GC–MS Analysis of Ring and Side Chain Regioisomers of Ethoxyphenethylamines

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Abstract

Mass spectral differentiation of 3,4-methylenedioxymethamphetamine (3,4-MDMA), a controlled drug, and its 2,3-regioisomer from the ring substituted ethoxyphenethylamines is possible after formation of the perfluoroacyl derivatives, pentafluoropropionamides (PFPA), and heptafluorobutyrylamides (HFBA). The ring substituted ethoxyphenethylamines constitute a unique set of compounds having an isobaric relationship with 3,4-MDMA. These isomeric forms of the 2-, 3-, and 4-ethoxy phenethylamines have mass spectra essentially equivalent to 3,4-MDMA; all have molecular weight of 193 and major fragment ions in their electron ionization mass spectra at *m/z* 58 and 135/136. All the side chain regioisomers of 2-ethoxy phenethylamine having equivalent mass spectra to 3,4-MDMA are synthesized and compared via gas chromatography–mass spectrometry to 2,3- and 3,4-methylenedioxymethamphetamine. The mass spectra for the perfluoroacyl derivatives of the primary and secondary amine regioisomers are significantly individualized, and the side chain regioisomers yield unique hydrocarbon fragment ions at *m/z* 148, 162, and 176. Additionally, the substituted ethoxymethamphetamines are distinguished from the methylenedioxymethamphet-amines via the presence of the *m/z* 107 ion. Gas chromatographic separation on relatively non-polar stationary phases successfully resolves these derivatives.

Introduction

The three ring substituted ethoxyphenethylamines have an isobaric relationship, equal mass but different elemental composition, to the methylenedioxyphenethylamines of equivalent side chain structure. Previous reports (1–8,15) in this series have described the gas chromatography–mass spectrometry (GC–MS) properties of several series of ring substituted methamphetamines and related phenethylamines having a regioisomeric and/or isobaric relationship to 3,4-methylenedioxymethamphetamine (3,4-MDMA). The GC–MS properties of the 10 possible ring substituted regioisomeric methoxy methyl methamphetamines were reported recently (5). The ethoxy-substituent has the same mass as the methoxy methyl disubstituted aromatic ring, however, only three possible substitution patterns relative to the alkylamine side chain. Earlier studies (1,4,5,13) have shown that a total of five uniquely regioisomeric side chains (the methamphetamine side chain and four regioisomeric equivalents) yield major imine fragment ions at the same mass, *m/z* 58. Thus, each ring substitution pattern in the phenethylamines has a total of five regioisomeric side chain structures of identical molecular weight with the potential to yield mass equivalent major fragment ions.

Regioisomer differentiation is a significant issue in forensic drug chemistry and has been addressed in a number of drug categories (9–11,14). The ability to distinguish between these

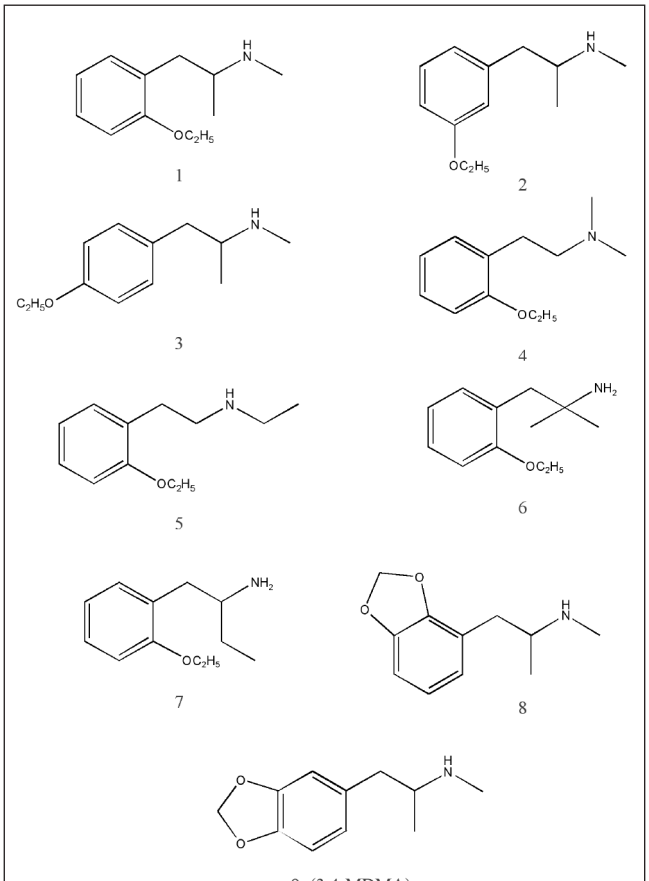

Figure 1. Structures of the regioisomeric and isobaric compounds in this study.

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regioisomers directly increases the specificity of the analysis for the target compound. The mass spectrum is usually the confirmatory piece of evidence for the identification of drugs in forensic laboratories. For major drugs of abuse such as the amphetamines and MDMAs, there are many positional isomers (regioisomers) in the alkyl side chain or in the aromatic ring substitution pattern that can yield identical major fragment ions in the mass spectrum, presenting a significant challenge for forensic differentiation. The differentiation of 3,4-MDMA from 2,3-MDMA (9,11) has been an issue of concern in forensic science for a number of years. Often the wording of legislation in various countries places only 3,4-MDMA under legal control. Thus, methods to differentiation 3,4-MDMA from the 2,3-isomer and other related regioisomeric and isobaric substances is a central issue in forensic drug chemistry.

While nuclear magnetic resonance (NMR) can be a useful method for differentiation of regioisomers, it is not a tool with direct application for all areas of forensic drug chemistry and not always readily available in most laboratories. Thus, the analysis of these samples of interest in forensic drug chemistry must depend heavily on chromatographic methods as well as MS.

