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Methcathinone and Designer Analogues: Synthesis, Stereochemical Analysis, and Analytical Properties

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Abstract

This paper describes the synthesis, stereochemical analysis, and analytical properties of methcathinone and related compounds. Methcathinone represents a new class of designer street drugs that can be prepared easily from readily available starting materials such as the ephedrines and pseudoephedrines. The oxidation of each individual isomer of ephedrine and pseudoephedrine produces homochiral methcathinone via conservation of configuration. Thus 1*R*,2*S*-ephedrine and 1*S*,2*S*-pseudoephedrine yield *S*-methcathinone, and 1*S*,2*R*-ephedrine and 1*R*,2*R*-pseudoephedrine produce *R*-methcathinone. The isomers of methcathinone were separated by gas chromatography as the diastereomeric amides following derivatization with *S*-(-)-*N*-(trifluoroacetyl)prolyl chloride (TPC).

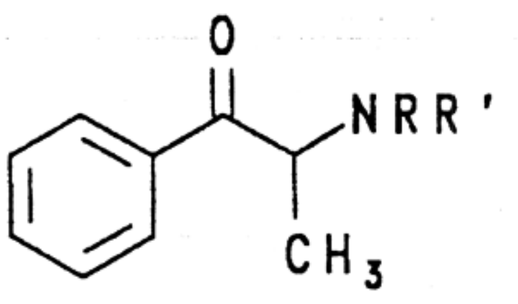
The gas chromatographic–mass spectrometric analysis of methcathinone and designer analogues showed a major chromatographic peak with a mass spectrum characteristic of the parent molecule. However, the major chromatographic peak was accompanied by a secondary, well-resolved peak that yielded a molecular ion 2 mass units less than that of the major peak. Deuterium labeling experiments showed this minor component to arise through the thermal oxidation of the 2,3-carbon–carbon bond of the side chain to yield the 2,3-enamine.

Cathinone, methcathinone, dimethcathinone, ethcathinone, and diethylcathinone (diethylpropion) were separated by reversed-phase liquid chromatography using a phenyl bonded stationary phase and an acidic (pH 3) mobile phase. Methcathinone and cathinone do not interfere or cross-react in standard drug abuse screening methods based on analysis by thin-layer chromatography or immunoassay.

Introduction

Methcathinone (ephedrone, α-methylaminopropiophenone, "CAT") is an amphetamine-type drug of abuse that was first discovered in clandestine drug samples obtained in the Upper Peninsula of Michigan in the early 1990s (1). More recently, this drug has been encountered in other portions of the United States, including the state of Washington (1). Furthermore, methcathinone abuse has been reported (2) in other countries for some time, particularly in the former Soviet Union where it is known as "Jeff". In an attempt to prevent the more widespread manufacture and use of methcathinone in the United States, it was recently (October 15, 1993) placed into Schedule I of the Federal Controlled Substances Act (1).

Methcathinone (Chart 1) is the *N*-methyl analogue of the natural product cathinone ("khat"), a psychoactive alkaloid present in the leaves of the khat shrub, *Catha edulis* (3,4). The khat plant grows in Eastern Africa and the Arabian Peninsula, and its leaves are distributed to countries throughout the region, including Somalia. The leaves are chewed to release cathinone, which produces stimulant-like effects similar to amphetamine. It appears that only fresh khat leaves contain the active alkaloid, thus leaves must be imported daily to provide a continuous supply of the drug. This factor has historically restricted the availability of the khat leaves. However, with increased transportation efficiency, khat leaves have achieved wider distribution to more distant countries with significant African and Arab immigrant populations. Although khat use



R = R' = H: CATHINONE
R = H, R' = CH_3: METHCATHINONE
R = R' = CH_3: DIMETHCATHINONE
R = H, R' = CH_2CH_3: ETHCATHINONE
R = R' = CH_2CH_3: DIETHYLPROPION

Chart 1. Structure of methcathinone and related compounds.

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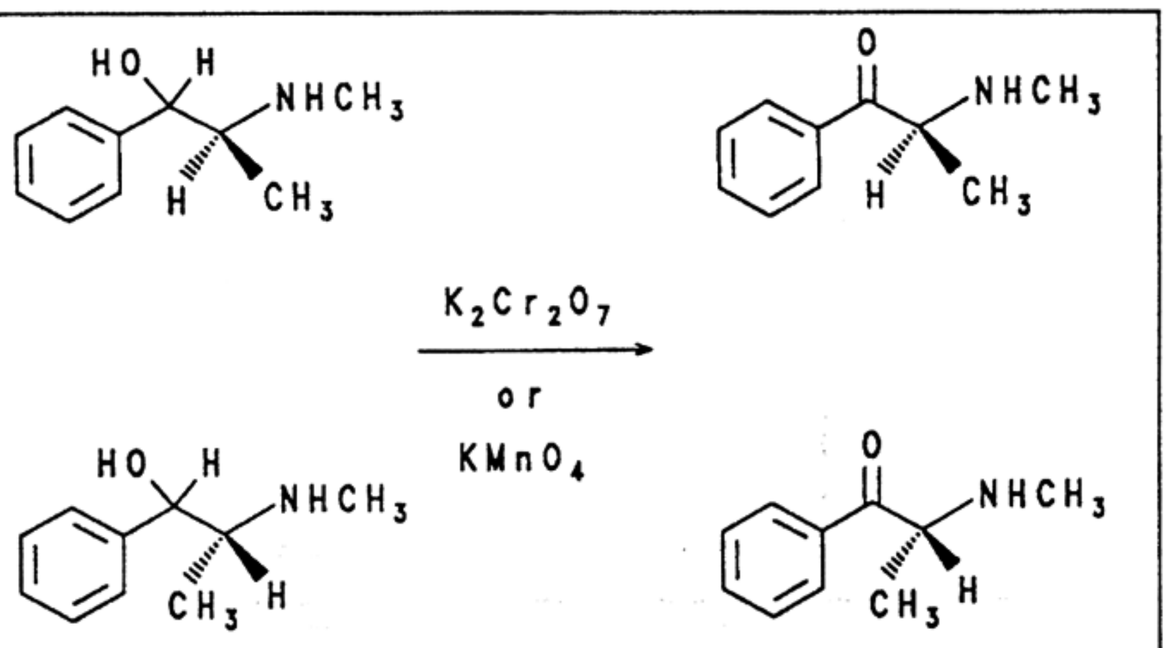
does not appear to be a significant problem in the United States, the synthetic analogue, methcathinone, has been encountered with greater frequency, suggesting the potential for future epidemic abuse (1). The abuse of this drug, like cathinone, appears to result from its ability to produce stimulant effects by neurochemical mechanisms similar to those of amphetamine and methamphetamine (4,5).

Methcathinone was originally investigated as a potential pharmaceutical agent to treat obesity and the symptoms of depression in the 1950s and 1960s (6). However, as a result of its severe side effect profile and high addiction potential, methcathinone was never marketed in the United States. It is a synthetic derivative of cathinone prepared from ephedrine by direct oxidation with dichromate or permanganate (2,6). Ephedrine is widely marketed in the United States as an "over-the-counter" dietary agent and stimulant or energy drug ("pep pills"). Thus clandestine laboratory operators can obtain ephedrine without restriction and have developed methods to convert it to methcathinone using common chemicals such as battery acid, drain cleaner, and epsom salts (1,7).

Like methamphetamine, methcathinone contains a chiral carbon at the 2-position of the side chain and therefore can exist in two enantiomeric forms. Preliminary pharmacological evidence indicates that stimulant activity resides primarily in the *S*-(-)-isomer of methcathinone (8). Although the literature (1,6) suggests that *S*-(-)-methcathinone can be synthesized stereospecifically by oxidation of 1*R*,2*S*-ephedrine, no direct evidence confirming the stereochemical composition of the methcathinone products is provided in these reports. Gas chromatographic and mass spectral data have been reported for methcathinone, but there are no reports on the stability of methcathinone during these analytical procedures. In our preliminary studies, methcathinone decomposition was observed during attempts at gas chromatographic–mass spectrometric (GC–MS) analysis. In this report, we describe the thermal decomposition products of methcathinone and designer analogues as well as their liquid chromatographic (LC) separation and the stereochemical aspects of their synthesis.



Scheme 1. Synthesis of methcathinone by oxidation of ephedrines and pseudoephedrines.

