Chromatographic and Mass Spectral Studies on Methoxy Methyl Methamphetamines Related to 3,4-Methylenedioxymethamphetamine

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Abstract

The methoxy methyl methamphetamines are a unique set of compounds having an isobaric relationship with the controlled drug substance 3,4-methylenedioxymethamphetamine (3,4-MDMA or Ecstasy). The various isomeric forms of the methoxy methyl methamphetamines 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. Mass spectral differentiation of 3,4-MDMA from some of the methoxy methyl methamphetamines was possible after formation of the perfluoroacyl derivatives, pentafluoropropionamides (PFPA) and heptafluorobutyramides (HFBA). Perfluoroacyl derivatization provided unique and characteristic mass spectral fragment ions when the methoxy group is substituted at the 2- or 4-position of the aromatic ring relative to the alkylamine side chain group. Perfluoroacyl derivatization did not offer any characteristic ions for discrimination of 3,4-MDMA from the 3-methoxy ring substituted methyl methamphetamines. Gas chromatographic separation on non-polar stationary phases successfully resolved subsets of the methoxy methyl methamphetamines, based on ring position of the methoxy group, from 2,3- and 3,4-MDMA as the PFPA and HFBA derivatives.

Introduction

Previous studies (1–4) in this series have shown the 10 direct regioisomeric substances, 3,4-methylenedioxymethamphetamine (3,4-MDMA) (Ecstasy) and its nine regioisomeric equivalents, have identical molecular weights and mass spectral fragments of equivalent mass-to-charge ratios. Therefore, analysis of the underivatized regioisomers by electron ionization mass spectrometry (MS) does not provide data for the specific differentiation and identification of one of these regioisomers (specifically the drug of abuse Ecstasy, 3,4-MDMA) to the exclusion of all the other isomers. All 10 compounds of MW = 193 showed major fragment ions for the imine at *m/z* 58 and the benzyl fragment at *m/z* 135/136. Thus, the specific identification must be based on a combination of MS data as well as chromatographic resolution of these regioisomeric substances. Further studies have demonstrated that some of these compounds have very similar gas chromatographic (GC) retention properties; indeed, 3,4-MDMA was found to coelute with one of its non-drug regioisomeric equivalents (1) under common conditions used to identify Ecstasy (3,4-MDMA) in forensic drug samples. Additional studies (2) have shown that all 10 compounds can be resolved using the more polar GC stationary phases and specific temperature programming conditions. Additional background information on the structures of these 10 regioisomeric substances as well as their individual MS and chromatographic properties can be found in the literature (1, 2).

A recent report (4) showed that the perfluoroacyl derivatives of the eight primary and secondary amines provide unique mass spectral fragment ions to differentiate among the side-chain substitution patterns for the direct regioisomers of MDMA. The present work focuses on preparation and analytical evaluation of the ring-substituted methoxy methyl methamphetamine series of isobaric compounds related to 3,4-MDMA. These isobaric methoxy methyl methamphetamines have the same nominal mass but with different elemental composition, yet they are expected to yield MS fragments of the same structure for *m/z* 58 ion as that observed for 2,3- and 3,4-MDMA. Additionally, the various isobaric ring substituted methoxy methyl benzyl $(C_9H_{11}O)^+$ fragments have the same mass as the methylenedioxybenzyl $(C_8H_7O_2)^+$ cation observed in the MDMAs and occurring at *m/z* 135. The 10 methoxy methyl methamphetamines were compared to 2,3- and 3,4-MDMA. All 12 of these compounds have the same side chain structure for the *m/z* 58 ion which is the base peak in the electron ionization MS for the underivatized amines. Differentiation of regioisomers and isobaric substances is a significant issue in forensic drug chemistry and has been addressed in a number of drug categories (5–9).

Experimental

GC–MS analysis was performed with an HP-5890 GC coupled with a HP-5970 mass selective detector (Hewlett Packard, Palo

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Alto, CA). The mass spectrometer was operated on the electron impact (EI) mode using ionization voltage of 70 eV and a source of temperature of 230°C. The mass spectra presented in Figures 1–3 were obtained by background subtraction and are the average of at least five scans. The mass spectral scan rate was 1.2 s per scan. Samples were dissolved in high-performance liquid chromatography (HPLC)-grade acetonitrile (Fisher Scientific, Fair Lawn, NJ) and manually introduced (1 µL), individually and in physical mixture, using a 10-µL Hamilton syringe (Hamilton Co., Reno, NV).

The separation was carried out on four capillary GC columns with the same dimensions, 30 m × 0.25 mm-i.d, and the same film depth, 0.25 µm. The stationary phases compared were the relatively nonpolar phases, 100% dimethyl polysiloxane (Rtx-1), 95% dimethyl-5% diphenyl polysiloxane (Rtx-5), 65% dimethyl-35% diphenyl polysiloxane (Rtx-35), and the more polar trifluoropropyl methyl polysiloxane (Rtx-200). All columns were purchased from Restek Corporation (Bellefonte, PA).

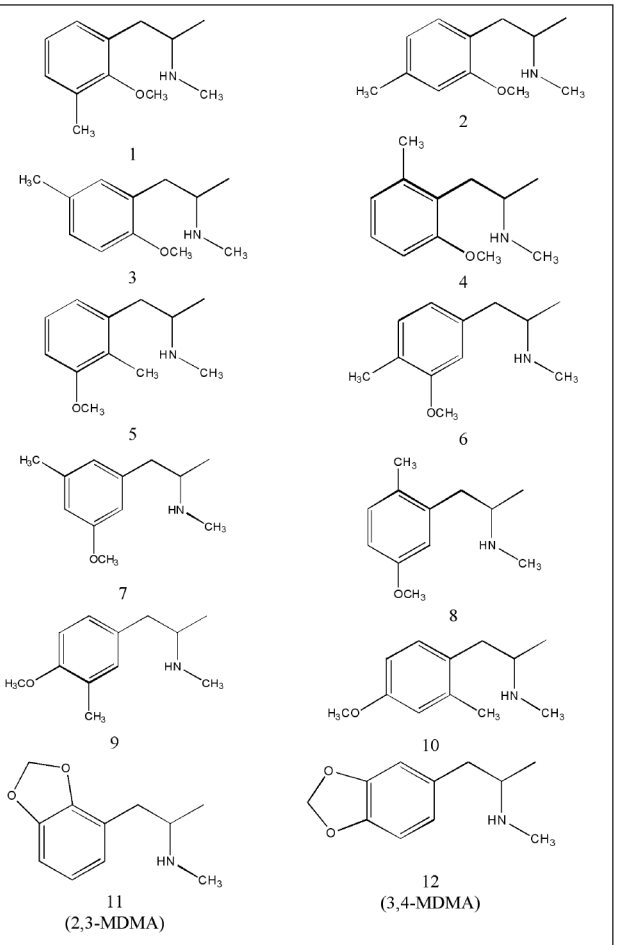

Figure 1. Structures for the substituted methoxy methyl methamphetamines, 2,3-MDMA and 3,4-MDMA.