When other compounds exist with the ability to produce nearly identical mass spectra as the drug of interest, the identification by GC–MS must focus on the ability of the chromatographic system to separate the "non-drug" regioisomers from the drug of interest. The regioisomers that coelute with the drugs of interest in chromatographic separations could be mistaken for the drug itself. Without the appropriate standards, thorough method validation is not possible, and thus coelution of the regioisomer (the non-drug) with the drug would remain a possibility.

The targets of this study are a series of ethoxy-substituted phenethylamines (see Figure 1) with molecular weight 193 and the potential to produce mass spectra with major fragment ions at *m/z* 58 for the imine and *m/z* 135/136 for the substituted benzyl fragment. The major fragment ions observed in the EI mass spectrum for 3,4-MDMA (MW = 193) occur at equivalent masses. Therefore, analysis of the underivatized regioisomers by electron ionization MS alone may not provide significant data for the specific differentiation of one of these regioisomers to the exclusion of the other isomers. The specific identification must be based on a combination of mass spectral data as well as chromatographic resolution of these substances.

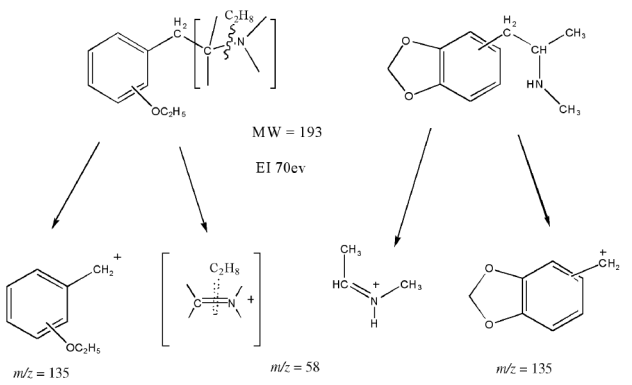

Figure 2. EI fragmentation pattern for compounds 1–7.

Experimental

Analytical

Analytical studies were conducted using an Agilent Technologies (Santa Clara, CA) 7890A GC and an Agilent 7683B auto injector coupled with a 5975C VL Agilent mass selective detector. The mass spectral scan rate was 2.86 scans per second. The GC was operated in splitless mode with a carrier gas (Helium grade 5) flow rate was 0.7 mL/min and a column head pressure of 10 psi.

The mass spectrometer was operated in the electron impact (EI) mode using an ionization voltage of 70 eV and a source temperature of 230°C. The GC injector was maintained at 250°C and the transfer line at 280°C. The mass spectra reported were obtained by background subtraction and are the average of at least five scans. Samples were diluted in HPLC grade acetonitrile (Fisher Scientific, NJ) and introduced via the auto injector as individual solutions and in physical mixture.

The chromatographic separations (and collection of retention data) were carried out on a 30 m × 0.25 mm-i.d. column coated with 0.25 µm 100% dimethyl polysiloxane (Rtx-1) purchased from Restek Corporation (Bellefonte, PA).

The retention data in Table I were generated using a temperature program consisting of an initial hold at 100°C for 1 min, ramped up to 180°C at a rate of 9°C per min followed by a hold at 180°C for 2 min then ramped to 200°C at a rate of 10°C per min.

Drugs and reagents

All laboratory reagents and chemicals were obtained from Aldrich Chemical Company (Milwaukee, WI) or Fisher Scientific (Atlanta, GA). Pentafluoropropionic anhydride and heptafluorobutyric anhydride were purchased from UCT (Bristol PA).

Samples of 2,3- and 3,4-MDMA and the other regioisomeric amines described in this study were synthesized as described in previous publications (1,3,5,15) from this laboratory. The syn-

Table I. Relative Retention of the Underivatized, HFBA and PFPA Derivatives of Compounds 1–9*

Compound	Rtx-1†		
		Derivatives‡	
Number	Underivatized	HFBA	PFPA
1	0.879	0.856	0.867
2	0.934	0.914	0.923
3	0.963	0.955	0.956
4	0.851	N/A	N/A
5	0.927	0.901	0.947
6	0.855	0.802	0.805
7	0.947§	0.822	0.826
8	0.949§	0.928	0.930
9	1	1	1
(3,4-MDMA)	(13.079 min)	(17.363 min)	(16.681 min)

* Results are the average of at least three experiments.
† Rtx-1 is a 30 m x 0.25 mm-i.d. column coated with 0.25 µm 100% dimethyl polysiloxane.
‡ Abbreviations: PFPA, pentafluoropropionamide; HFBA, heptafluorobutyrylamide.
§ Underivatized compounds 7 and 8 co-eluted under the evaluated chromatographic condtion.