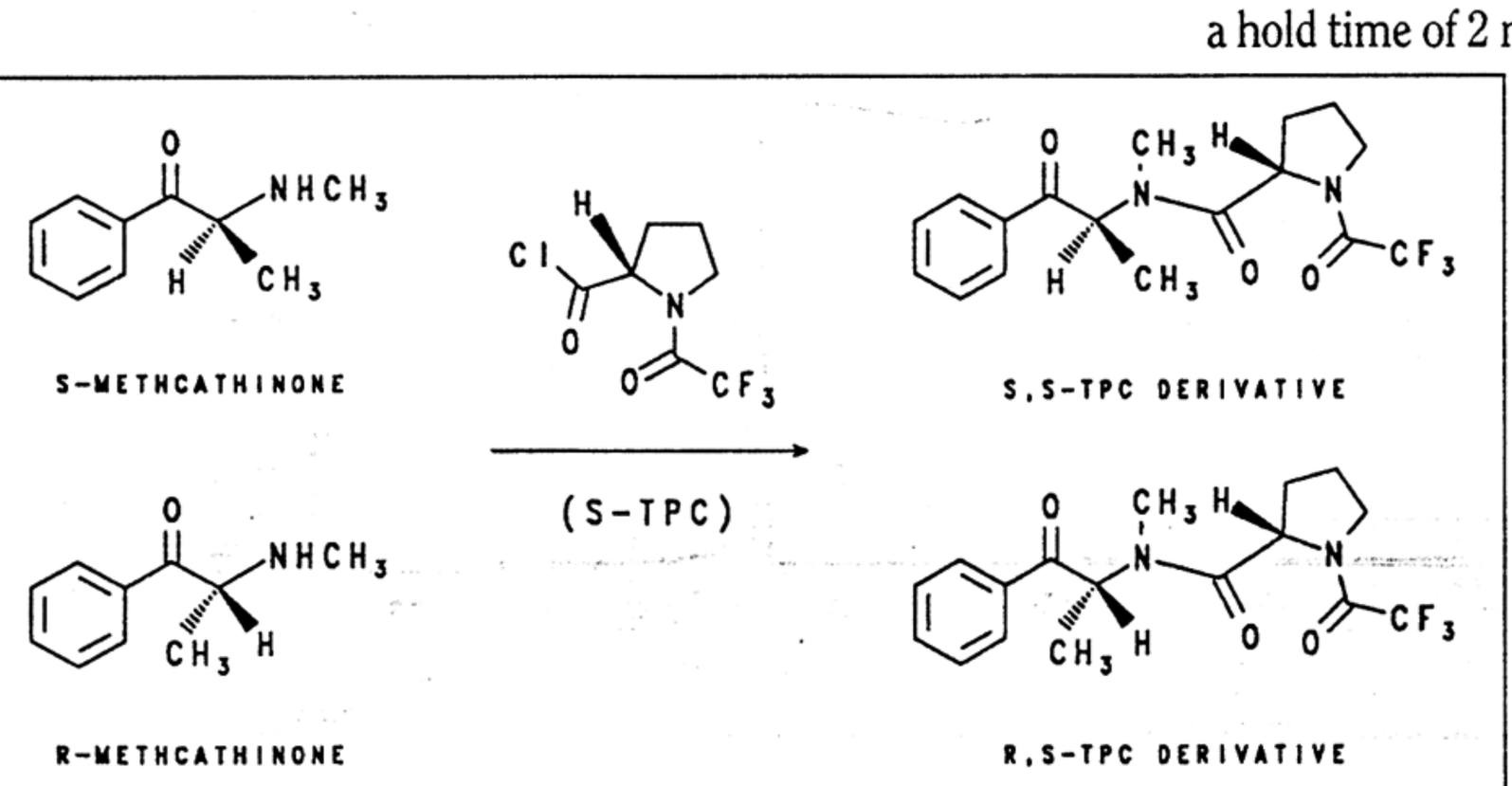
Experimental

S-(-)-N-(Trifluoroacetyl)prolyl chloride derivatization

Approximately 1 mg of each methcathinone enantiomer or 2 mg of racemic methcathinone was dissolved in 10% aqueous sodium bicarbonate. This solution was extracted with approximately 1 mL of chloroform. *S*-(-)-*N*-(Trifluoroacetyl) prolyl chloride (TPC) reagent (250 µL of 1.0M solution in methylene chloride) (Aldrich Chemical; Milwaukee, WI) was added to the chloroform solutions and allowed to react for 10 min at room temperature. The solution was washed with 0.5N NaOH to remove unreacted TPC, filtered, and placed in a 2-mL capped autosampler vial for injection into the GC–MS.

Gas chromatography and mass spectrometry

GC–MS analyses were performed using a Hewlett-Packard 5970B mass selective detector (Wilmington, DE). All methcathinone samples and methcathinone–TPC derivatives, except that shown in Figure 7, were introduced into the mass spectrometer via a GC equipped with a 12-m × 0.20-mm i.d. fused-silica column with a 0.33-µm film thickness of methylsilicone (HP-1, Hewlett-Packard). For the methcathinone–TPC derivatives, the column temperature was held at 70°C for 1 min and programmed to 200°C at a rate of 7.5°C/min and from 200 to 275°C at a rate of 10°C/min. For the underivatized methcathinone samples (except Figure 7), the column temperature was held at 70°C for 2 min and programmed to 170°C at a rate of 10°C/min and from 170 to 275°C at a rate of 25°C/min with a hold time of 2 min. The injector port temperature was 175°C. The sample shown in Figure 7 was introduced via a GC equipped with a 10-m × 0.20-mm i.d. fused-silica column with a 0.33-µm film thickness of 5% cross-linked phenylmethylsilicone gum phase (DB-5, J&W; Folsom, CA). The column temperature was held at 40°C for 1 min and then programmed to 150°C at a rate of 15°C/min and from 150 to 250°C at a rate of 25°C/min.



Scheme 2. Derivatization of methcathinone enantiomers with *S*-(-)-*N*-(trifluoroacetyl)prolyl chloride (TPC).

Liquid chromatography

The liquid chromatograph (LC) consisted of a Laboratory Data Control Constametric 3000 pump (Rivera Beach, FL), 3100 Spec-