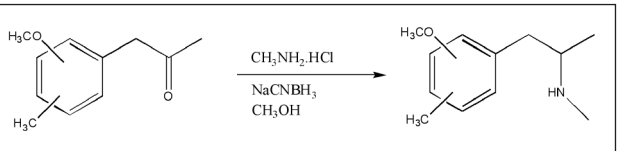

Figure 2. Synthesis of the methoxy methyl methamphetamines from the corresponding ring-substituted methoxy methyl phenyl-2-propanones.

The retention data in Tables I and II were generated with a temperature program set to hold the column temperature at 70°C for 1 min, ramped to 150°C at 7.5°C/min, hold at 150°C for 2 min, and finally ramped to 250°C at 10°C/min.

Drugs and reagents

Samples of 3,4- and 2,3-MDMA were synthesized as previously described (1). Ring-substituted methoxy methyl phenyl-2-propanones as precursors of the isobaric methoxy methyl methamphetamines were synthesized as previously described (10). Other laboratory reagents and chemicals were obtained from Aldrich Chemical Company (Milwaukee, WI) or Fisher Scientific (Fair Lawn, NJ).

Synthesis of methoxy methyl methamphetamines

A solution of the appropriately ring-substituted methoxy methyl phenyl-2-propanone in methanol was stirred with methyl amine hydrochloride and sodium cyanoborohydride. Isolation of the basic fraction gave light yellow oils, which were converted to the corresponding ring substituted methoxy methyl methamphetamine hydrochloride salts using gaseous HCl.

Derivatization procedure

Each perfluoroamide was prepared individually from the corresponding amine hydrochloride salts by dissolving approximately 0.3 mg (1.33×10^{-5} mole) of each amine in 50 µL of ethyl acetate followed by addition of a 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.

Results and Discussion

Synthesis

The ten methoxy methyl methamphetamines (Compounds 1–10, Figure 1) were prepared (Figure 2) by reacting the appropriately substituted methoxy methyl phenyl-2-propanone with methylamine and sodium cyanoborohydride.

Ring-substituted methoxy methyl phenyl-2-propanones constitute the key intermediate in synthesizing the desired methoxy methyl methamphetamines. The methods used to prepare all ten ring substituted methoxy methyl phenyl-2-propanones from commercially available precursors have been reported (10).

The methods for the preparation of the 2,3- and 3,4-methylenedioxymethamphetamines (Compounds 11 and 12, Figure 1) have been described in previous reports (1). 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).

MS

MS is the primary method for confirming the identity of drugs and other substances of abuse in forensic samples. The MS of 3,4-methylenedioxymethamphetamine (MW = 193) is characterized by a base peak at *m/z* 58, the *N*-methyl imine of acetaldehyde, and the 3,4-methylenedioxybenzyl fragment at mass 135/136 (for the cation and the radical cation, respectively). The molecular ion is a peak of relatively low abundance in the MS of most amines (11).

The ten possible methoxy methyl ring substitution patterns of methamphetamine (Compounds 1–10, Figure 3) have the potential to yield mass spectra essentially equivalent to 3,4-

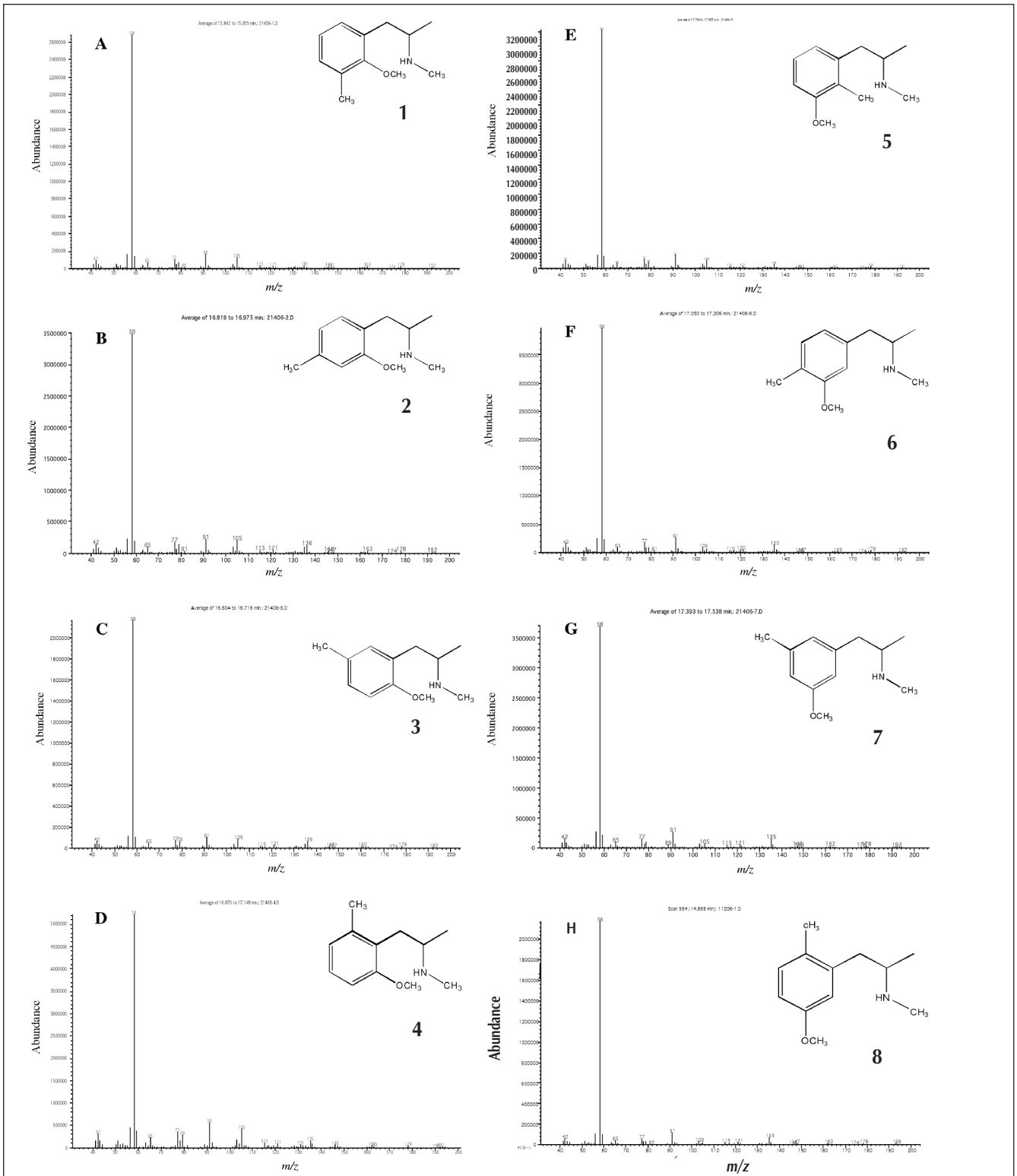

Figure 3. Mass spectra for compounds 1–12.

