatives.

tamines **1**–**3** show virtually identical mass spectra (Fig. 3, **1**–**3**).

The mass spectra of the isomeric fluoro-methoxyamphetamines **4** and **5** are dominated also by their intense immonium ions at *m/z* 44 and the molecular ions at *m/z* 183 have very low intensities (Fig. 3, **4** and **5**). The analogous cleavage of the benzyl bond (Scheme 2) gives fluoromethoxy-substituted benzyl or tropylium cations at *m/z* 139. There is no significant fragment to allow differentiation between the two isomeric fluoromethoxyamphetamines **4** and **5,** so that mass spectrometry is not sufficient to identify these underivatized compounds unambiguously. The 4-fluoromethamphetamine **6** shows the expected immonium ion at *m/z* 58 and a low intensity molecular ion at *m/z* 167 (Fig. 3, **6**).

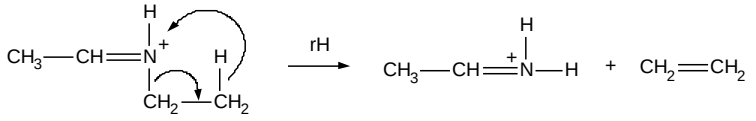
The mass spectra of the fluorophenethylamines **7** and **8** show the expected intense immonium ions at *m/z* 72 and 58, respectively and fluorobenzyl cations at *m/z* 109 (Fig. 3, **7** and **8**). The fragment at *m/z* 44 in the mass spectrum of *N*-ethyl-4-fluoroamphetamine **7** (Fig. 3, **7**) can be explained by an olefin loss reaction of immonium ions with an ethyl or larger alkyl group at the nitrogen producing other immonium ions by loosing the whole side-chain (Scheme 3) [19].

3.2.2. Mass spectrometry of the derivatized compounds

The unfavorable mass spectrometric properties of the pure compounds caused us to study the mass spectra of the acetylated and trifluoroacetylated compounds (Figs. 4–6). It was found that the mass spectrum of the acetylated 4-fluoroamphetamine **3** (Fig. 4, **3**) showed a significant fragment at *m/z* 136 with an abundance of about 20%. The mass spectra of the acetylated **1** and **2** (Fig. 4, **1** and **2**) show this fragment with a much lower relative abundance of about 5–6%. These measurements were reproducible so that the higher relative abundance of about 20% of the fragment at *m/z* 136 seems to be a good indicator for the acetylated **3**. This fragment is generated by the inductive route of the McLafferty rearrangement (Scheme 4) [19]. The radical electron at the oxo-group rearranges the H-atom at the γ-position (rH) of the aliphatic chain. A following inductive cleavage (i) by the positive charge at the carbonyl C-atom breaks the β-bond, forming a neutral enolized acetamide and an ionized 3(4-fluorophenyl)-propene with *m/z* 136.

The mass spectra of the acetylated **4** and **5** (Fig. 5) show the analogous fluoromethoxy McLafferty products at *m/z* 166. The spectra of these isomeric compounds show a significant abundance difference for the fragments at *m/z* 139 and 109 (Fig. 5). The acetylated **4** shows a relative intense ion at *m/z* 109 (9%), but a very low relative abundance for the fragment at *m/z* 139 (3%). The acetylated **5** on the other hand presents a relatively low abundance ion at *m/z* 109 (1.5%), but a relative high abundance ion at *m/z* 139 (9%). The fragment at *m/z* 139 corresponds to the mass of a fluoromethoxybenzyl cation, which could yield a fluorobenzyl cation at *m/z* 109 by loss of formaldehyde. It seems that the high intensity of the fluoromethoxybenzyl cation at *m/z* 139 in the mass spectrum of acetylated **5** could find an explanation in the negative inductive effect of the fluoro atom *ortho* to the leaving methoxy group.

The mass spectra of the trifluoroacetylated compounds **4** and **5** show other differences (Fig. 6). The mass spectrum of the trifluoroacetylated **4** shows three significant fragments with *m/z* 109 (fluorobenzyl cation), 140 and 166 (McLafferty product). The odd electron ion at *m/z* 140 is generated by a γ-H-atom rearrangement to the aromatic *ortho* position, which is known to accompany the benzyl bond cleavage reaction common in alkyl aromatics [19] (Scheme 5). The radical of an ionized aromatic π-bond rearranges a γ-H-atom of the



Scheme 3. Olefine loss reaction of immonium ions with an ethyl or larger alkyl group.