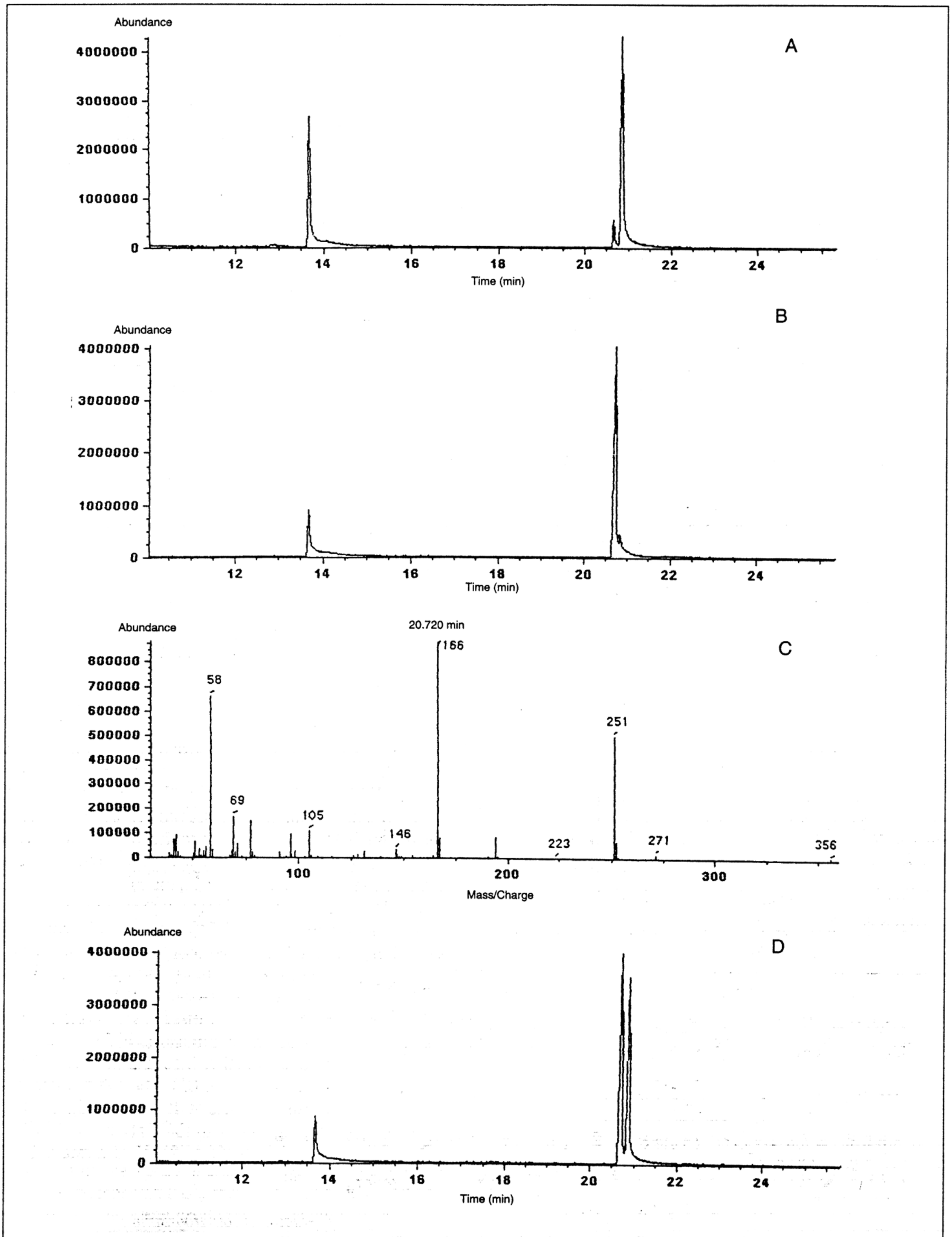


Figure 1. Gas chromatographic and mass spectral analysis of methcathinone-TPC derivatives: A, chromatogram of 1*R*,2*S*-ephedrine; B, chromatogram of 1*S*,2*R*-ephedrine; C, mass spectrum of methcathinone–TPC; D, chromatogram from racemic ephedrine.

tromonitor UV detector, CI 4100 integrator, and a Rheodyne 7125 injector (Cotati, CA). The analytical column had dimensions of 25 cm × 4.6-mm i.d. and was packed with 5-µm Spherisorb-phenyl (Chromanetics). The amines (1 mg/mL) were dissolved in HPLC-grade methanol and separated using a mobile phase of pH 3.0 phosphate buffer, methanol, and triethylamine (600:100:1). The pH 3.0 phosphate buffer was prepared by mixing 9.2 g monobasic sodium phosphate (NaH_2PO_4) in 1 L of double-distilled water and adjusting the pH to 3.0 with H_3PO_4. The mobile phase flow rate was 1.5 mL/min, and the detector was operated at 240 nm. A 5-µL aliquot of each amine solution was injected into the liquid chromatograph.

EMIT analyses

Volumes of 0.5, 0.4, 0.3, 0.2, and 0.1 mL were removed from a 1 mg/mL solution of each compound and placed in separately labeled 13- × 100-mm test tubes. Acidified methanol (100 µL) was added to each tube, and the solutions were carefully evaporated to dryness in a Pierce Reacti-Therm III Heating Module at 40°C under dry air. Drug free urine (1 mL) was added to each tube, and the tubes were vortexed for 1 min to achieve thorough reconstitution. The samples were analyzed on a Monarch 2000 Chemistry Analyzer (Lexington, MA) using Syva's Monoclonal Amphetamine–Methamphetamine EMIT II Assay (San Jose, CA). Three separate stock solutions were prepared for

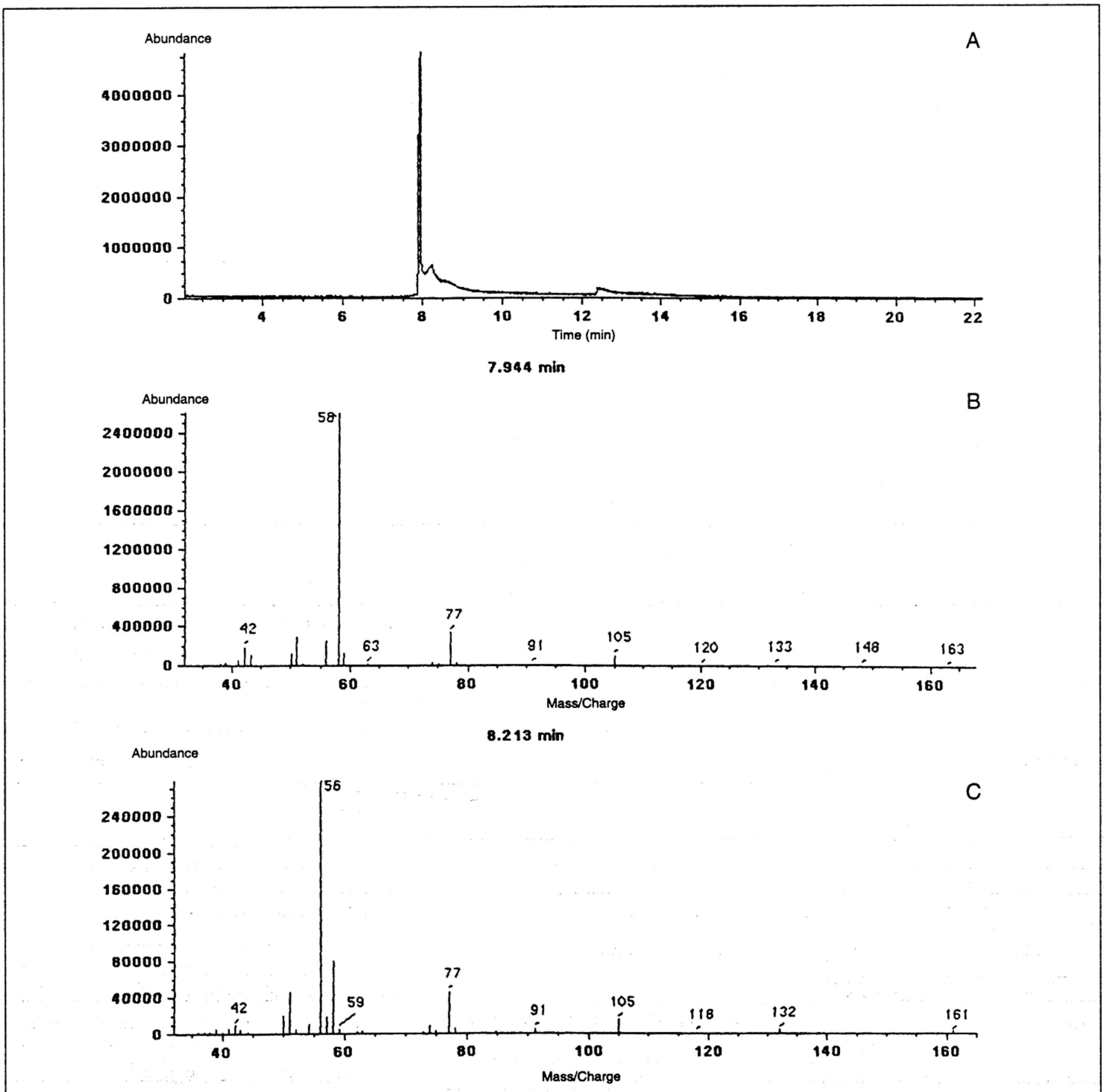


Figure 2. Gas chromatographic and mass spectral analysis of underivatized methcathinone; A, chromatogram; B, mass spectrum of peak eluting at 7.944 min; C, mass spectrum of peak eluting at 8.213 min.

each compound analyzed, and the assay was run once from each stock solution.

Thin-layer chromatography

Thin-layer chromatography (TLC) was performed using the Toxi-Lab commercial TLC kit (Irvine, CA). Solutions of each compound were prepared in drug free urine at a concentration of 7 µg/mL and extracted using Toxi-A extraction tubes. Chromatograms were developed with the Toxi-A developing solvents and then processed for visualization using normal protocols. Samples were assayed along with standards containing amphetamine and methamphetamine as reference compounds to standardize R_f values.