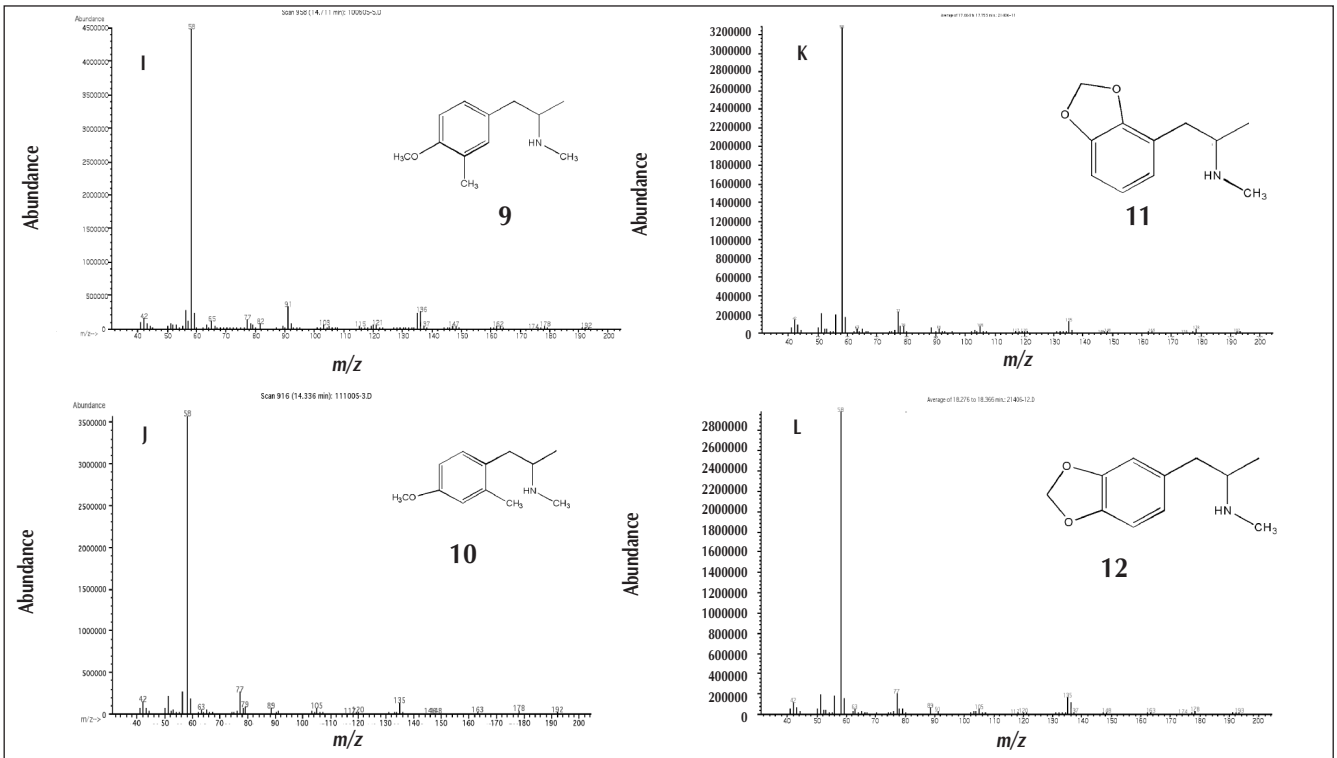

Figure 3. (Continued) Mass spectra for compounds 1–12.

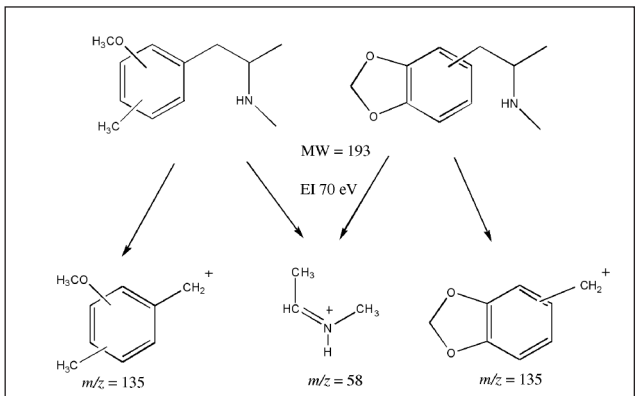

Figure 4. EI Fragmentation patterns of compounds 1–12.

MDMA (and 2,3-MDMA). All have molecular weight of 193 and major fragment ions in their electron ionization mass spectra at *m/z* 58 and 135/136 (Figure 3). The isobaric methoxy methyl 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 methoxy methyl methamphetamines is the same imine structure as that obtained in the MS of both 2,3 and 3,4-MDMA (Figure 4). The individual MS for 2,3- and 3,4-MDMA are also presented in Figure 3 (Compounds 11 and 12).

The mass spectra for the ten ring-substituted methoxy methyl methamphetamines in Figure 3 show only the major fragment ions at equivalent masses. This lack of mass spectral specificity in addition to the possibility of chromatographic coelution with 3,4-MDMA could result in misidentification of the target drug. Furthermore, the lack of available reference samples for all ten of these isobaric methoxy methyl methamphetamines complicates the individual identification of any one of these substances. This constitutes a significant analytical challenge, where the specific identification by GC–MS must be based primarily upon the ability of the chromatographic system to separate the regioisomeric/isobaric nondrug from the actual drug of interest. Additionally, the ability to distinguish between these regioisomers directly enhances the specificity of the analysis for the target drugs of interest.

In the next phase of this study, various perfluoroacylated derivatives of the methoxy methyl methamphetamines were prepared and evaluated in an effort to individualize their mass spectra and maintain or improve chromatographic resolution. Acylation of the amines significantly lowers the basicity of nitrogen and can allow other fragmentation pathways to play a more prominent role in the mass spectra (4). However, in these substances, the perfluoroacyl derivatives were less successful at differentiating among the various ring-substituted methamphetamines. Because all ten of the methoxy methyl methamphetamines have the same side chain and have ten different ring substitution patterns, perfluoroacylation did not allow for complete compound individualization based only on the observed mass spectra.

The mass spectra for the pentafluoropropionamines (PFPA) and heptafluorobutyramides (HFBA) are shown in Figures 5 and 6, respectively. From these spectra, a common peak occurs at *m/z* 204 and 254, which corresponds to the loss of 135 mass units from the molecular ions at 339 and 389 for PFPA and HFBA amides. This ion at *m/z* 204 and 254 is the PFPA and HFBA imine species likely formed from the alpha cleavage of the amide nitrogen to eliminate the methoxy methyl benzyl and the 2,3- and 3,4-methylenedioxybenzyl radicals. Thus, the *m/z* 204 and 254 ions in these PFPA and HFBA amides are anal-