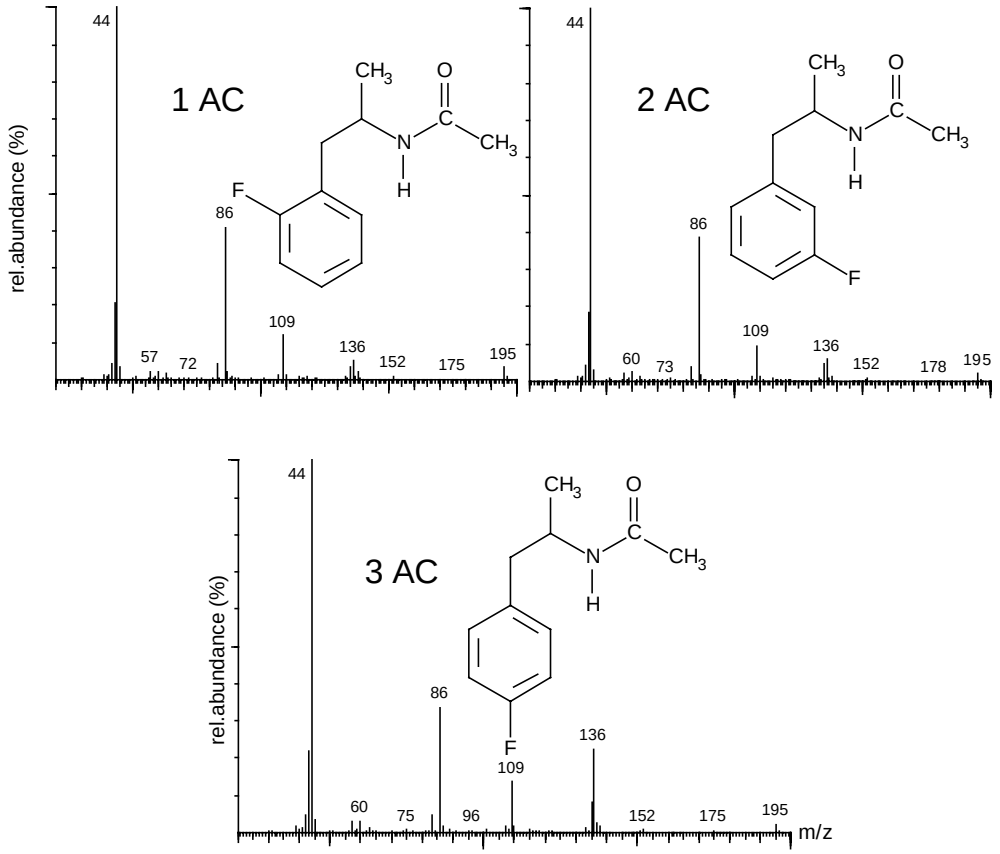


Fig. 4. EI mass spectra for the acetylated fluoroamphetamines **1**–**3**.

alkyl chain or an amino group to the aromatic *ortho* position. A following α-cleavage reaction at the benzyl bond generates an odd electron ion at *m*/*z* 140. The positional isomeric trifluoroacetylated **5** on the other hand shows only two significant fragments with *m*/*z* 139 (fluoromethoxybenzyl cation) and the McLafferty product at *m*/*z* 166. Trifluoroacetylation, therefore, proves to be an excellent method for the differentiation of 5-fluoro-2-methoxyamphetamine **4** from its regioisomeric 3-fluoro-4-methoxyamphetamine **5**.

The trifluoroacetylation of the compounds **1**–**3** showed no improvement regarding their mass spectral differentiation.

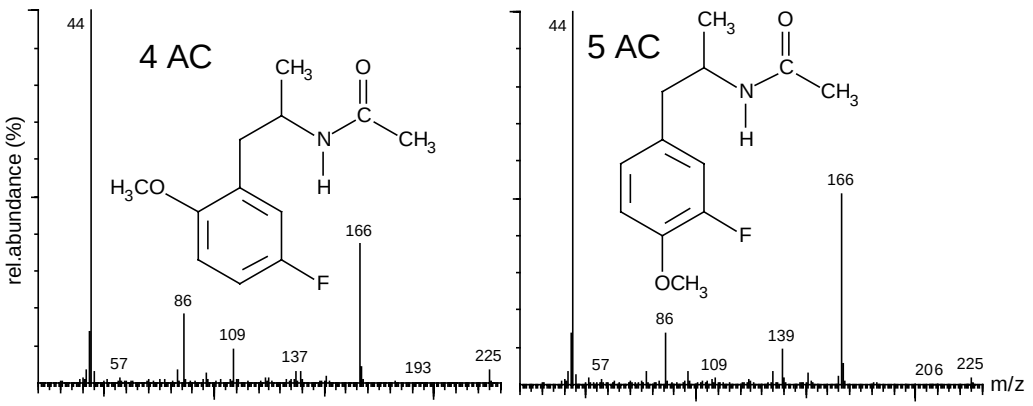


Fig. 5. EI mass spectra for the acetylated fluoromethoxyamphetamines **4** and **5**.

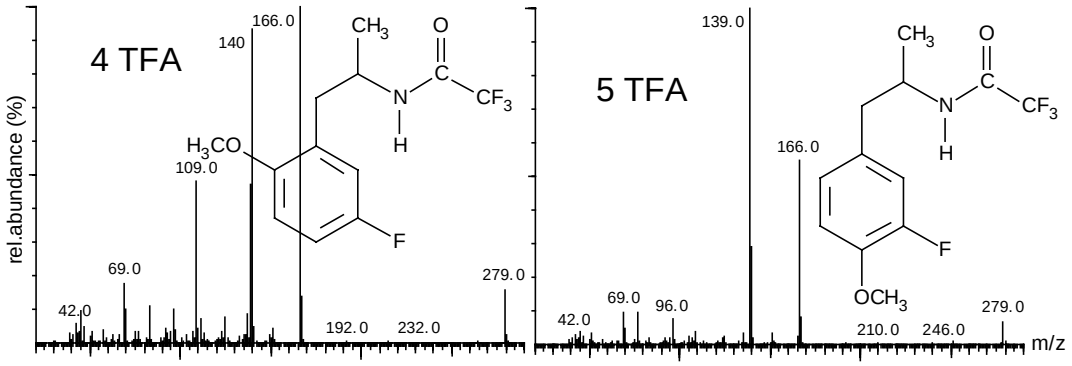
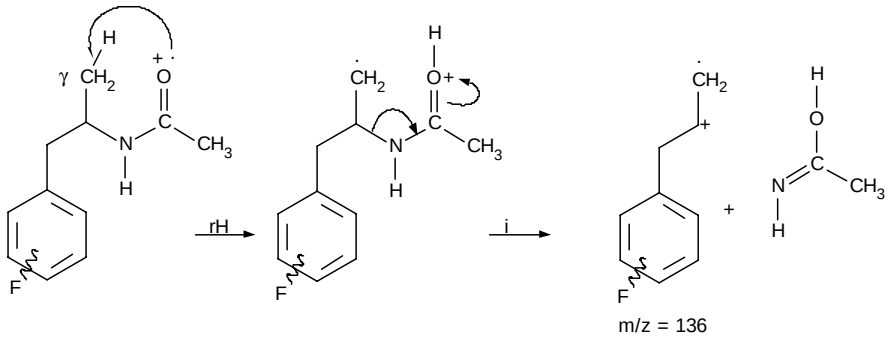