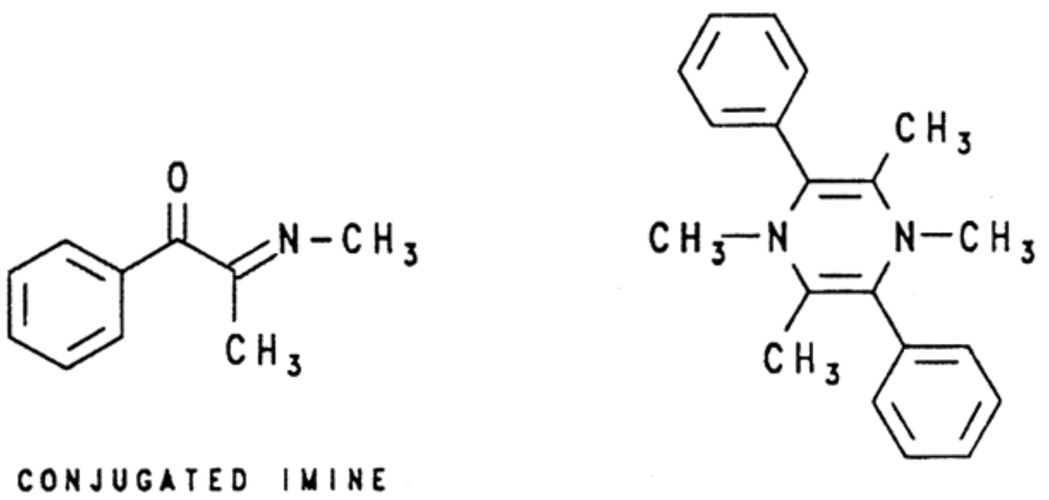


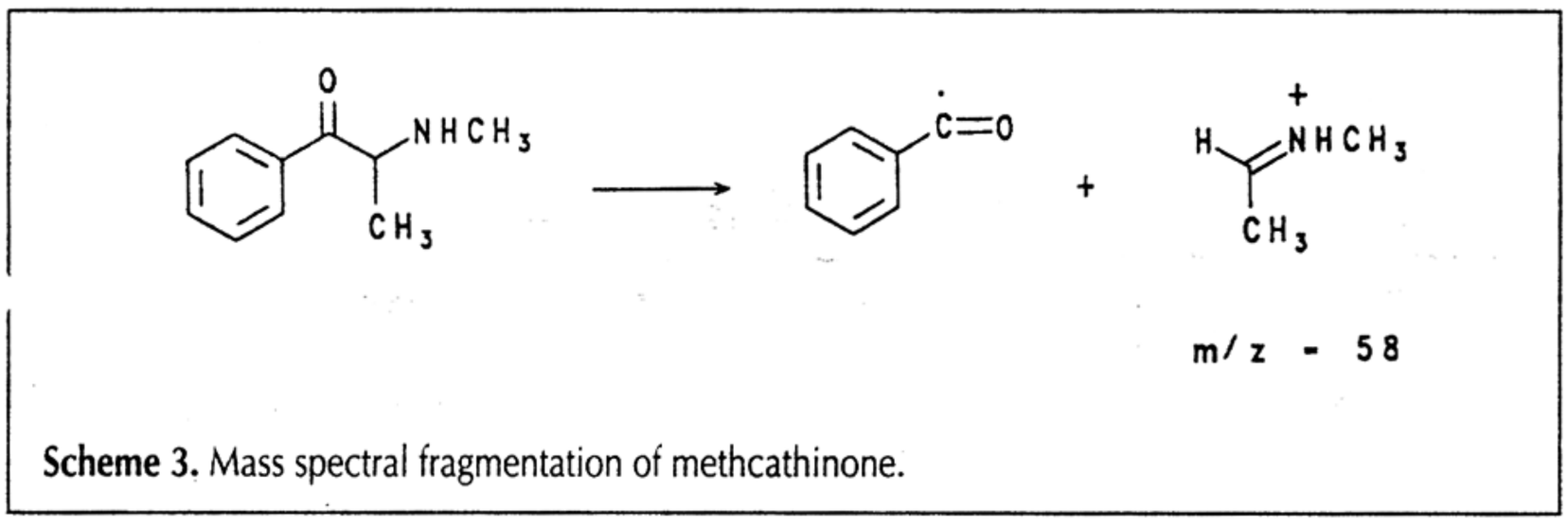
Chart 2. Structure for the conjugated imine and dimer of methcathinone proposed by Beckett and co-workers (10).

Synthesis of methcathinone by potassium permanganate oxidation

A mixture of ephedrine or pseudoephedrine (2.0 g, 10 mmol), potassium permanganate (2.0 g), methylene chloride (200 mL), water (100 mL), and acetic acid (10 mL) was stirred at room temperature for 30 min. Sufficient sodium hydrogen sulfite was added to reduce the precipitated manganese dioxide. The aqueous phase was made alkaline by the addition of 5N NaOH, and the methylene chloride layer was separated and extracted with 0.5N H_2SO_4 (50 mL). The acid extract was made alkaline by the addition of $NaHCO_3$ and extracted with methylene chloride (3 × 50 mL). The combined methylene chloride extracts were evaporated to dryness under reduced pressure with minimal heating to yield the methcathinone products as light yellow oils.

Synthesis of methcathinone and dimethcathinone by potassium dichromate oxidation

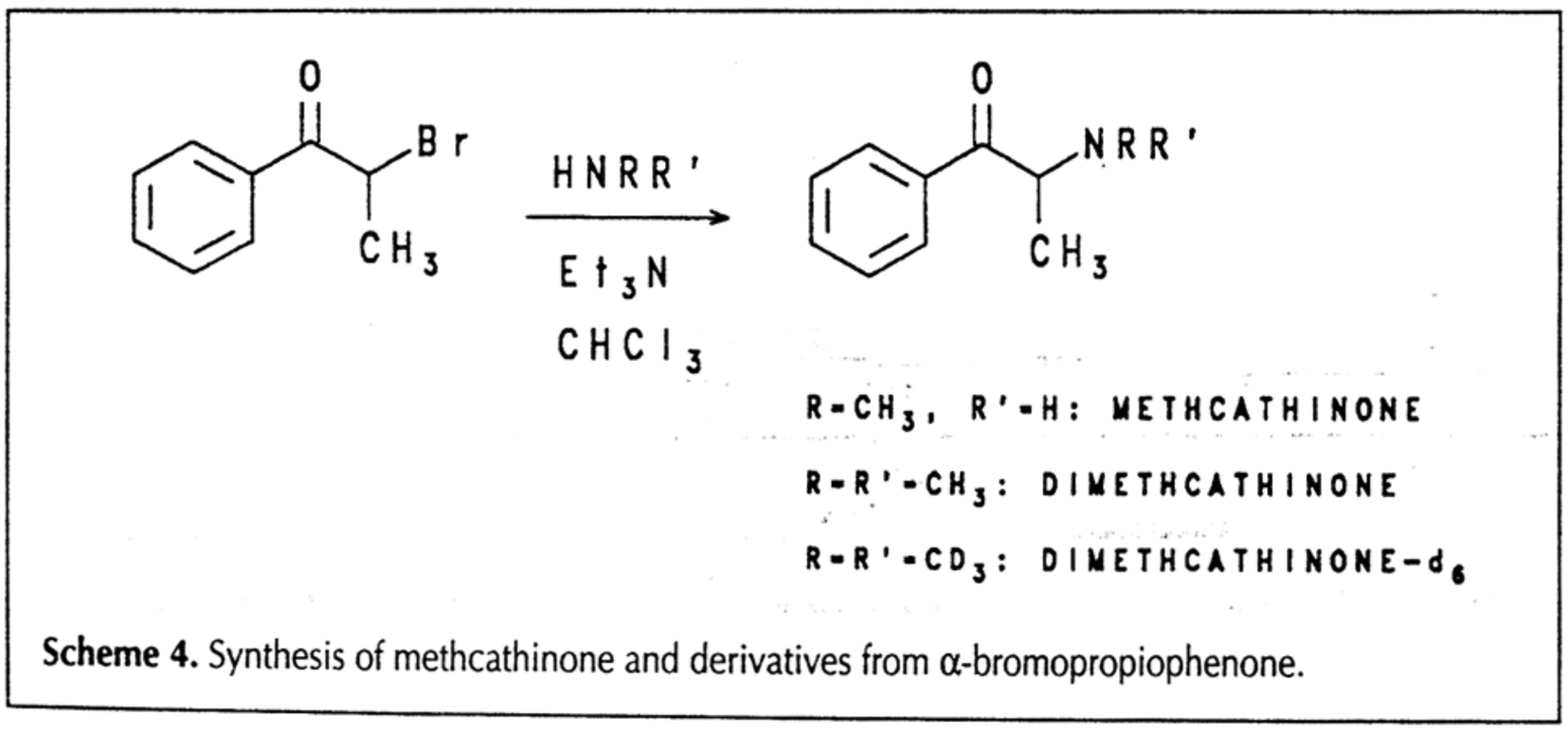
A solution of potassium dichromate (1.70 g) in concentrated sulfuric acid (8.0 mL) was added to a solution of ephedrine, pseudoephedrine, or *N*-methylephedrine (10.0 mmol) in water (15 mL) over 30 min. After the addition was complete, the reaction mixture was stirred at room temperature for 12–18 h. The reaction mixture was cooled (ice bath) and made alkaline (pH 11) by the addition of cold 10% NaOH. The resulting green suspension (approximately 100 mL) was extracted with toluene (2 × 200 mL), and the combined toluene extracts were filtered and dried over anhydrous sodium sulfate. After filtration, HCl gas was bubbled into the toluene solution, and the solvent volume was reduced (to 50 mL) under reduced pressure with minimal heating. Anhydrous ether was added to the toluene solution, and the mixture was stirred with cooling (ice bath) to yield the product hydrochlorides as white solids. The product salts were isolated by filtration, washed with anhydrous ether, and recrystallized from 2-propanol/ether.