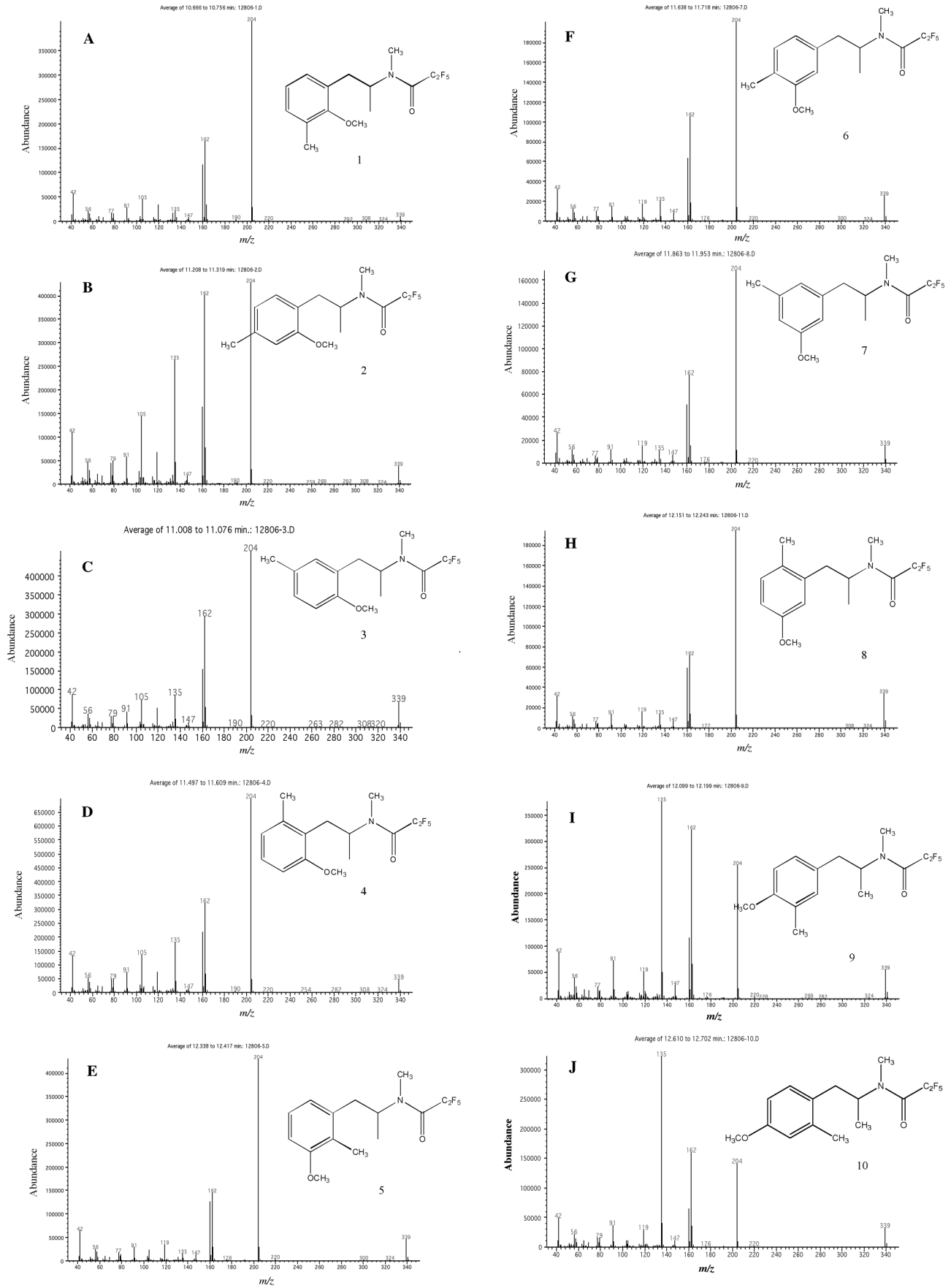

Figure 5. Mass spectra of the PFPA derivatives of compounds 1–12.

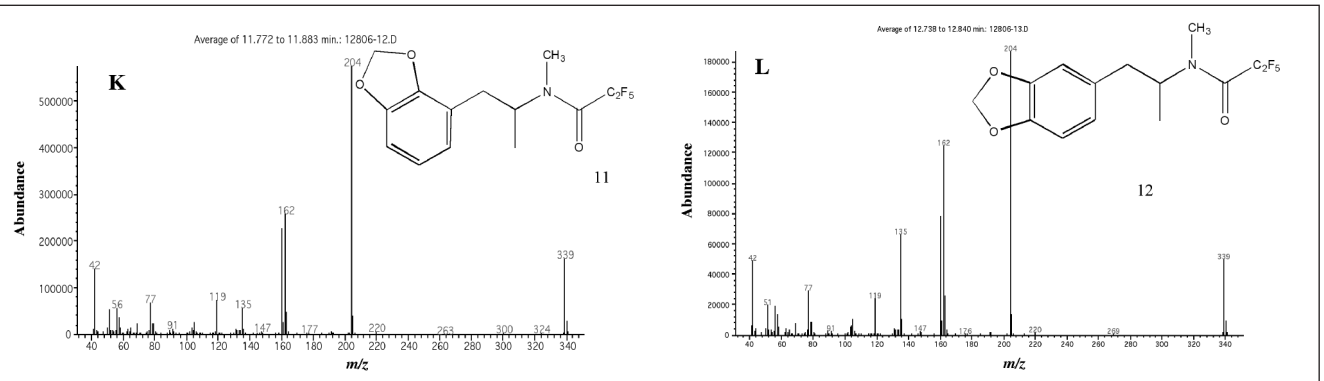

Figure 5. (Continued) Mass spectra of the PFPA derivatives of compounds 1–12.

ogous 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 methoxymethylbenzyl cation and radical cation at *m/z* 135/136 is also a common fragment in most of the spectra in Figures 5 and 6 (see Figure 4). The identical fragmentation pathways for the PFPA and HFBA derivatives of 2,3- and 3,4-MDMA produced ions of the same structure at *m/z* 204 and 254 and isobaric ions at equivalent masses for the benzylic species at *m/z* 135/136.

The mass spectra for all derivatives (Figures 5 and 6) show a common peak at *m/z* 162 corresponding to the alkene radical cation which occurs from hydrogen rearrangement and subsequent fragmentation of the alkyl carbon to nitrogen bond of the side chain (Figure 8). Additionally, the isobaric methylenedioxyphenylpropene radical cation occurring by an analogous process is observed in the mass spectrum of the PFPA and HFBA derivatives of 2,3- and 3,4-MDMA (see Figures 5 and 6). The presence of the *m/z* 162 ion indicates that a three-carbon chain is attached directly to the aromatic ring in an uninterrupted manner. The companion ion identifying the substituent on nitrogen as the *N*-methyl group (see Figure 9) occurs at *m/z* 160 in the PFPA derivatives (Figure 5) and at *m/z* 210 in the HFBA derivatives (Figure 6). Previous studies on the PFPA and HFBA derivatives of d_3- and d_5-MDMA (4) as well as d_3-, d_5-, and d_8-methamphetamine (8) lend support to the proposed structure for the unique *m/z* 160 and *m/z* 210 fragments.

As expected in this study, acylation of the side chain nitrogen in these isobaric methamphetamines did not individualize the resulting mass spectra. Thus, differentiation among these compounds and differentiation from 3,4-MDMA remains a significant challenge for chromatographic studies. However, the mass spectra obtained for the PFPA and HFBA derivatives do provide information that could allow these ten methoxy methyl methamphetamines to be divided into three subsets based on the position of the methoxy-group ring substitution.