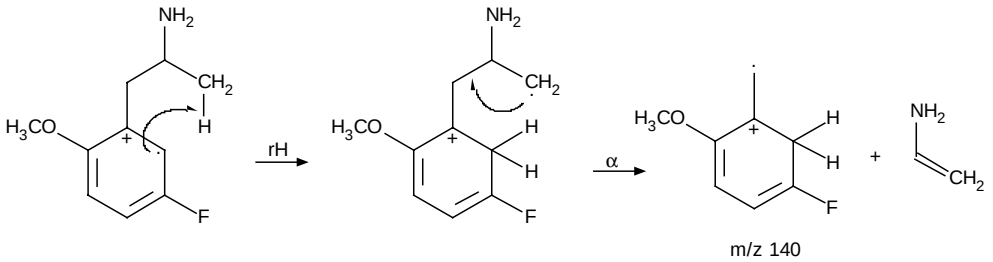
Fig. 6. EI mass spectra for the trifluoroacetylated fluoromethoxyamphetamines **4** and **5**.

3.3. NMR spectroscopy

Conventional ^{1}H- and broadband decoupled ^{13}C-NMR spectra of compounds **1**–**8** were recorded. When first looking at the aliphatic region of the ^{1}H-NMR spectra at 300 MHz of compounds **1**–**8** the typical $ABMX_3$ pattern is exhibited (Fig. 7) in the region from 2.7 to 3.6 ppm and at 1.3 ppm. The M part, i.e. the methine proton H_M, shows further coupling with the protons of the ammonium group leading to a broad and not fully resolved multiplet at 3.45 ppm. The denomination of the different spin systems of the fluorine-substituted amphetamines and the numbering used in Tables 1 and 2 are given in Fig. 8. The NH protons showed a broad signal between 8 and 10 ppm and do not deliver any structural information. A detailed analysis of the coupling constants in the aliphatic region of substituted amphetamines has been reported already in 1971 [26]. In order to explore the substitution pattern of the aromatic ring, coupling of the protons with the fluorine substituent has to be considered as well. Coupling constants over three, four, and five bonds in aromatic systems are observable using routine techniques,



Scheme 4. The McLafferty rearrangement in the acetylated fluoroampheamines **1**–**3**.



Scheme 5. γ-H-atom rearrangement (rH) of the alkyl chain to the aromatic *ortho* position.

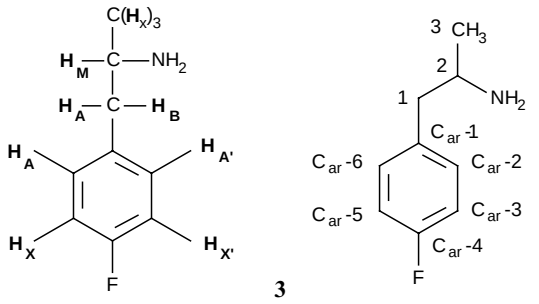


Fig. 7. Solid phase IR-spectra of the fluoro-methoxy-phenylalkylamines (H_2SO_4: **1**, HCl: **2**–**8**).

which are in the order of 9, 5, and 1–2 Hz, respectively [27]. For the methylene group of propanamine **1**, a $^4J_{HF}$ coupling with the fluorine atom in *ortho* position of the aromatic ring is observed (see Table 1, $^4J_{HF} = 1.2$ Hz). The data obtained by first order analysis of the multiplets are summarized in Table 1.

The 4-substituted amphetamines **3**, **6**–**8** show an AA′XX′ system for the aromatic protons (6.9–7.3 ppm), with additional $^3J_{HF}$ and $^4J_{HF}$ splitting. The $H_{XX'}$ and $H_{AA'}$ signals appear as a pseudo-triplet at 7.0 ppm and as a doublet of doublets at 7.2 ppm, see Fig. 7. In these cases, the 4-position of the fluorine atom is easily determined.

For structures **2**, **4**, and **5**, with the fluorine in *meta* position to the alkyl chain, overlapping multiplets are observed. To analyze these spin systems a two-dimensional ^{1}H-*J*-resolved technique was used [28,29]. This allowed the separation of HH and HF couplings and the determination of chemical shift and coupling constants of the aromatic protons in amphetamines **2** and **4** (see Table 1). Only for **5** this technique was not successful. In amphetamine derivative **5**, the two protons *ortho* to the alkyl chain and one proton *ortho* to the methoxy group were identified by a HH-long range correlation spectrum [28,29].