Scheme 3. Mass spectral fragmentation of methcathinone.

Synthesis of methcathinone derivatives from α-bromopropiophenone

A solution of α-bromopropiophenone (0.38 mL, 2.5 mmol) in methylene chloride (15 mL) was added over 30 min to a stirred solution of the appropriate amine hydrochloride (2.5 mmol) and triethylamine (0.7 mL, 5 mmol) in methylene chloride (25 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 4–8 h. Water (50 mL) was added to the reaction mixture, and the pH was adjusted to 1 by the addition of 3N HCl. The acidic aqueous layer was separated and washed with an additional portion (40 mL) of methylene chloride. The aqueous solution was made alkaline (pH 11) by the addition of NaOH pellets and extracted with methylene chloride (2 × 50 mL). The combined methylene chloride extracts were evaporated under reduced pressure with minimal heating, and the resulting product oils were dried under high vacuum at room temperature. The product oils were dissolved in anhydrous ether, and HCl gas was added to yield the hydrochloride salts. The salts were isolated by filtration and recrystallized from 2-propanol/anhydrous ether.



Scheme 4. Synthesis of methcathinone and derivatives from α-bromopropiophenone.

Synthesis of deuterio-dimethcathinone derivatives

Dimethcathinone-d_6 was synthesized by reaction of dimethylamine-d_6 HCl and α-bromopropiophenone using the method described above. Dimethcathinone-d was synthesized by stirring a solution of dimethcathinone HCl (20 mg) in D_2O (1.0 mL) containing anhydrous potassium carbonate (10 mg) for 24 h at room temp. The reaction mixture was extracted with ether (2 × 1.0 mL). The combined ether extracts were evaporated under reduced pressure, and the product was analyzed without further purification.

Results and Discussion

The synthesis of methcathinone is generally accomplished by oxidation of ephedrine-type compounds using either dichromate or permanganate (Scheme 1). Ephedrine and pseudoephedrine yield methcathinone upon oxidation of the benzylic hydroxyl group to the corresponding carbonyl-containing aminoketone. Recent studies on the behavioral effects of the individual stereoisomers of cathinone (8) and methcathinone (M.E. Bronson, C.R. Clark, J. DeRuiter, and W. Jiang: unpublished results) have shown the *S*-(-)-isomers to be more potent than the *R*-(+)-enantiomers. The initial phase of this study focused on the stereochemistry of the methcathinone products obtained by oxidation of the individual enantiomers of ephedrine and pseudoephedrine. Ephedrine and pseudoephedrine represent the two diastereomeric forms of *N*-methyl-1-phenyl-1-hydroxy-2-propanamine. The two chiral centers in this structure produce four possible stereoisomers: the ephedrines are the 1*R*,2*S*- and 1*S*,2*R*-enantiomers, and the pseudoephedrines are the 1*S*,2*S*- and 1*R*,2*R*-enantiomers. Oxidation of the hydroxyl group at the 1- or benzylic position of ephedrine or pseudoephedrine to the corresponding ketone yields the enantiomeric methcathinones.

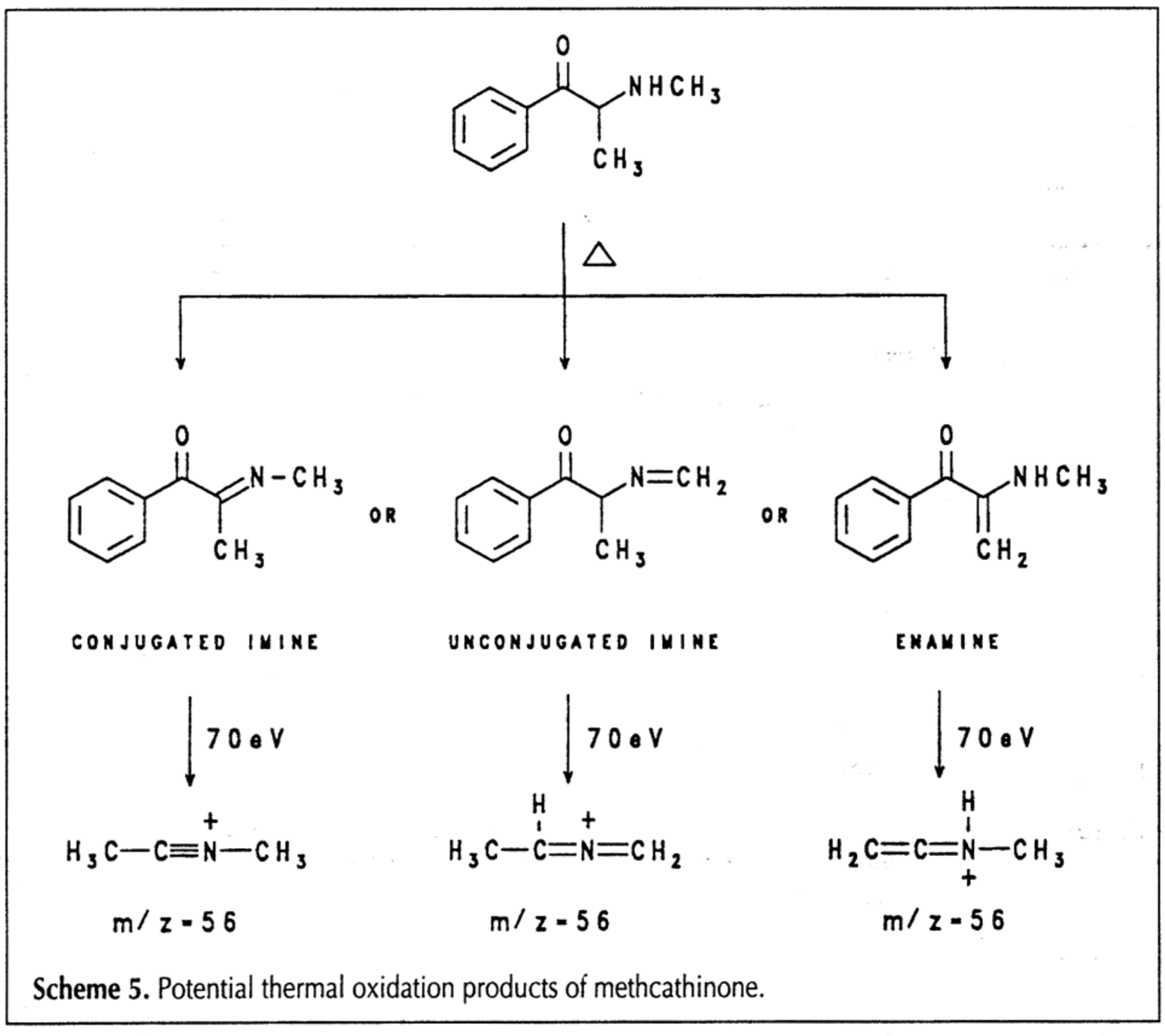
The individual enantiomers of ephedrine and pseudoephedrine were oxidized using potassium dichromate and the methcathinone products, which were isolated as free bases and then converted to hydrochloride salts. The structure of the products were confirmed by infrared and nuclear magnetic resonance spectroscopy as well as GC–MS. Determination of the stereochemical composition of the methcathinone products was accomplished using diastereomeric derivatization (Scheme 2) followed by GC analysis of the derivatives on an achiral stationary phase. The homochiral derivatizing agent TPC, upon amide formation with *S*- or *R*-methcathinone, yields diastereomeric amides (*S,S* or *S,R*). These diastereomeric amides are volatile products separable on achiral stationary phases commonly used in GC.

Figure 1 shows the GC–MS analysis of methcathinone obtained from oxidation of 1*R*,2*S*-ephedrine (Figure 1A) and 1*S*,2*R*-ephedrine (Figure 1B). These methcathinone products were prepared under identical reaction conditions using potassium dichromate. The mass spectrum in Figure 1C is characteristic for both chromatographic peaks eluting in the 21-min range in Figures 1A and 1B because stereoisomers usually do not show any differences by MS.

The two peaks in the 21-min range were confirmed as the TPC derivatives of *S*- and *R*-methcathinone by analysis of a racemic mixture of methcathinone. Figure 1D shows the results of the analysis of a TPC-derivatized sample obtained following oxidation of a racemic ephedrine sample. The two peaks eluting in the 21-min range again show the same mass spectrum, which is consistent with that of TPC–methcathinone.