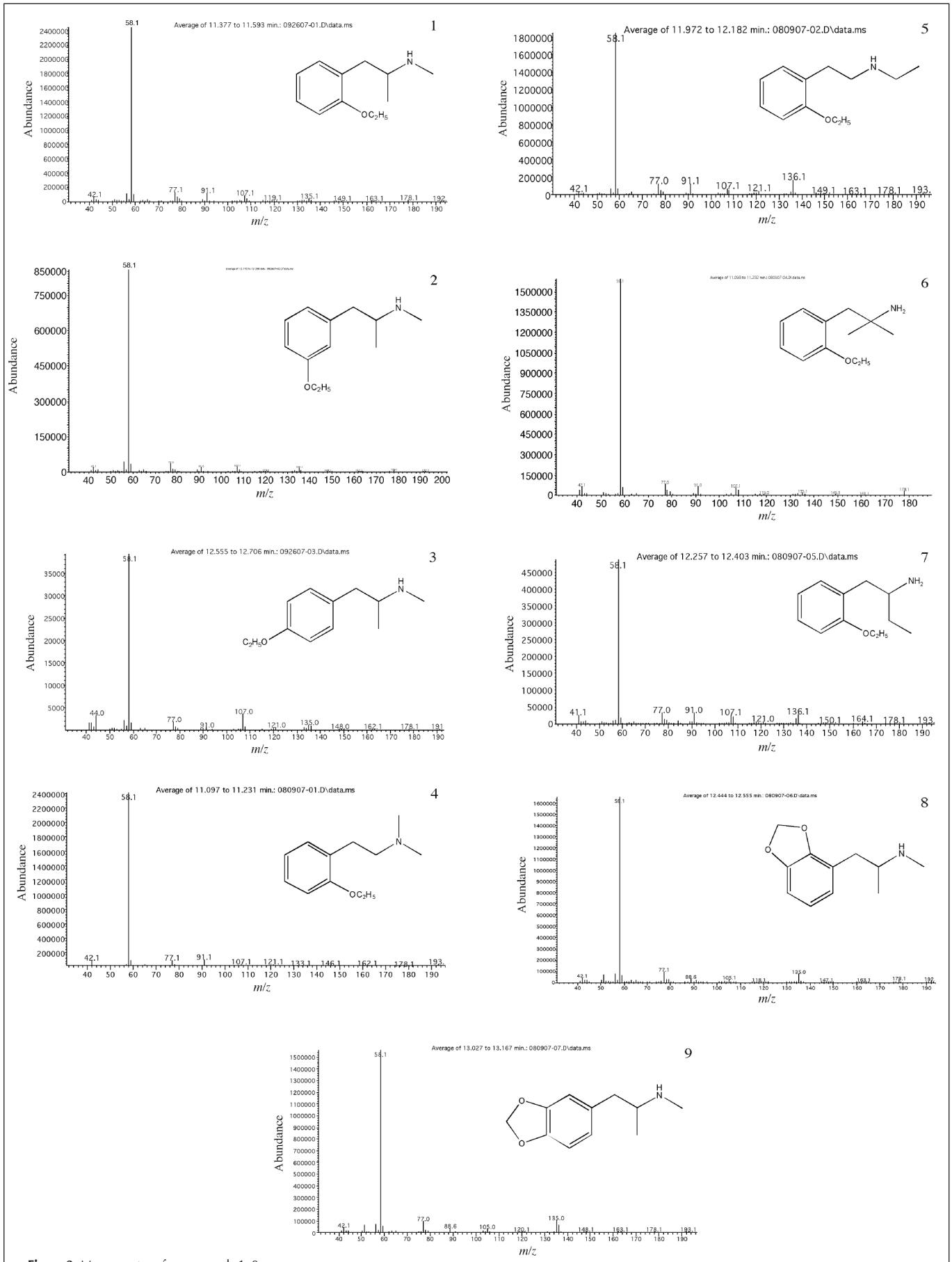

Figure 3: Mass spectra of compounds 1–9.

thetic procedures all used the corresponding ring substituted benzaldehydes as the starting precursor substance.

Derivatization procedure

Each perfluoroamide was prepared individually from the hydrochloride salts of the regioisomers by dissolving approximately 0.3 mg (1.32×10^{-6} mole) of each amine in 50 µL of ethyl acetate followed by addition of large excess (250 µL) of the appropriate derivatizing agent (pentafluoropropionic anhydride or heptafluorobutyric anhydride) and the derivatization reaction mixtures were incubated in capped tubes at 70°C for 20 min. Following incubation, each sample was evaporated to dryness under a stream of air at 55°C and reconstituted with 200 µL of ethyl acetate and 50 µL of pyridine.

General synthetic methods

Condensation of the 2-ethoxy benzaldehyde with a nitroalkane (nitromethane, nitroethane, or 1-nitropropane) under basic conditions yields the 1-(2-ethoxy phenyl)-2-nitroalkene, which upon reduction with lithium aluminum hydride (LAH) yields the primary amines. The *N*-methyl and *N*-ethyl analogues were prepared from the primary amines by acylation followed by LAH reduction. Alternately, the nitroalkanes are hydrolyzed to the corresponding 2-ethoxy phenylketones and reductively ami-