The mass spectra of the 2-methoxy-substituted methyl methamphetamine (the methoxy group substituted at the 2-position relative to the alkylamine side chain) derivatives shown in Figures 5A–5D for the PFPA derivatives and Figures 6A–6D for the HFBA derivatives show a more prominent *m/z* 105 ion than the other substitution patterns. This ion at *m/z* 105 represents the loss of 30 mass units (formaldehyde, CH_2O) from the methoxy-methylbenzyl cation at *m/z* 135. The further loss of formaldehyde (CH_2O) from those benzylic cations having a 2-methoxy group can be attributed to a 1,6-hydride shift from the carbon of the methoxy group to the methylene of the methoxymethyl benzyl cation followed by loss of formaldehyde to give the methyl benzyl cation at *m/z* 105 (Figure 10).

Thus, the mass spectra of the PFPA and HFBA derivatives of the 2-methoxy subset (Compounds 1–4) all show *m/z* 105 ions formed through the mechanism described in Figure 10. This ion does not occur to any significant extent in the derivatives of the 3-methoxy or 4-methoxy subsets. The *m/z* 105 ion is not observed in the mass spectrum of the PFPA and HFBA derivatives of 2,3- and 3,4-MDMA. Therefore, the *m/z* 105 ion may distinguish this 2-methoxy subset from MDMA, but no specific ions were observed to distinguish among the members of this subset, compounds 1–4.

The PFPA and HFBA derivatives of compounds 5–8 (methoxy group in the 3-position of the aromatic ring relative to the alkylamine side-chain) can be differentiated from the PFPA and HFBA derivatives of compounds 1–4 by the absence of *m/z* 105. Perfluoroacylation did not offer an advantage in distinguishing these compounds from each other and from the MDMAs.

The 4-methoxy subset, the PFPA and HFBA derivatives of compounds 9 and 10, show a very different distribution of ions than that observed for either of the other two subsets. The low mass ions at *m/z* 135 and 162 show a very high relative abundance and actually appear as the base peak in several spectra. These are the only derivatives not showing the perfluoroacylimine at *m/z* 204 or 254 as the base peak. Thus, the significant relative abundance of the *m/z* 135 and 162 ions distinguishes this 4-methoxy subset from the MDMAs and the other two subsets of methoxy methyl methamphetamines.

GC

The underivatized and derivatized (PFPA and HFBA) forms of the ring-substituted methoxy methyl methamphetamines were compared on four stationary phases using capillary columns of equivalent dimensions. Several temperature programs were evaluated, and one program showing the best compromises between resolution and analysis time was used to collect the retention data in Tables I and II and to generate

the chromatograms in Figures 11–15. Tables I and II show the relative retention of these compounds compared to *N*-methyl-3,4-methylenedioxyphenyl-2-propanamine (3,4-MDMA) under identical chromatographic conditions. The stationary phases compared were the relatively nonpolar phases, 100% dimethyl polysiloxane (Rtx-1), 95% dimethyl-5% diphenyl polysiloxane (Rtx-5), 65% dimethyl -35% diphenyl polysiloxane (Rtx-35), and the more polar trifluoropropyl methyl polysiloxane (Rtx-200).

The coelution of some underivatized PFPA and HFBA derivatives varied from one stationary phase to another. Underivatized compound 2 coelutes with compound 4; 10 coelutes with 12; and compound 6 coelutes with compounds 7 and 9 on the Rtx-1 stationary phase. The PFPA and HFBA derivatives of

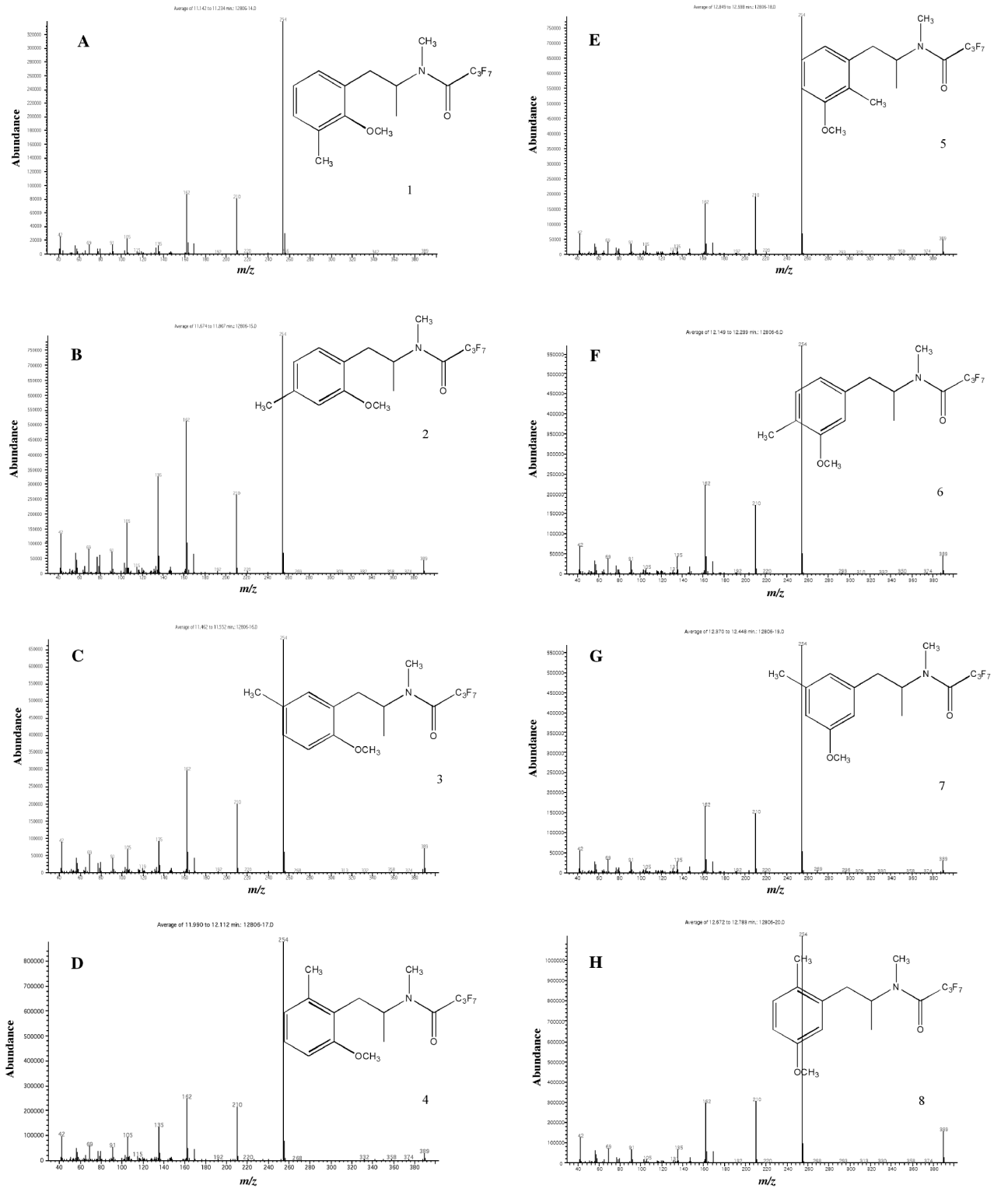

Figure 6. Mass spectra of the HFBA derivatives of compounds 1–12.