The product obtained from oxidation of 1*R*,2*S*-ephedrine is primarily a single isomer, *S*-methcathinone. Although a small peak eluting at the retention time for the TPC-derivative of *R*-methcathinone can be seen in Figure 1A, it should be noted that commercial samples of *S*-TPC contain approximately 5% of *R*-TPC. Derivatization of *S*-methcathinone with *R*-TPC will yield the *R,S*-derivative, and this isomer would have the same chromatographic elution properties on an achiral stationary phase as the *S,R*-derivative. Thus, the small peak in the 21-min range in Figure 1A may be the result of *R*-TPC in the derivatization reagent and not *R*-methcathinone in the sample. The chromatogram in Figure 1B was obtained following TPC derivatization of methcathinone obtained from dichromate oxidation of 1*S*,2*R*-ephedrine. The chromatogram shows the methcathinone to consist primarily of the *R*-enantiomer.

The individual enantiomers of pseudoephedrine were subjected to dichromate oxidation under reaction conditions identical to those used for the oxidation of the



Scheme 5. Potential thermal oxidation products of methcathinone.

ephedrines, and the results obtained were analogous to those for ephedrine. The oxidation of the benzylic hydroxyl group did not affect the stereochemistry at the 2-position; thus 1*S*,2*S*-pseudoephedrine yielded *S*-methcathinone, and 1*R*,2*R*-pseudoephedrine produced *R*-methcathinone. The GC–MS analysis of TPC–methcathinone prepared from the pseudoephedrine enantiomers were essentially identical to those in Figures 1A–1C. Furthermore, oxidation of the enantiomers of ephedrine and pseudoephedrine using potassium permanganate produced analogous results: The configuration at the 2-position was unaffected by oxidation at the 1-position.

The results of these experiments show that oxidation of a single enantiomer of ephedrine or pseudoephedrine yields a single enantiomer of methcathinone. Because the assignment of configuration for the homochiral methcathinone product was made without the aid of a stereochemical standard, it is important to point out the rationale for the stereochemical assignments. Each enantiomer of ephedrine and pseudoephedrine upon oxidation gave a homochiral methcathinone product. It is extremely unlikely that a complete stereochemical inversion would occur at a carbon adjacent to the reactive center. Furthermore, displacement of the benzylic hydroxyl group in ephedrine and pseudoephedrine by chlorine followed by hydrogenolysis to yield methamphetamine proceeds with

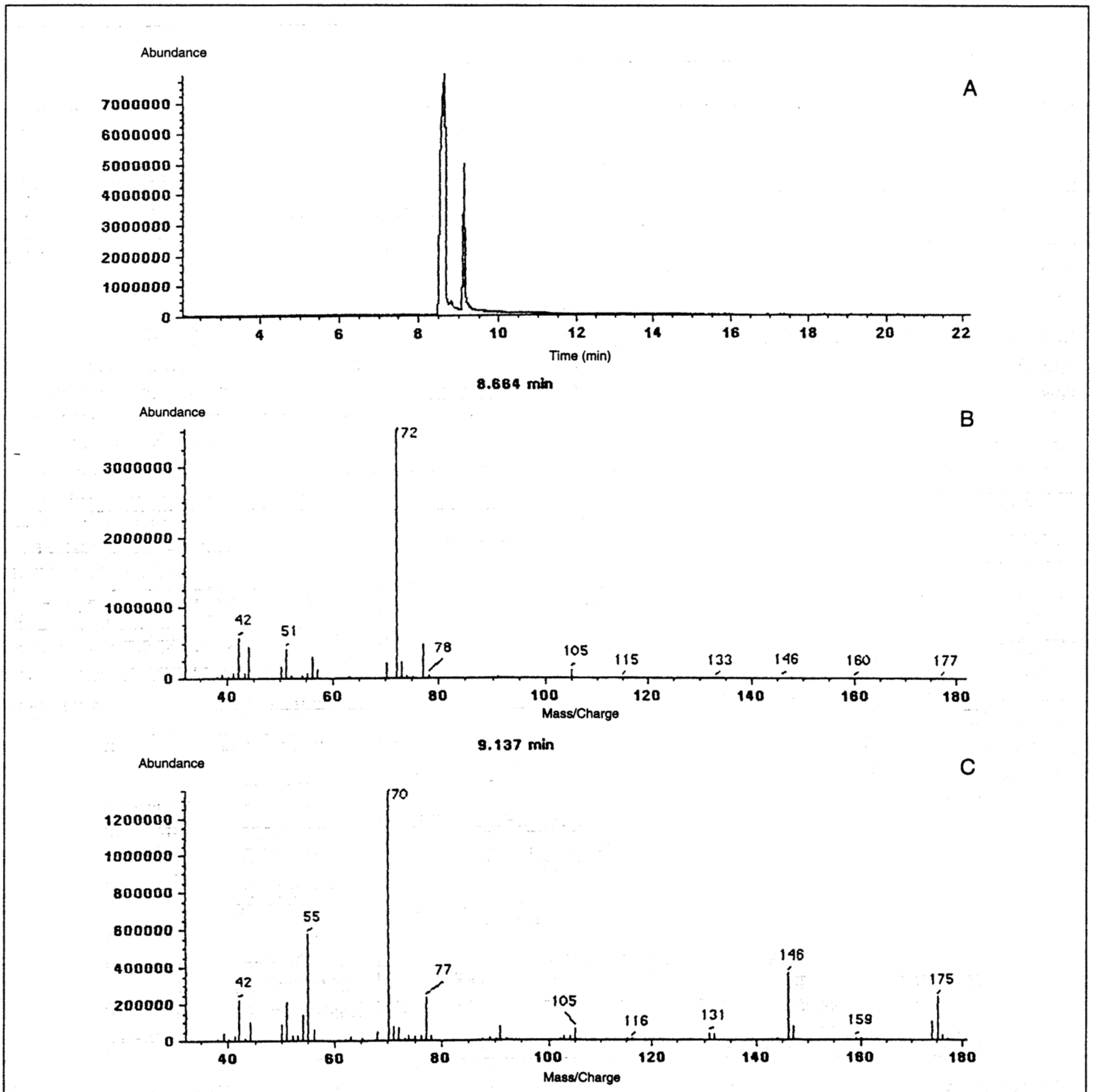
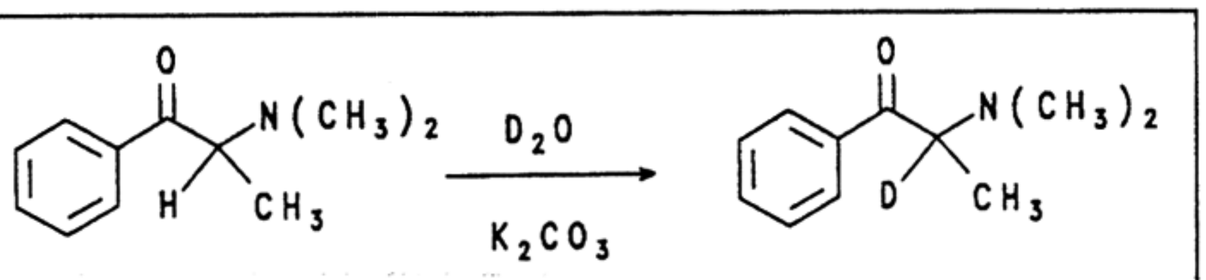


Figure 3. Gas chromatographic and mass spectral analysis of dimethcathinone: A, chromatogram; B, mass spectrum of peak eluting at 8.664 min; C, mass spectrum of peak eluting at 9.137 min.

complete retention of configuration at the 2-position (9). Thus, 1*R*,2*S*-ephedrine, upon chlorination by thionyl chloride followed by hydrogenation over palladium on carbon, yields homochiral *S*-methamphetamine. These data allow the assignment of the configuration of the homochiral methcathinone products obtained from the oxidation reactions.



Scheme 6. Deuteration of methcathinone.