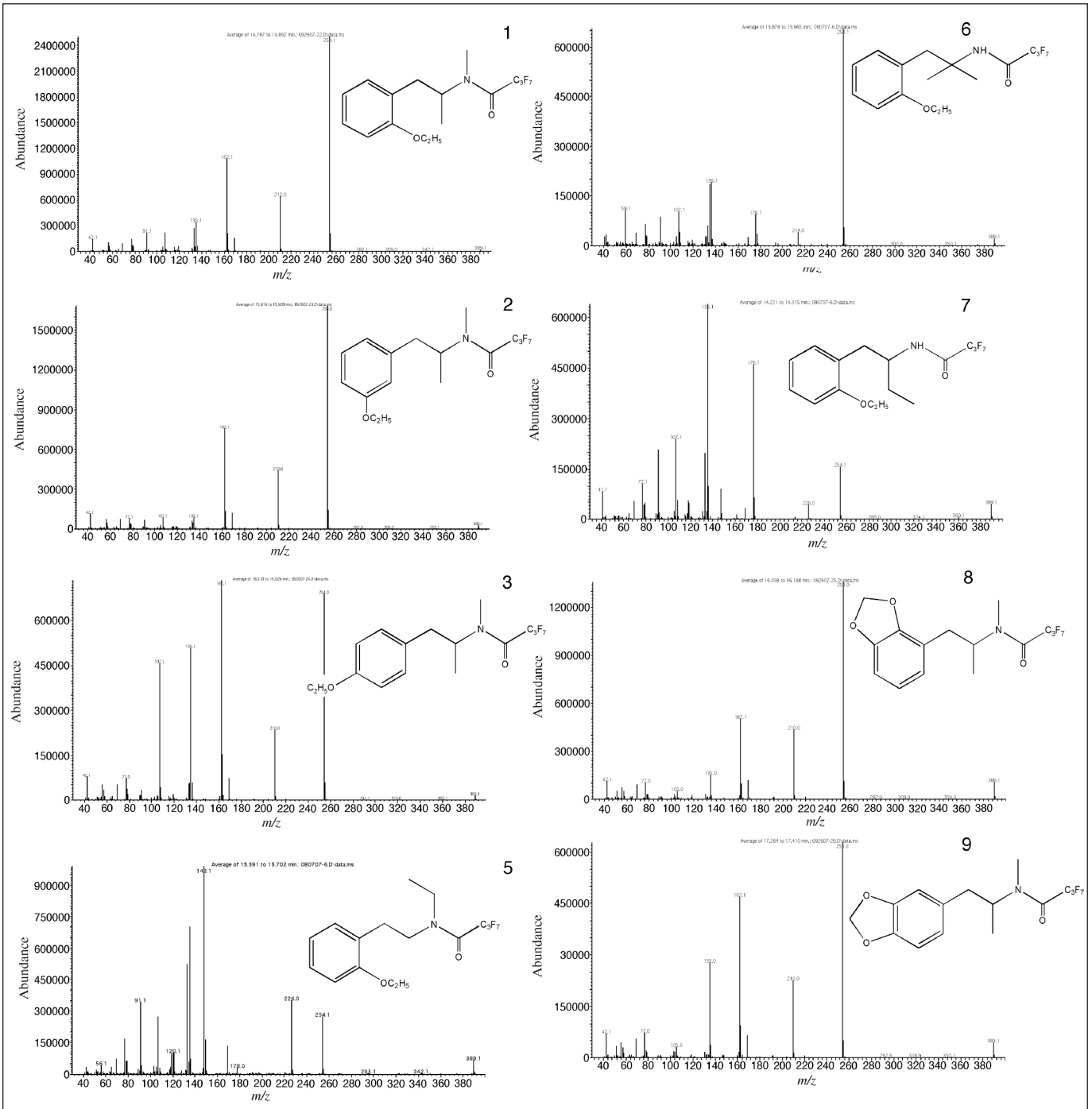

Figure 4. Mass spectra of the HFBA derivatives of compounds 1–3 and 5–9.

nated with methyl-, dimethyl-, or ethylamine in the presence of sodium cyanoborohydride. The 1-(2-ethoxy phenyl)-2,2-dimethylethanamine, was prepared from 2-ethoxy benzaldehyde via conversion to the corresponding benzylchloride and condensation with isobutyric acid. The resulting 2,2-dimethyl-3-(2-ethoxy)-1-propionic acid was treated sequentially with sodium azide, ethyl chloroformate and benzyl alcohol followed by catalytic hydrogenation under low pressure to yield the desired 1-(2-ethoxy phenyl)-2,2-dimethylethanamines (1). The methods for the preparation of the 2,3- and 3,4-methylenedioxy isomers have been described in previous reports (1,3,9,10,11). The general procedure for the synthesis of these compounds begins with 2,3-methylenedioxybenzaldehyde and 3,4-methylenedioxybenzaldehyde (piperonal) as starting materials. The preparation of 2,3-methylenedioxybenzaldehyde has been reported previously (1,11).

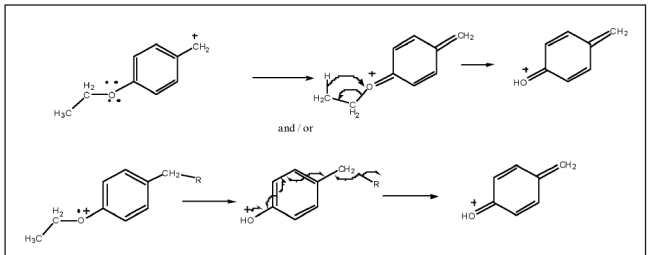

Figure 6. Mass spectral fragmentation of ethoxyphenethylamines yielding the cation at *m/z* 107.