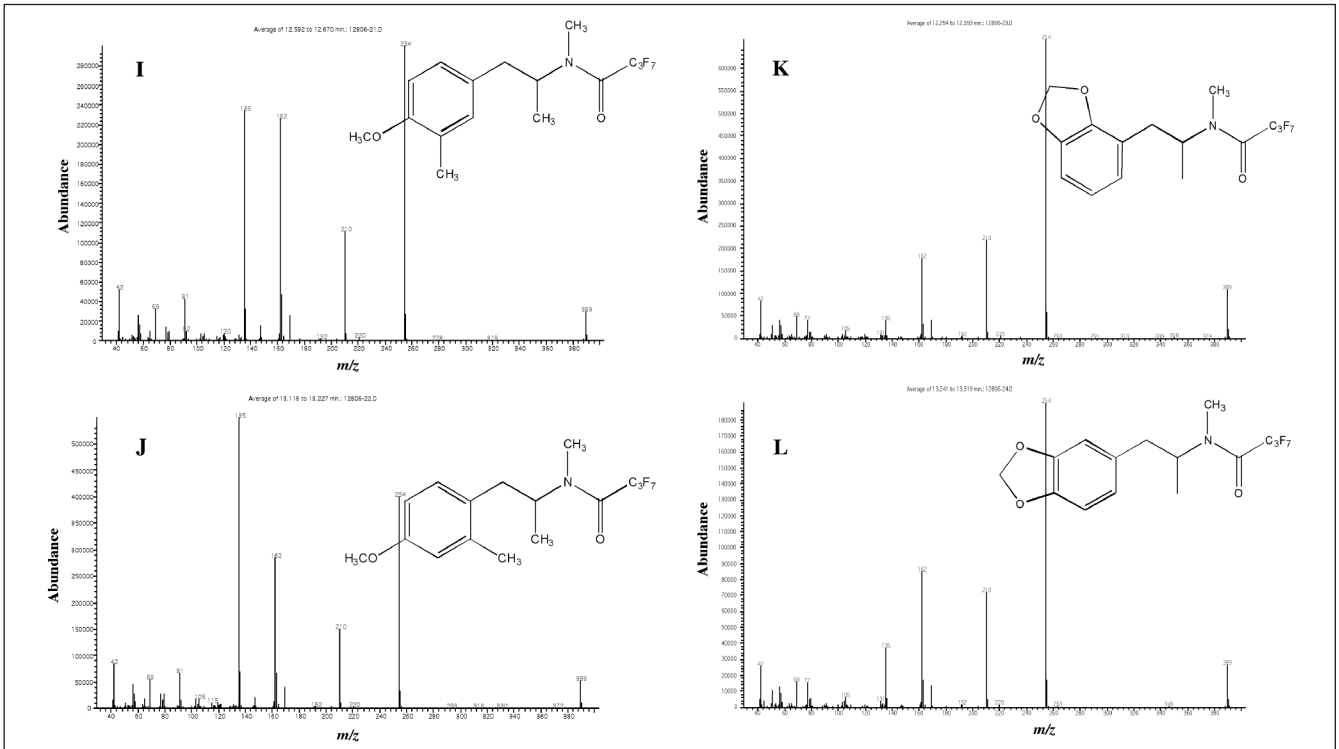

Figure 6. (Continued) Mass spectra of the HFBA derivatives of compounds 1–12.

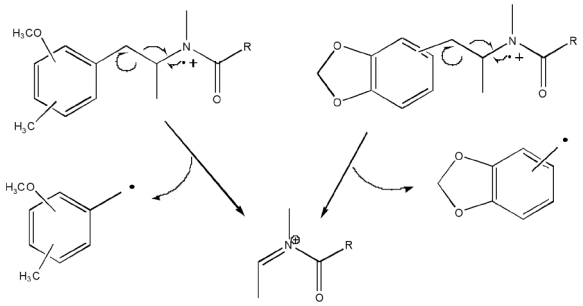

Figure 7. Formation of the *m/z* 204 (R = C_2F_5) and *m/z* 254 (R = C_3F_7) ions from perfluoroacyl derivatives of compounds 1–12.

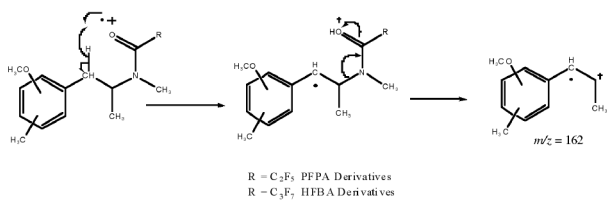

Figure 8. Formation of *m/z* 162 from perfluoroacyl derivatives of methoxy methyl methamphetamines.

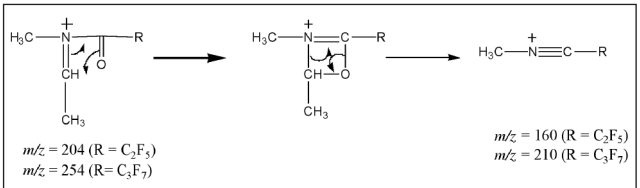

Figure 9. Formation of *m/z* 160 and 210 ions from the PFPA and HFBA derivatives of compounds 1–12.

compounds 8 and 9 coelute, and the HFBA derivatives of compounds 4 and 6 coelute on the Rtx-1 stationary phase (Table I).

Five sets of underivatized compounds were found to coelute on Rtx-5 (Table II): 2,3-MDMA (compound 11) coelutes with compound 6; compound 2 coelutes with compound 4; compound 5 coelutes with compound 8; compound 7 coelutes with compound 9; and, finally, compound 10 coelutes with compound 12. In the PFPA and HFBA derivatives, three sets of compounds co-elute on the Rtx-5 column (see Table II).

Three sets of underivatized compounds were found to coelute on Rtx-35 (Table I): compound 4 coelutes with compound 6; compound 5 coelutes with compound 8; and, finally, compound 7 coelutes with compound 9. For the PFPA derivatives, there are three sets of compounds that coelute: compound 5 coelutes with compound 9; compound 8 coelutes with compound 11; and compound 4 coelutes with compound 6. The HFBA derivatives of compounds 2, 8, and 9 coelute on the Rtx-35 column.

The best resolution among the evaluated columns was achieved on Rtx-200 where a physical mixture of the 12 PFPA-derivatized compounds yielded 11 peaks with compounds 7 and 9 coeluting (Figure 11). However, the mass spectra of these two compounds differ as previously described. Compound 9 (a 4-methoxy substituted amine) has a base peak at *m/z* 135 compared to *m/z* 204 base peak for compound 7 (a 3-methoxy substituted amine). Thus, a sample containing compound 7 or 9 could be identified based on MS. Additional resolution studies for this series of ring-substituted methamphetamines are ongoing.

The similarity in chromatographic properties among these regioisomeric and isobaric molecules in the derivatized and underivatized form provides for a significant chromatographic

challenge. However, all four of the stationary liquid phases evaluated in this study successfully resolved 3,4-MDMA from all the other isomers. The variation in chromatographic selectivity among the phases resulted in various coelution within the methoxy methyl methamphetamines. Because MS of the perfluoroacyl derivatives of the isobaric methoxy methyl methamphetamines (Compounds 1–10) successfully divided these compounds into subsets based on the ring position of the methoxy group, the chromatographic properties were evaluated using the same subsets. The chromatographic properties of each subset of compounds were compared to 2,3- and 3,4-MDMA.