The GC–MS analysis of a sample of underivatized methcathinone is shown in Figure 2. Although the mass spectrum of methcathinone and related compounds have been reported (1,2), the later eluting minor component proved to be interesting. The major chromatographic peak at 7.944 min produced the mass spectrum of methcathinone shown in Figure 2B. The major fragment at *m/z* 58 corresponds to the loss of C_6H_5CO from the parent molecule, as shown in Scheme 3, and this amine-dominated fragmentation produces the only significant fragment (*m/z* 58) in the mass spectrum. The minor component eluting at 8.213 min in Figure 2A is observed even following repeated purification (recrystallization) of the methcathinone sample. The mass spectrum of this minor compo-

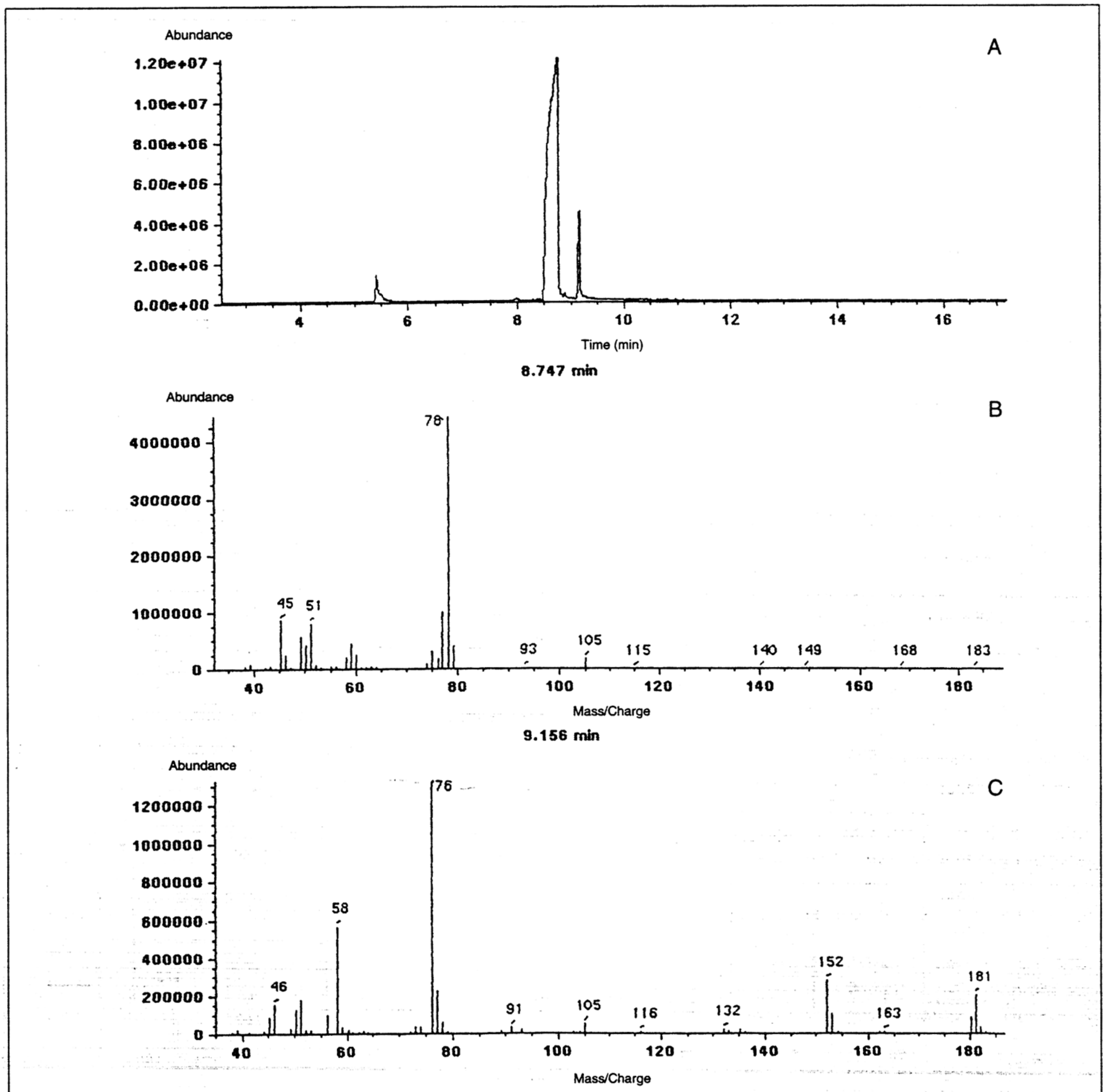


Figure 4. Gas chromatographic and mass spectral analysis of dimethcathinone-d_6: A, chromatogram; B, mass spectrum of major peak eluting at 8.747 min; C, mass spectrum of minor peak eluting at 9.156 min.

nent is shown in Figure 2C, indicating a base peak at *m/z* 56 and an apparent molecular ion at *m/z* 161. These data can be compared with the base peak for methcathinone at *m/z* 58 and its molecular ion at *m/z* 163, thus suggesting a decomposition product having a molecular weight that is 2 mass units less than methcathinone. The 2 mass unit difference is within the side chain imine fragment such that loss of the C_6H_5CO radical yields *m/z* 56 instead of *m/z* 58. This minor component appeared in all samples of methcathinone regardless of the stereochemistry of the starting material or the nature of the oxidizing agent. Methcathinone was synthesized by a nonoxidative method in an effort to determine if the minor component was the result of some secondary oxidative process. The displacement of bromine by methylamine from α-bromopropiophenone was accomplished in methylene chloride in the presence of triethylamine base to yield methcathinone (Scheme 4). GC–MS analysis of this sample of methcathinone showed the same chromatographic results as those shown in Figure 2A. Furthermore, the chromatographic bands produced mass spectra identical to those in Figures 2B and 2C, indicating that the minor component was produced during the GC analysis of the sample.

Beckett and co-workers (10) reported the appearance of a base peak of *m/z* 56 in the sharply tailing edge of the GC peak for methcathinone. The methcathinone sample was prepared by oxidation of ephedrine with silver carbonate in benzene, and

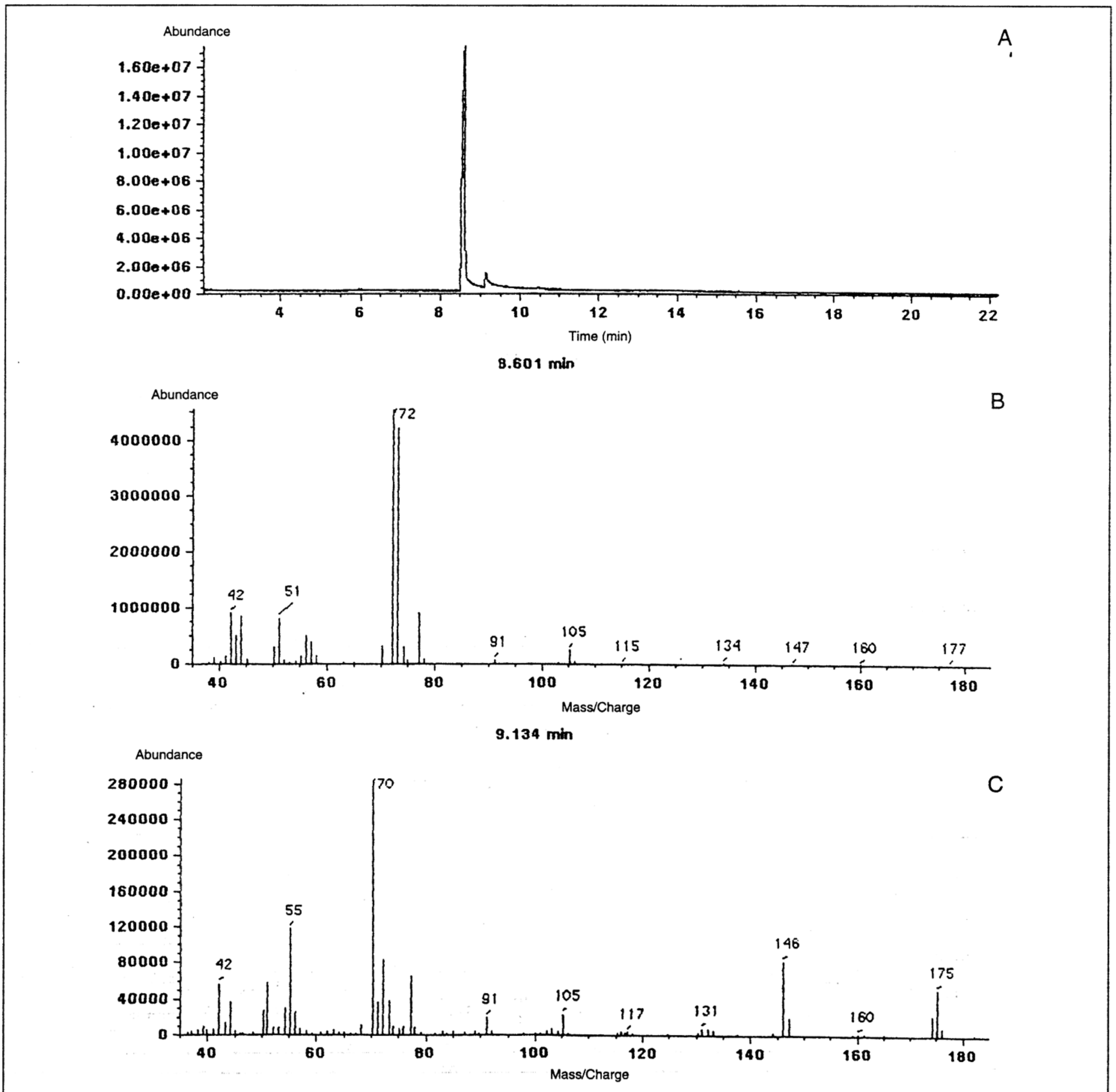


Figure 5. Gas chromatographic and mass spectral analysis of dimethcathinone-d: A, chromatogram; B, mass spectrum of peak eluting at 8.601 min; C, mass spectrum of peak eluting at 9.134 min.