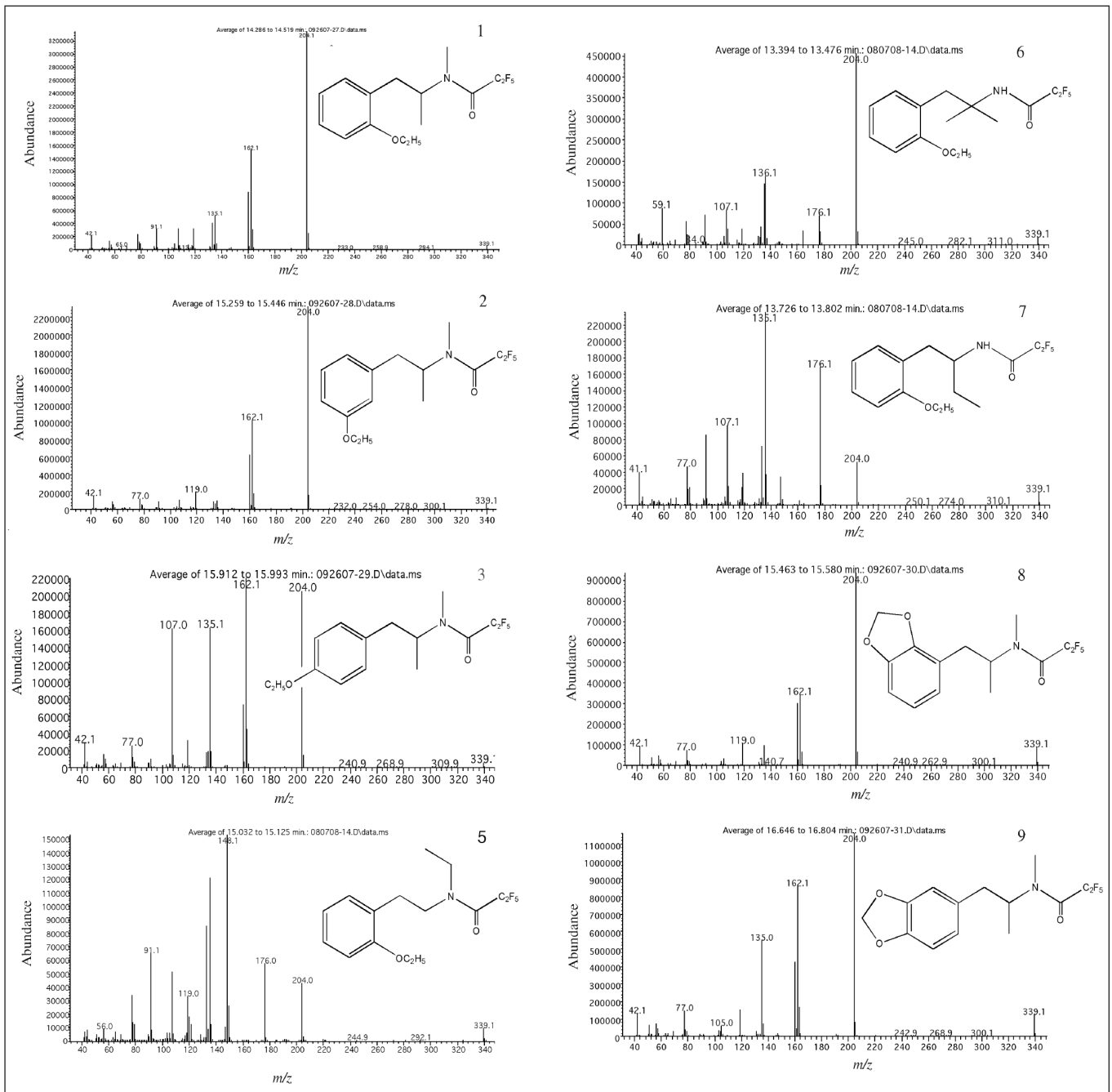

Figure 5. Mass spectra of the PFPA derivatives of compounds 1–3 and 5–9.

Results and Discussion

Mass spectrometry

MS is the primary method for confirming the identity of drugs and related substances in forensic samples. The mass spectra of phenethylamines are characterized by a base peak formed from an amine initiated alpha-cleavage reaction involving the carbon–carbon bond of the ethyl linkage between the aromatic ring and the amine. In 3,4-methylenedioxymethamphetamine (MW = 193) the alpha-cleavage reaction yields the substituted imine fragment at *m/z* 58 and the 3,4-methylenedioxybenzyl fragment at mass 135/136 (for the cation and the radical cation, respectively). Thus, the mass spectrum for 3,4-methylenedioxymethamphetamine contains major ions at *m/z* 58 and 135/136 as well as other ions of low relative abundance (1). The ring substituted ethoxy methamphetamines (Compounds 1–3, Figure 1) have the potential to yield a mass spectrum essentially equivalent to 2,3- and 3,4-MDMA. There are five possible side chain regioisomers for each one of these ring substitution patterns. The five side chain regioisomers of 2-ethoxyphenethylamine included in this study are shown in Figure 1 (Compounds 1, 4–7). All five side chain regioisomers have molecular weight of 193 and major fragment ions in their electron ionization mass spectra at *m/z* 58 and 135/136 (Figure 2). The individual mass spectra for 2,3- and 3,4-MDMA are also presented in Figure 2 (Compounds 8 and 9). The isobaric ethoxy benzyl $(C_9H_{11}O)^+$ fragments have the same mass as the methylenedioxybenzyl $(C_8H_7O_2)^+$ cation occurring at *m/z* 135. Furthermore the *m/z* 58 ion in the 2-ethoxyphenethylamines is regioisomeric with that obtained in the mass spectra of both 2,3 and 3,4-MDMA (Figure 3). This lack of mass spectral specificity for the isomers shown in Figure 2, in addition to the possibility of chromatographic co-elution with 3,4-MDMA, could result in misidentification in this series of drugs and drug-like substances.

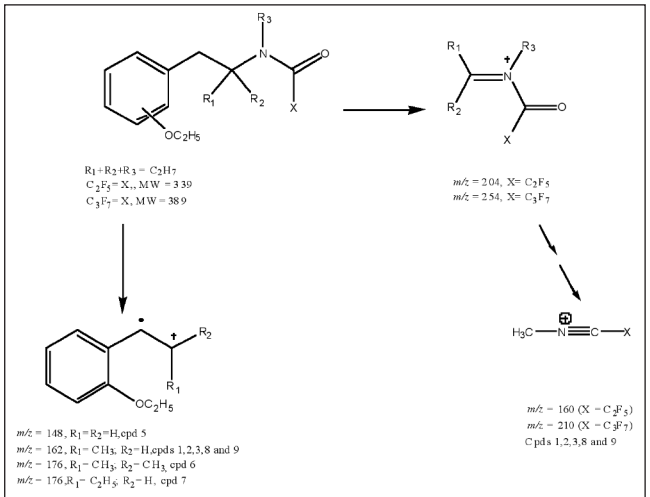

Figure 7. Mass spectral fragmentation products for the acylated ethoxy phenethylamines.