^{1}H decoupled ^{13}C-NMR spectra of the amphetamines **1**–**8** were also recorded, and the chemical shifts and the corresponding carbon fluorine couplings are given in Table 2. The coupling constants are in the order of 250 Hz ($^1J_{CF}$), 10–25 Hz ($^2J_{CF}$), and 2–10 Hz ($^3J_{CF}$) and ($^4J_{CF}$) for the aromatic ring. In all 4-substituted amphetamine derivatives **3**, **6**–**8** the ^{13}C-NMR spectra show only four signals for the aromatic carbon atoms due to the symmetry of the structure.

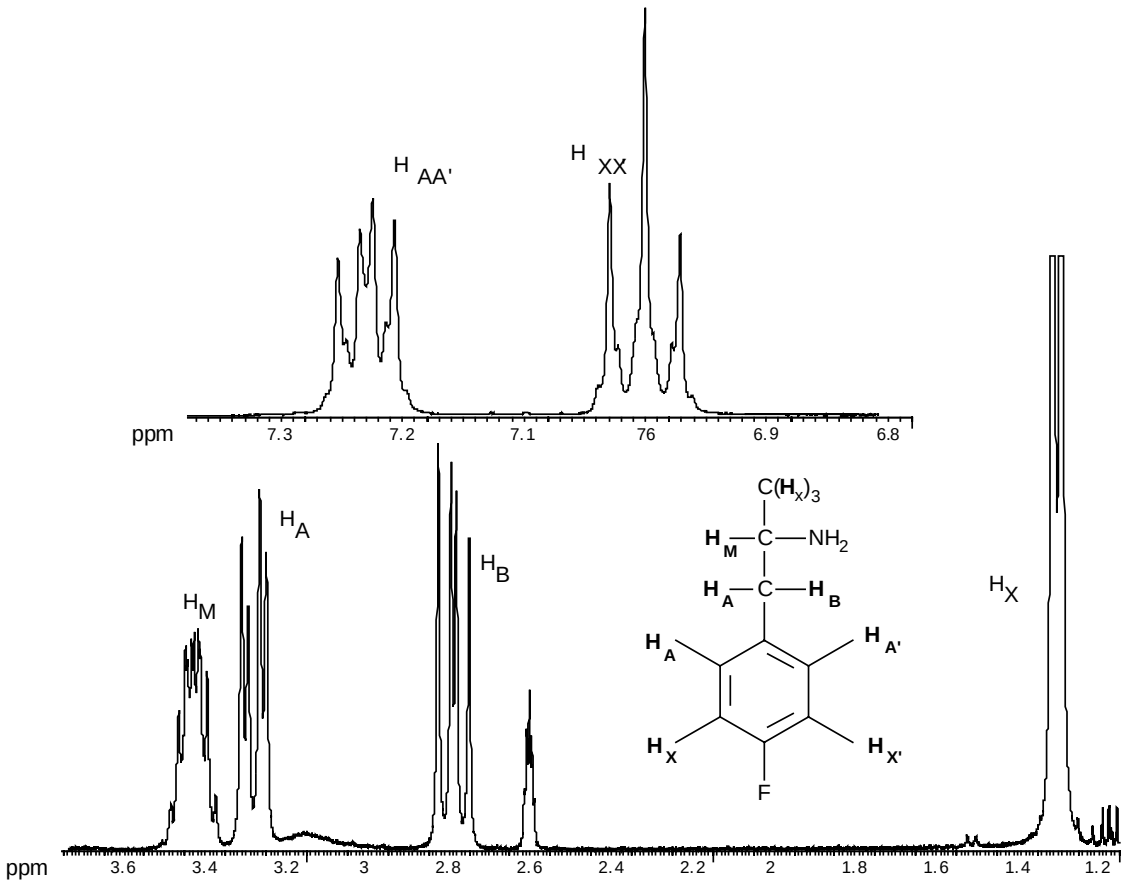


Fig. 8. Vapor-phase IR-spectra of the fluoro-methoxy-phenylalkylamines **1**–**8**.

Table 1
^{1}H-NMR chemical shifts and coupling constants (in Hz) of compounds **1–8**[a] in a 9/1 mixture (v/v) of $CDCl_3$ and DMSO-d_6