Table I. Retention Data of the Underivatized HFBA and PFPA Derivatives of Compounds 2,3- and 3,4-MDMA and Ring-Substituted Methoxy Methyl Methamphetamines Collected on Rtx-1 and Rtx-35

Compound Number	Rtx-1*			Rtx-35†		
		Derivatives‡			Derivatives‡	
	Underivatized	HFBA	PFPA	Underivatized	HFBA	PFPA
1	0.864	0.898	0.891	0.867	0.880	0.878
2	0.932††	0.926	0.924	0.922	0.957	0.908
3	0.911	0.916	0.912	0.908	0.897	0.897
4	0.933††	0.941††	0.938	0.933††	0.920	0.925††
5	0.992	0.982	0.980	0.973§	0.966	0.966§
6	0.972§	0.949††	0.946	0.934††	0.930	0.928††
7	0.976§	0.960	0.958	0.953**	0.943	0.944
8	0.996	0.973§	0.968§	0.970§	0.957§	0.957**
9	0.997§	0.970§	0.957§	0.954**	0.957§	0.961§
10	1.013*	0.993	0.993	0.984	0.978	0.977
11	0.995	0.955	0.951	0.996	0.962	0.952**
12	1*	1	1	1	1	1
3,4-MDMA	(14.909 min)	(18.931 min)	(18.497 min)	(18.333 min)	(20.893 min)	(20.909 min)

* Rtx-1 is a 30 m × 0.25-mm i.d. column coated with 0.25 µm 100% dimethyl polysiloxane
† Rtx-35 is a 30 m × 0.25-mm i.d. column coated with 0.25 µm 65% dimethyl–35%diphenyl polysiloxane
‡ Abbreviations: PFPA, pentafluoropropionamide; HFBA, heptafluorobutyrylamide.
§, **, and †† compounds that share the same sign coelute on the same column.

Table II. Retention Data of the Underivatized, HFBA and PFPA Derivatives of Compounds 2,3 and 3,4-MDMA and Ring-Substituted Methoxy Methyl Methamphetamines Collected on Rtx-5 and Rtx-200

Compound Number	Rtx-5*			Rtx-200†		
		Derivatives‡			Derivatives‡	
	Underivatized	HFBA	PFPA	Underivatized	HFBA	PFPA
1	0.859	0.916‡‡	0.889	0.849	0.777	0.781
2	0.930‡‡	0.923	0.921	0.904	0.803	0.811
3	0.910	0.912‡‡	0.909	0.891	0.784	0.792
4	0.937‡‡	0.938	0.935	0.918	0.827	0.832
5	0.985§	0.979	0.977	0.959††	0.915	0.914
6	0.953††	0.947	0.944	0.933**	0.851	0.853
7	0.969**	0.957††	0.956††	0.973	0.887**	0.890**
8	0.984§	0.970	0.968‡‡	0.993‡‡	0.908	0.908
9	0.969**	0.968	0.967‡‡	0.939**	0.882**	0.889**
10	1.003*	0.992*	0.991*	0.994*	0.961	0.962
11	0.955††	0.956††	0.953††	0.946††	0.873	0.876
12	1*	1*	1*	1*	1	1
3,4-MDMA	(15.682 min)	(19.387 min)	(19.022 min)	(17.298 min)	(19.854 min)	(19.139 min)

* Rtx-5 is a 30 m × 0.25-mm i.d. column coated with 0.25 µm 95% dimethyl–5% diphenyl polysiloxane
† Rtx-200 is a 30 m × 0.25-mm i.d. column coated with 0.25 µm trifluoropropyl methyl polysiloxane
‡ Abbreviations: PFPA, pentafluoropropionamide; HFBA, heptafluorobutyrylamide.
§, ** , ††, *, and ‡‡ compounds that share the same sign coelute on the same separation column.
Results are the average of three expirments

In all the chromatographic studies, 3,4-MDMA elutes last in every subset and in every form (derivatized and underivatized). In the first subset (the 2-methoxy substituted aromatic ring), compounds 1–4, along with 2,3-MDMA and 3,4-MDMA, the elution order of the perfluoroacyl derivatives of these compounds was compound 1 followed by 3, 2, 4, 11, and finally 3,4-MDMA (compound 12). The elution order on Rtx-1 and Rtx-35 was the same for this subset of compounds. (See example chromatograms in Figures 12 and 13.) Additionally, this subset of methoxy methyl methamphetamines was identified in mass spectral studies as having a significant and characteristic *m/z* 105 ion.

In the second subset (the 3-methoxy substituted aromatic ring), which included compounds 5–8, along with 11 and 12 (2,3-MDMA and 3,4-MDMA), the HFBA derivative of compound 6 elutes first followed by 11 then 7, 8, 5, and finally 3,4-MDMA-HFBA (Compound 12) on the Rtx-1 phase (Figure 14). The elution order is the same for the PFPA derivatives of the same compounds on Rtx-1 (chromatogram not presented). The Rtx-35 did not produce complete resolution of this entire subset of six compounds; however, 3,4-MDMA did not coelute with any other compound in the subset. It is this subset of isobaric amines that showed no distinguishing characteristics (neither unique fragment ions nor unique relative abundance of fragment ions) in their mass spectra. Thus, coelution of one of the 3-methoxy methyl methamphetamines (Compounds 5–8) with 3,4-MDMA (Compound 12) could represent a significant analytical challenge.

In the third subset (the 4-methoxy substituted aromatic ring), which included compounds 9, 10, 2,3-MDMA (11), and 3,4-MDMA(12), the elution order of the perfluoroacyl derivatives was 11 followed by 9, 10, and finally 12. The elution order was the same on both Rtx-1 and Rtx-35, and a representative chromatogram is shown in Figure 15. It is this subset of compounds that showed mass spectra most easily distinguished from the other subsets and from 2,3- and 3,4-MDMA.

Conclusion

The methoxy methyl methamphetamines have an isobaric relationship to the 2,3- and 3,4-methylenedioxymethamphetamines and represent a unique analytical challenge in forensic drug chemistry. Each of these compounds has a molecular weight of 193 and yields a base peak for the *N*-methyl imine of acetaldehyde at *m/z* 58 in the mass spectrum. This ion represents the loss of 135 mass units from the molecular ion corresponding to the substituted benzyl species, $C_8H_7O_2$ (methylenedioxybenzyl) and $C_9H_{11}O$ (methoxy methyl benzyl). Thus, the traditional electron impact mass spectrum provides little structural information for differentiating among these 12 compounds. Because of the unique similarity of these compounds by MS, the specific identification of a compound such as 3,4-MDMA requires methods to eliminate the other isomers.