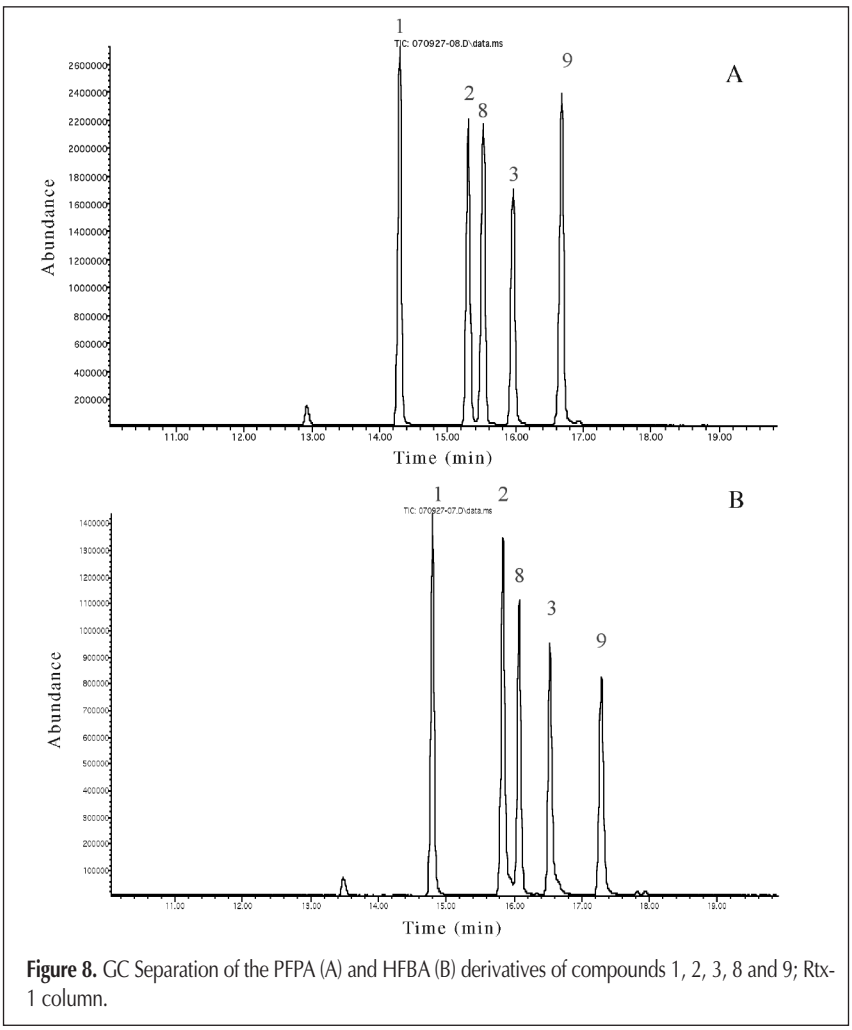

Figure 8. GC Separation of the PFPA (A) and HFBA (B) derivatives of compounds 1, 2, 3, 8 and 9; Rtx-1 column.

In the next phase of this study, various acylated derivatives of the ring substituted ethoxy methamphetamines and the primary and secondary amines of the side chain regioisomers of 2-ethoxyphenethylamine were prepared and evaluated in an effort to individualize their mass spectra and provide unique marker ions for specific identification. Acylation of the amines significantly lowers the basicity of nitrogen and can allow other fragmentation pathways to play a more prominent role in the resulting mass spectrum (4,5,15). Of course the tertiary amine (compound 4) does not form a stable amide derivative.

The mass spectra for the pentafluoropropionyl and heptafluorobutyryl amides are shown in Figures 4 and 5, respectively. Perfluroacyl derivatives of the ring substituted ethoxy methamphetamines (Compounds 1–3) have almost identical mass spectra with the derivatized 2,3- and 3,4-MDMA (Compounds 8 and 9) except for a unique ion at *m/z* 107. This ion at *m/z* 107 represents the loss of 28 mass units (ethylene, C_2H_4) from the ethoxybenzyl cation at *m/z* 135 (Figure 6). Although the relative abundance varies significantly, the *m/z* 107 ion is present in all mass spectra of the PFPA and HFPA of compounds (1–3 and 5–7) and offers a unique fragment ion to discriminate these compounds

from 3,4- and 2,3-MDMA. The *m/z* 107 ion is also present in relatively low abundance in the mass spectra of the underivatized ethoxy amines shown in Figure 2.

These spectra in Figures 4 and 5 show a common peak at *m/z* 204 and 254, which corresponds to the loss of 135 mass units from the molecular ions at 339 and 389 for the PFPA and HFBA amides. This ion at *m/z* 204 and 254 is the PFPA and HFBA imine species formed from the alpha cleavage of the amide nitrogen to eliminate the ethoxy benzyl radical or the methylenedioxybenzyl radical. Thus the *m/z* 204 and 254 ions in the PFPA and HFBA amides are analogous to *m/z* 58 in the underivatized species because all these ions represent the $(M-135)^+$ species. The general fragmentation pattern and structures for the *m/z* 204 and 254 ions are shown in Figure 7. The ethoxy benzyl cation (*m/z* 135) and the methylenedioxybenzyl cation (*m/z* 135) are fragments common to all spectra in Figures 4 and 5. However, the ethoxy benzyl cation in the perfluoroacyl derivatives shows a very high relative abundance in some of these isobaric compounds. Indeed the *m/z* 135 ion is the base peak in the PFPA and HFBA derivatives of Compound 7. This would suggest that the perfluoroacyl derivatives offer some level of discrimination between the methylenedioxy and ethoxy ring substitution patterns based on the difference in relative abundances of the substituted benzyl cation at *m/z* 135.