Compound	H-1_A	H-1_B	H-2	H-3	NH	H_{ar}-2	H_{ar}-3	H_{ar}-4	H_{ar}-5	H_{ar}-6	other
1[b]	2.89, dd, $^2J_{HH} = 13.7$, $^3J_{HH} = 8.3$, $^4J_{HF} \approx 1.2$	3.14, br dd, $^2J_{HH} = 13.7$, $^3J_{HH} = 5.8$, $^4J_{HF} \approx 1.2$	3.50, sextet, $^3J_{HH} = 6.5$	1.14, d, $^3J_{HH} = 6.6$	–	–	7.19 t[c], $^3J_{HF} = 10.8$, $^3J_{HH} = 8.5$, $^4J_{HH} = 1.2$	7.38 t[c], $^4J_{HF} = 6.0$, $^3J_{HH} = 7.2$, $^3J_{HH} = 7.2$, $^4J_{HH} \approx 2.0$	7.24 t[c], $^3J_{HH} = 7.5$, $^3J_{HH} = 7.5$, $^4J_{HH} = 1.2$	7.40 d[c], $^4J_{HF} = 8.0$, $^3J_{HH} = 7.6$, $^4J_{HH} \approx 1.5$	
2	2.83, dd, $^2J_{HH} = 13.3$, $^3J_{HH} = 9.7$	3.34, dd, $^2J_{HH} = 13.3$, $^3J_{HH} = 4.7$	3.52, br m	1.34, d, $^3J_{HH} = 6.5$	8.49, br s	6.98, dt[c], $^3J_{HF} = 9.6$, $^4J_{HH} \approx 2.0$, $^4J_{HH} \approx 1.6$	–	6.94, td[c], $^3J_{HH} \approx 7.9$, $^3J_{HF} \approx 8.8$, $^4J_{HH} \approx 2.4$, $^4J_{HH} \approx 1.3$	7.28, td, $^3J_{HH} = 7.8$, $^3J_{HF} = 7.8$, $^4J_{HF} = 6.3$	7.03, br d, $^3J_{HH} = 7.7$, $^4J_{HH} \approx 1.4$, $^4J_{HH} \approx 1.4$	
3	2.78, dd, $^2J_{HH} = 13.4$, $^3J_{HH} = 9.5$	3.27, dd, $^2J_{HH} = 13.4$, $^3J_{HH} = 4.8$	3.43, br m	1.29, d, $^3J_{HH} = 6.5$	8.48, br s	7.23, dd, $^3J_{HH} = 8.7$, $^4J_{HF} = 5.5$	6.99, t, $^3J_{HH} = 8.7$, $^3J_{HF} = 8.7$	–	6.99, t, $^3J_{HH} = 8.7$, $^3J_{HF} = 8.7$	7.23, dd, $^3J_{HH} = 8.7$, $^4J_{HF} = 5.5$	
4	2.88, dd, $^2J_{HH} = 13.2$, $^3J_{HH} = 8.3$	3.16, dd, $^2J_{HH} = 13.2$, $^3J_{HH} = 5.9$	3.62, br m	1.34, d, $^3J_{HH} = 6.6$	8.42, br s	–	6.79, dd, $^3J_{HH} = 8.9$, $^4J_{HF} = 4.8$	6.91, td, $^3J_{HH} = 8.9$, $^3J_{HF} = 8.2$, $^4J_{HH} = 3.1$	–	6.96, dd, $^3J_{HF} = 8.5$, $^4J_{HH} = 3.1$	OCH_3: 3.80, s
5	2.73, dd, $^2J_{HH} = 13.4$, $^3J_{HH} = 9.4$	3.21, dd, $^2J_{HH} = 13.5$, $^3J_{HH} = 4.8$	3.40, br m	1.30, d, $^3J_{HH} = 6.5$	8.38, br s	6.90–7.02, complex m	–	–	6.90–7.02, complex m	6.90–7.02, complex m	OCH_3: 3.86, s
6	2.82, dd complex m, $^2J_{HH} = 13.0$, $^3J_{HH} = 10.0$	3.40, dd, $^2J_{HH} = 13.1$, $^3J_{HH} = 3.4$	3.32, br m	1.30, d, $^3J_{HH} = 6.5$	9.51, very br s	7.23, dd, $^3J_{HH} = 8.6$, $^4J_{HF} = 5.4$	7.01, t, $^3J_{HH} = 8.7$, $^3J_{HF} = 8.7$	–	7.01, t, $^3J_{HH} = 8.7$, $^3J_{HF} = 8.7$	7.23, dd, $^3J_{HH} = 8.6$, $^4J_{HF} = 5.4$	N-CH_3: 2.70, t, $^3J_{HH} = 5.5$
7	2.82, dd, $^2J_{HH} = 13.0$, $^3J_{HH} = 10.5$	3.45, dd, $^2J_{HH} = 13.1$, $^3J_{HH} = 3.5$	3.33, br m	1.29, d, $^3J_{HH} = 6.5$	9.49, very br s	7.23, dd, $^3J_{HH} = 8.6$, $^4J_{HF} = 5.4$	7.00, t, $^3J_{HH} = 8.7$, $^3J_{HF} = 8.7$	–	7.00, t, $^3J_{HH} = 8.7$, $^3J_{HF} = 8.7$	7.23, dd, $^3J_{HH} = 8.6$, $^4J_{HF} = 5.4$	N-CH_2CH_3:CH_2: 3.05, very br m, CH_3: 1.47, t, $^3J_{HH} = 7.2$
8	2.91, dd, $^2J_{HH} = 13.7$, $^3J_{HH} = 8.5$	3.22, dd, $^2J_{HH} = 13.7$, $^3J_{HH} = 5.4$	3.31, br m	1.72, quint., $^3J_{HH} = 7.2$	8.46, br s	7.23, dd, $^3J_{HH} = 8.6$, $^4J_{HF} = 5.4$	6.99, t, $^3J_{HH} = 8.7$, $^3J_{HF} = 8.7$	–	6.99, t, $^3J_{HH} = 8.7$, $^3J_{HF} = 8.7$	7.23, dd, $^3J_{HH} = 8.6$, $^4J_{HF} = 5.4$	4-CH_3:1.05, t, $^3J_{HH} = 7.5$

[a] Analysis of the multiplets (AB-part-systems and AA′XX′-systems) according to first order, absolute values of the coupling constants are given.
[b] In 50% D_2O/50% acetone-d_6, partially.
[c] Overlapping signals, further splitting due to $^4J_{HH}$ and $^4J_{HH}$ couplings.