The ring-substituted methoxy methyl methamphetamines were evaluated for their chromatographic and mass spectral properties compared to 2,3- and 3,4-MDMA. The mass spectra studies showed almost identical mass spectra for all 10 methoxy methyl methamphetamines and 2,3- and 3,4-MDMA. The perfluoroacylated derivatives of the 10 methoxy methyl methamphetamines were prepared and evaluated for their

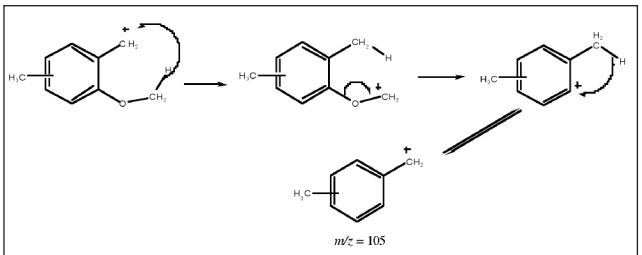

Figure 10. Formation of *m/z* 105 ions from the 2-methoxymethylbenzyl cations.

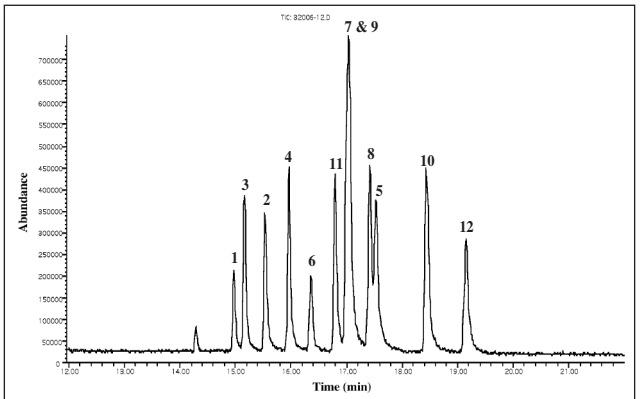

Figure 11. GC analysis of the PFPA derivatives of compounds 1–12. Rtx-200 column.

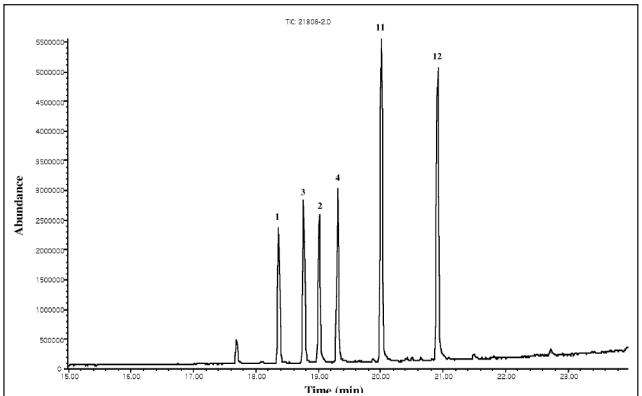

Figure 12. Capillary GC separation of the PFPA derivatives of the 2-methoxy methyl methamphetamine regioisomers (compounds 1–4) and 2,3- and 3,4-MDMA (compounds 11 and 12). Rtx-35 column.

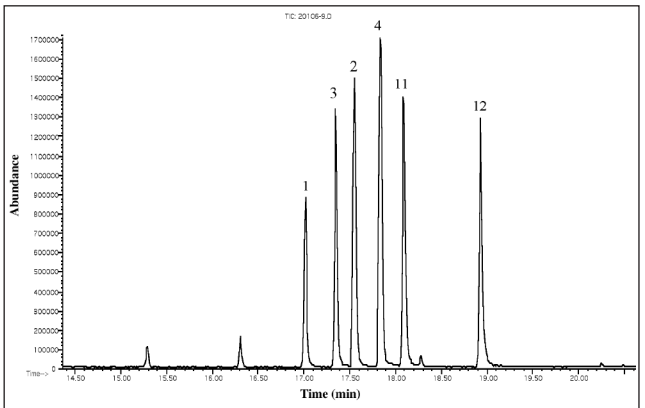

Figure 13. Capillary GC separation of the HFBA derivatives of the 2-methoxy methyl methamphetamine regioisomers (compounds 1–4) and 2,3- and 3,4-MDMA (compounds 11 and 12). Rtx-1 column.

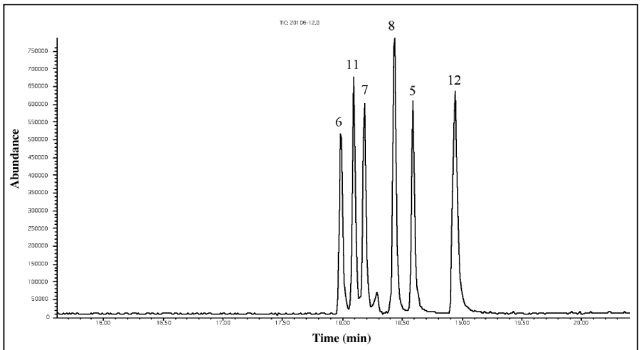

Figure 14. Capillary GC separation of the HFBA derivatives of the 3-methoxy methyl methamphetamine regioisomers (compounds 5–8) and 2,3- and 3,4-MDMA (compounds 11 and 12). Rtx-1 column.

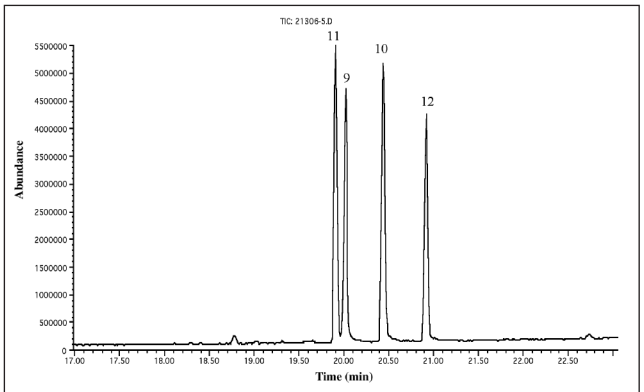

Figure 15. Capillary GC separation of the PFPA derivatives of the 4-methoxy methyl methamphetamine regioisomers (compounds 9 and 10) and 2,3- and 3,4-MDMA (compounds 11 and 12). Rtx-35 column.

ability to individualize the mass spectra of these compounds and to maintain or improve chromatographic resolution. The perfluoroacylation process did not produce unique mass spectra characteristic of each compound. However, derivatization did subdivide the methoxy methyl methamphetamines into subgroups based on the position of the methoxy group on the aromatic ring relative to the alkylamine side-chain. The presence of the *m/z* 105 ion suggests the methoxy group is in the 2-position relative to the alkylamine side-chain, and the significant abundance of the low mass ions at *m/z* 135 and *m/z* 162 indicates the methoxy group is substituted at the 4-position of the aromatic ring. The 3-substituted aromatic ring methoxy group isomers did not show any unique fragments to distinguish them from 2,3- and 3,4-MDMA as the perfluoroacylated derivatives.

Different stationary phases and temperature programs were used in an effort to separate the methoxy methyl methamphetamines from 2,3- and 3,4-MDMA. The best resolution among the evaluated columns was achieved on Rtx-200, where a mixture of the 12 compounds gave 11 peaks and only the PFPA derivatives of methoxy methyl methamphetamines 7 and 9 coelute. The perfluoroacyl derivatives of the methoxy methyl methamphetamines were divided into three subsets based on the ring substitution pattern of the methoxy group. The derivatives of the individual subsets were each resolved on Rtx-1. Additional resolution studies on this series of substituted methamphetamines are ongoing in our laboratory.

Acknowledgement

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