The decreased role for the alpha cleavage reaction in the fragmentation of these amides allows the formation of ions more diagnostic of individual side chain isomers. Acylation weakens the bond between nitrogen and the alkyl carbon of the phenethyl side chain, allowing the formation of charged hydrocarbon species of increased relative abundance. These hydrocarbons of varying mass significantly individualize the mass spectra and provide specific structural information. The mass spectra in Figures 4 and 5 illustrate the role of hydrocarbon fragments at *m/z* 148, 162, and 176 in the electron impact mass spectral discrimination among the side chain regioisomers.

The spectra for the *N*-ethyl isomer (compound 5) in Figures 4(5) and 5(5) show a base peak at *m/z* 148 corresponding to the alkene radical cation which occurs from hydrogen rearrangement and subsequent fragmentation of the alkyl carbon to nitrogen bond of the phenethylamine side chain (see Figure 7). This ion at *m/z* 148 would only occur for the *N*-ethyl regioisomer. The spectra in Figures 4(1), 4(2), 4(3), 4(8),4(9), 5(1), 5(2), 5(3), 5(8), and 5(9) show the substituted phenylpropane hydrocarbon ion at *m/z* 162, identifying these molecules as the PFPA and HFBA derivatives of 2-, 3-, 4-ethoxymethamphetamines and the 2,3-, 3,4-methylenedioxymethamphetamines, respectively. However, the base peak of *m/z* 162 and relatively high abundance *m/z* 107 in the spectra of the perfluroacyl derivatives of compound 3 offer a significant discrimination of 4-ethoxymethamphetamines over the 2-, 3-ethoxymethamphetamines and the two isobaric methylenedioxymethamphetamines isomers (Compounds 1, 2, 8, and 9 in Figures 4 and 5). The spectra for the PFPA and HFBA derivatives of the primary amines (compounds 6 and 7 in Figure 4 and 5) show ions at *m/z* 176 from the corresponding substituted phenylbutene radical cation. The lower abundance of *m/z* 176 for the 2-ethoxy phentermine (Compound 6) may be attributed to steric inhibition of hydrogen transfer in the alpha, alpha-dimethyl substitution pattern.

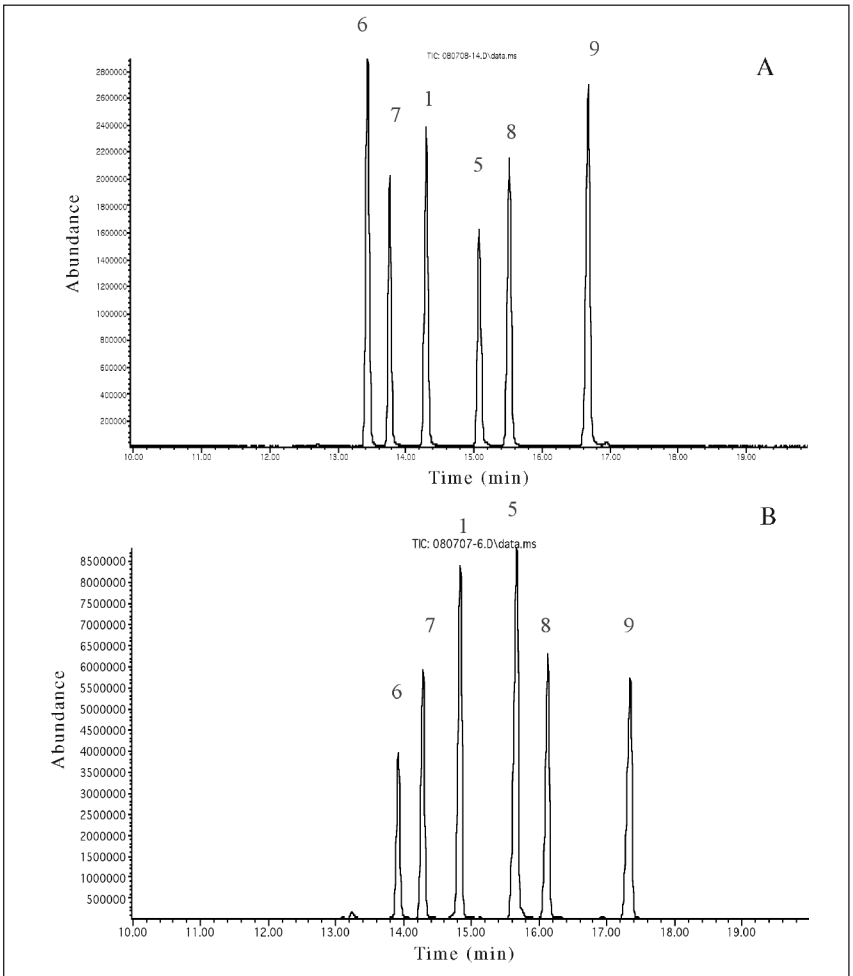

Figure 9: GC Separation of the PFPA (A) and HFBA (B) derivatives of compounds 1, 5, 6, 7, 8 and 9; Rtx-1 column.