Table 2
^{13}C-NMR chemical shifts in ppm and J_{CF} coupling constants (Hz) of compounds **1–8** in a 9/1 mixture (v/v) of $CDCl_3$ and DMSO-d_6

Compound	C-1	C-2	C-3	C_{ar}-1	C_{ar}-2	C_{ar}-3	C_{ar}-4	C_{ar}-5	C_{ar}-6	Other
1[a]	33.0, $^3J = 1.8$	47.6, $^4J = 1.8$	16.9	122.2, $^2J = 15.8$	160.6, $^1J = 244$	115.1, $^2J = 22.0$	129.9, $^3J = 8.3$	124.2, $^4J = 3.4$	131.4, $^3J = 4.4$	
2	40.4, $^4J = 1.7$	49.2	17.8	139.1, $^3J = 7.4$	116.2, $^2J = 21.2$	162.8, $^1J = 246$	113.9, $^2J = 20.9$	130.2, $^3J = 8.4$	125.1, $^4J = 2.9$	
3	39.8	49.1	17.6	132.5, $^4J = 3.4$	130.9, $^3J = 7.9$	115.4, $^2J = 21.4$	161.7, $^1J = 245$	115.4, $^2J = 21.4$	130.9, $^3J = 7.9$	
4	35.8, $^4J = 1.2$	47.7	18.3	126.4, $^3J = 7.3$	153.8, $^4J = 2.0$	111.3, $^3J = 8.3$	114.2, $^2J = 22.6$	156.6, $^1J = 238$	118.1, $^2J = 23.1$	OCH_3: 55.8
5	39.6, $^4J = 1.2$	49.1	17.7	129.5, $^3J = 6.3$	116.8, $^2J = 18.1$	152.0, $^1J = 246$	146.4, $^2J = 10.5$	113.6, $^3J = 2.3$	125.2, $^4J = 3.6$	OCH_3: 56.2
6	38.5	56.7	15.2	131.9, $^4J = 3.4$	130.9, $^3J = 7.9$	115.6, $^2J = 21.4$	161.9, $^1J = 246$	115.6, $^2J = 21.4$	130.9, $^3J = 7.9$	N–CH_3: 31.0
7	40.0	55.1	15.2	132.3, $^4J = 3.2$	130.9, $^3J = 8.0$	115.5, $^2J = 21.3$	161.8, $^1J = 245$	115.5, $^2J = 21.3$	130.9, $^3J = 8.0$	N–CH_2CH_3: CH_2 38.5, CH_3 11.5
8	37.6	54.7	24.6	132.2, $^4J = 3.3$	131.0, $^3J = 7.8$	115.5, $^2J = 21.2$	161.8, $^1J = 245$	115.5, $^2J = 21.2$	131.0, $^3J = 7.8$	4–CH_3: 9.9

[a] Measured in D_2O.

The signal of the fluorine-substituted carbon atom is found at approximately 160 ppm and is easily identified as a doublet. In all derivatives **1–8**, the fluorine and also the methoxy group lead to high frequency shifted signals in the range of 150–160 ppm (see Table 2). Furthermore, the aromatic carbon atom bearing the alkyl chain is revealed by its low intensity under the experimental conditions of the recording of the spectra. The evaluation of the coupling constant of the doublets of this carbon atom (C_{ar}-1) allows the determination of the position of the fluorine atom in the monosubstituted fluoroamphetamines **1** and **2** as well. The fluorine in *ortho* position leads to a splitting of about 16 Hz corresponding to a $^2J_{CF}$ coupling for compound **1**. For the amphetamine **2**, a coupling constant of ca. 8 Hz is observed for C_{ar}-1, which is characteristic for a $^3J_{CF}$ coupling constant, thus showing the fluorine atom positioned *meta* to the aliphatic chain.

The methoxy-substituted fluoroamphetamines **4** and **5** require are more detailed discussion because the J_{CF} coupling constants are also influenced by the methoxy group: in **5**, the methoxy group vicinal to the fluorine atom is proven by the splitting of the methoxy carbon signal (C_{ar}-4) due to a $^2J_{CF}$ coupling of 10.5 Hz, which is not observable in compound **4**. The *meta* position of the fluorine atom in **5** on the other hand is shown by a $^3J_{CF}$ coupling, leading to a doublet for C_{ar}-1 (Fig. 8). The same reasoning holds for compound **4**, but the small coupling of only 2.0 Hz shows the methoxy group to be in para position to the fluorine atom.

A further diagnostic tool is the small splitting of the benzylic and homobenzylic carbon atoms of the alkyl chain in the range of 1–2 Hz in those cases where the fluorine atom is positioned either *ortho* or *meta* to the propanamine residue.

For both the ^{1}H- and ^{13}C-NMR spectra the chemical shifts of the aromatic group were found to be in the same range and order when compared with calculated shifts using tabulated increments for the aromatic ring [27].

In summary, conventional ^{13}C-NMR spectra recorded under routine conditions of the fluorinated amphetamine derivatives **1–8** in a suitable solvent, together with a detailed analysis of the carbon fluorine coupling constants, allows the unambiguous assignment of the substitution pattern of the aromatic ring.

3.4. IR spectroscopy

For most organic compounds, the absorbances in the region from 1600 to 900 cm^{-1} are due to skeletal vibrations of the whole molecule and usually not characteristic for functional groups. This fingerprint region, therefore, has importance in differentiating aromatic positional isomers. The solid- and vapor-phase IR-spectra of all studied compounds **1–8** (Figs. 9 and 10) show significant differences in this region and allowed their identification unambiguously. The solid phase IR-spectra show N–H stretching vibration at about 3450 cm^{-1} and broad $-NH_3^+$ absorption bands from about 2700 to 2250 cm^{-1} due to intermolecular hydrogen bonding (Fig. 9) [30].

The IR-spectra of isolated molecules in the vapor phase differ significantly from the corresponding condensed-phase spectra. The absorption bands of vapor-phase spectra shift to higher wave numbers and exhibit less fine splitting due to rotational bands (Fig. 10).

The N–H absorption bands near 3450 cm^{-1} become quite weak in the vapor phase and may be lost in noise [31].

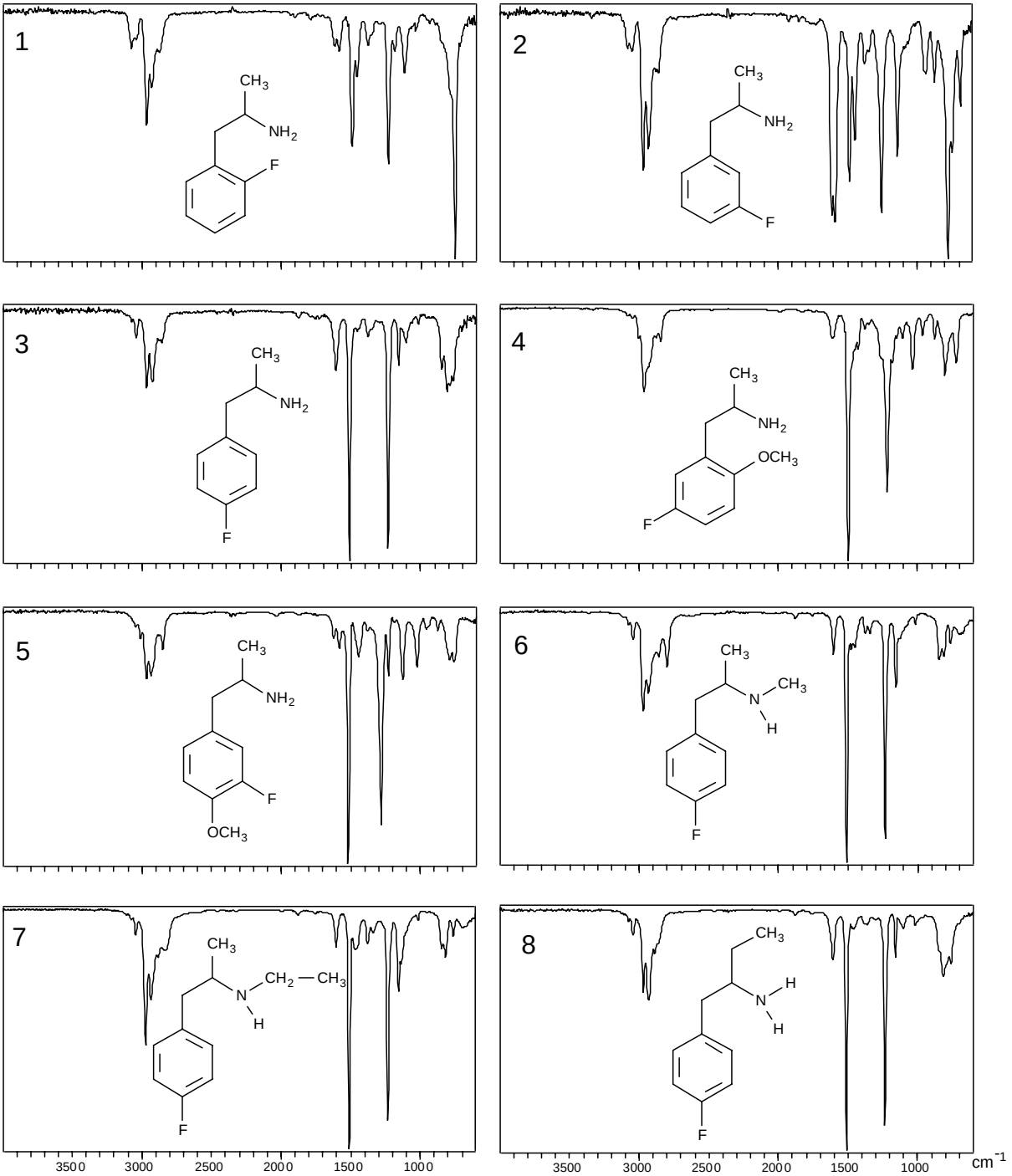


Fig. 9. Denomination of the two independent spin systems of the aliphatic and aromatic protons (in bold) and the numbering of the protons and carbon atoms of fluoroamphetamines **1**–**8** used in Tables 1 and 2.

Consequently, all studied compounds **1**–**8** showed no visible N–H stretching bands in the vapor-phase IR-spectra. The NH_2-deformation band for primary amines is found at about 1600–1610 cm^{-1} in the solid-phase spectra and at about 1608–1623 cm^{-1} in the vapor-phase spectra. For symmetry reasons, the IR-spectra of the 4-fluoro-substituted phenalkylamines **3**, **6**–**8** are less complex and their vapor-phase spectra show two intense bands at 1234 and