While the alkene ions at 148, 162, and 176 help to identify the side chain regioisomers, one complicating factor in the PFPA derivatives for the *N*-ethylphenethylamines [Figure 5(5)] is the appearance of an ion at *m/z* 176 in addition to the base peak at *m/z* 148. The 176 ion might suggest a four carbon chain directly attached to the aromatic ring as occurs for the alpha-ethyl- (Compound 7) and alpha, alpha-dimethyl- (Compound 6) phenethylamines [Figures 4(6), 4(7), and 5(6), 5(7)]. The *m/z* 176 ion in the spectra for the PFPA derivatives of the *N*-ethyl regioisomers [Figure 5(5)] is a rearrangement of the *m/z* 204 ion resulting in the loss of mass 28 (the *N*-ethyl group) via hydrogen transfer. This coincidental common mass from two different fragmentation pathways is confirmed by examining the mass spectra for the HFBA derivatives of the *N*-ethyl-phenethylamines shown in Figure 4(5). The loss of 28 mass units from the

acylimine fragment at *m/z* 254 yields the equivalent fragment ion at *m/z* 226. Thus, the HFBA derivatives may offer more characteristic ions for individualization of these regioisomeric substances.

A comparison of the mass spectra for the PFPA and HFBA derivatives of all ring substituted methamphetamines (Compounds 1, 2, 3, 8, and 9) indicates unique ions at *m/z* 160 and *m/z* 210 [see Figures 4(1), 4(2), 4(3), 4(8), 4(9), 5(1), 5(2), 5(3), 5(8), and 5(9)]. This mass difference of 50 (CF_2) suggests these ions contain the perfluoroalkyl group for each derivative, C_2F_5 and C_3F_7, respectively. An evaluation of the masses of the components which make up the fragment at *m/z* 160 for example include C_2F_5 (119 mass units) and CH_3 (15 mass units). Previous deuterium labeling studies have confirmed that methyl group on nitrogen is a part of this resulting fragment (4). The remaining mass 26 would correspond to CN and the proposed structures of *m/z* 160 and 210 are shown in Figure 7. An equivalent fragmentation pathway has been reported (13) for methamphetamine and further supported by the analysis of the mass spectra of the PFPA and HFBA derivatives of d_3- and d_5-MDMA in a previous study (4).

Gas chromatography

The PFPA and HFBA derivatives of the ring substituted ethoxy methamphetamines and the primary and secondary side chain regioisomers of the 2-ethoxyphenethylamine were compared on the relatively nonpolar 100% dimethyl polysiloxane (Rtx-1). Four physical mixtures were prepared, two containing the HFBA and the PFPA derivatives of 2-, 3-, and 4-ethoxymethamphetamine along with 2,3- and 3,4 MDMA, while the other two contained the side chain regioisomers of 2-ethoxyphenethylamine (Compounds 1, 5, 6 and 7) with the isobaric 2,3- and 3,4-MDMAs. Several temperature programs were evaluated and one program showing the best compromise between resolution and analysis time was used to generate the retention data in Table I and the chromatograms in Figures 8 and 9. Table I shows the relative retention of these compounds compared to *N*-methyl-3,4-methylenedioxymethamphetamine (3,4-MDMA) under identical chromatographic conditions. The data in Table I shows that 3,4-MDMA has the highest affinity for the stationary phase among this set of compounds both in the free amine form and the two amide forms investigated in this study.

The chromatograms in Figure 8 show the separation of the PFPA (Figure 8A) and HFBA (Figure 8B) derivatives of the five compounds having the methamphetamine side chain. This common side chain allows for a comparison of relative stationary phase affinity as a function of ring substituents in this set of compounds. The 2-ethoxy substitution pattern shows the least retention and compound 1 has the lowest retention time. The 3-ethoxymethamphetamine (Compound 2) elutes second followed by 2,3-MDMA (Compound 8) then the 4-ethoxy substituent compound 3. The compound showing the highest retention time and eluting last is 3,4-MDMA (Compound 9). Among the ethoxy substituents the 2-isomer shows the least retention followed by the 3-isomer, and the 4-ethoxy isomer has the greatest retention on the Rtx-1 phase. The elution order is the same for both the PFPA and HFBA derivatives with the HFBA derivatives having slightly greater retention under identical chromatographic conditions.

The chromatograms in Figure 9 show the separation of the side chain regioisomers as the ring substitution pattern is held constant (2-ethoxy). The side chain elution order is secondary amides (Compounds 6 and 7) before the tertiary amides (Compounds 1 and 5) and in this limited set of examples branched isomers elute before the more linear ones. Therefore, the amides of compound 6 elute first followed by the amide of compound 7 (both secondary amides), then the amides of compound 1 (the methamphetamine side chain) and finally the amides of compound 5 (the more linear of the tertiary amides). The methylenedioxy isomers (Compounds 8 and 9) elute later than any of the side chain isomers of the 2-ethoxy ring substitution pattern. Thus, these chromatographic results coupled with the mass spectral data allow for the individualization of each member of this series. The derivatized side chain isomers separated in Figure 9 can be differentiated by unique fragment ions in their mass spectra in addition to the well resolved chromatographic results. The compounds having a common side chain are well resolved in Figure 8 and the *m/z* 107 fragment ion allows for the identification of those compounds having the ethoxy ring substituent.

Conclusions

3,4-MDMA, 2,3-MDMA, and the three ring substituted ethoxy methamphetamines are a unique subset of regioisomeric and isobaric molecules; each compound has a molecular weight of 193 and yields a base peak at *m/z* 58 in the mass spectrum from the loss of the corresponding methylenedioxybenzyl and ring substituted ethoxybenzyl groups, respectively. The traditional electron impact mass spectrum provides little structural information for differentiating among these seven compounds.

Derivatization with acylating agents yields amides with improved resolution compared to the underivatized amines by capillary gas chromatography on the Rtx-1 stationary phase. Additionally, the perfluoroacyl derivatives significantly individualize the mass spectra for these amides and allow for specific identification. The ring substituted ethoxy methamphetamines are characterized from 2,3- and 3,4-MDMA by the presence of *m/z* 107. Side chain regioisomers yield unique hydrocarbon fragment ions at *m/z* 148, 162 and 176.

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