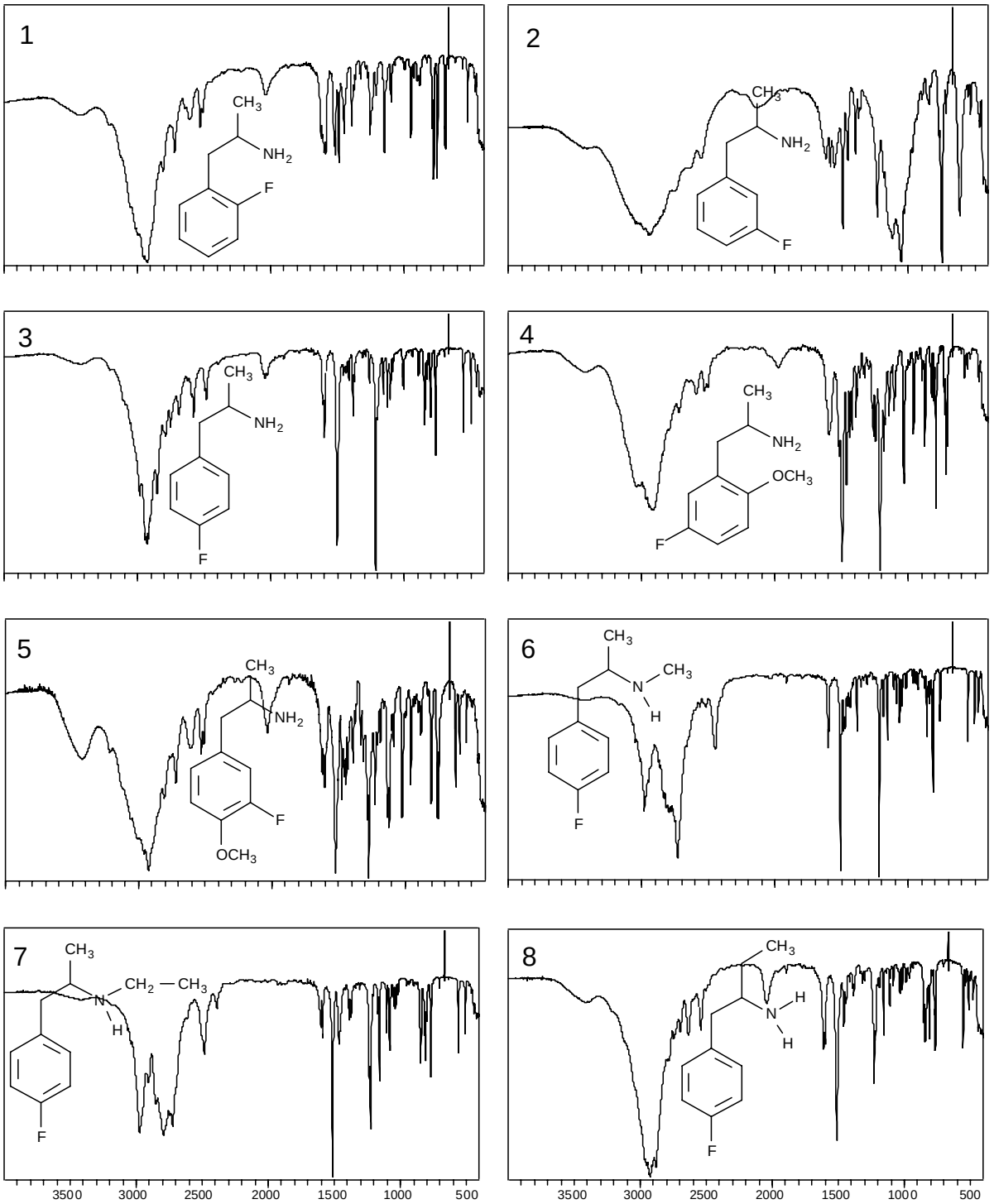


Fig. 10. Aromatic (top) and aliphatic (bottom) region of the ^{1}H-NMR spectrum of 4-fluorophenethylamine (**3**), signals originating from the nmr solvent (2.6 ppm), water (3.2 ppm), and sample impurities (1.2 ppm) are not assigned.

1512 cm^{-1} due to aromatic ring vibrations. These compounds therefore can be easily identified from the other regioisomeric compounds.

4. Conclusion

In conclusion, this work represents the detection and identification of clandestinely produced regioisomeric fluoro-methoxy-substituted amphetamines **1–5** with gas chromatography–mass spectrometry, which is seriously affected by their virtually identical mass spectra. This situation is further complicated by the almost identical retention times of the regioisomeric fluoroamphetamines **2** and **3**, which made a separation impossible by GC–MS. Even on a separately operated gas chromatograph and optimized GC conditions, only partial separation of **2** and **3** was achieved.

The acetylation of the regioisomeric fluoroamphetamines **1–3** provided no better gas chromatographic results, but allowed a mass spectroscopic differentiation of the 4-fluoroamphetamine **3** from its isomers **1** and **2** by its more intense McLafferty product at *m/z* 136.

Trifluoroacetylation on the other hand proved to be an excellent method for the mass spectroscopic differentiation of 5-fluoro-2-methoxyamphetamine **4** from its regioisomeric 3-fluoro-4-methoxyamphetamine **5**.

The ^{1}H- and ^{13}C-NMR spectra allowed an unequivocal determination of the aromatic substitution pattern and of the aliphatic structure of all compounds.

IR-spectroscopy using solid- or vapor-phase IR-spectra allowed the identification and differentiation of all studied fluoromethoxy amphetamines **1–8** without difficulties. The insufficient gas chromatographic separation of the regioisomeric **2** and **3** still remains a problem also for these techniques. In the real life of forensic laboratories, this situation is further complicated by complex matrices like blood or urine due to separation problems and the low sensitivity of NMR spectroscopy.

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