the minor component (*m/z* 56 base peak) was observed following injections of solutions of either the free base or the hydrochloride salt. The likely structure of the *m/z* 56 ion was suggested by the authors to be CH_3-C≡N^+–CH_3 or CH_2=C=N^+HCH_3. Beckett and co-workers postulated that the source of these ions could be the conjugated imine of methcathinone or, alternatively, a dimer of methcathinone resulting from amine–carbonyl condensation (Chart 2). The likelihood of the dimer serving as the source of the compound generating a base peak of *m/z* 56 was dismissed by Beckett and co-workers because no peaks of higher mass were observed in the mass spectrum. Beckett and co-workers (10) pointed out that the dimer should yield other intense ions in the high mass region. Our studies are in agreement with their work, indicating no ions beyond the 161 range in the mass spectrum of the minor component. Additional GC–MS analysis of the methcathinone sample using methane chemical ionization in our laboratories showed major ions at *m/z* 164 and 162 in the chemical ionization mass spectrum. These peaks correspond to protonated $(M+1)^+$ ions for methcathinone and the oxidation product, respectively. Furthermore, no ions were observed above the *m/z* 162–164 region. These data all point to the mass 161 peak as the molecular ion of the minor component.

A component of 2 mass units less than the parent molecule resulting from decomposition of the parent compound suggests oxidation to eliminate a molecule of hydrogen (H_2), yielding a double bond. Because the base peak in the spectrum of the minor component is 2 mass units less than that of the parent methcathinone (*m/z* 56 instead of *m/z* 58), the additional double bond is in the imine fragment. For methcathinone, the structures that fit these MS data are the two possible imines and the enamine shown in Scheme 5. Each of these three structures would have a molecular ion at *m/z* 161 and could fragment to yield a base peak at *m/z* 56.

The two imine structures must arise by loss of hydrogen from the nitrogen atom to produce the product 2 mass units lower than methcathinone. The enamine structure involves the formation of a carbon–carbon double bond not directly involving the side chain nitrogen. In an effort to differentiate among these possible structures for the minor decomposition product, a sample of *N,N*-dimethylcathinone was prepared by treating α-bromopropiophenone with dimethylamine (Scheme 4). If an analogous decomposition product was observed in the GC–MS analysis of this product, then the corresponding imines would be unlikely candidate structures. Furthermore, the dimerization reaction would be extremely unlikely for the tertiary amine because the resulting compound would be a diquaternary ammonium compound of relatively low volatility. Figure 3A shows the results of chromatographic analysis of the dimethcathinone sample, indicating the presence of two compounds. The earlier eluting peak at 8.664 min produced the mass spectrum in Figure 3B, showing a molecular ion at *m/z* 177 and a base peak at *m/z* 72 consistent with the loss of C_6H_5CO from the parent dimethcathinone. The second peak at 9.137 min shows a more abundant molecular ion at *m/z* 175 and a base peak at *m/z* 70. Thus dimethcathinone appears to show a decomposition product analogous to that observed for methcathinone.

Dimethcathinone was also prepared by dichromate oxidation of commercially available *N*-methylephedrine, and its GC–MS analysis was identical to that shown in Figure 3. Thus, as was observed for methcathinone, a decomposition product with a mass 2 units lower than that of the parent molecule is present in dimethcathinone samples, regardless of the route of synthesis.

A sample of dimethcathinone-d_6 was prepared by treatment of α-bromopropiophenone with dimethylamine-d_6. The GC–MS analysis of this product is shown in Figure 4 and reveals a major product at 8.747 min having a molecular ion at *m/z* 183 and a base peak at *m/z* 78; both ions occur 6 mass units higher than the analogous ions in

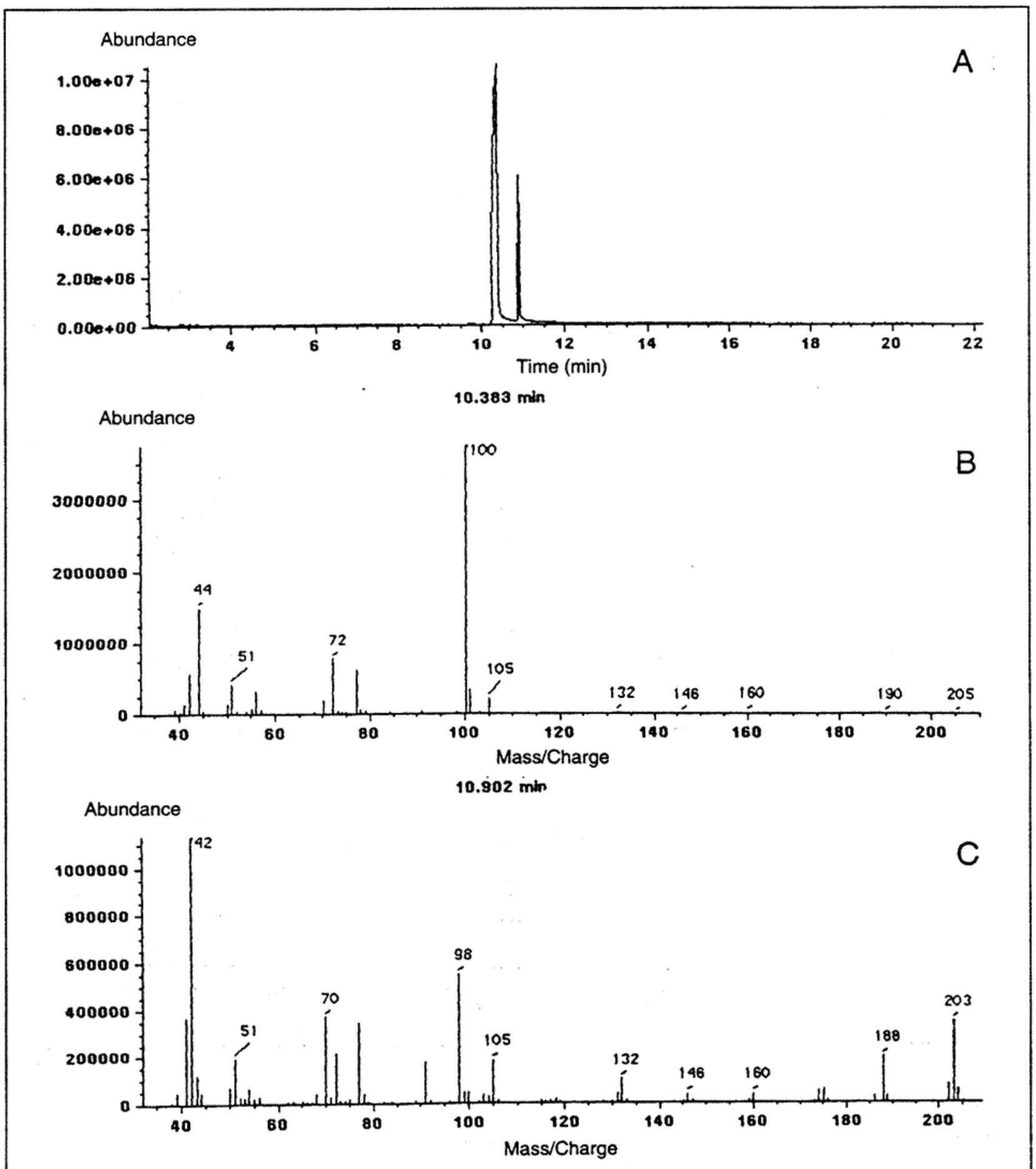


Figure 6. Gas chromatographic and mass spectral analysis of diethylpropion: A, chromatogram; B, mass spectrum of peak eluting at 10.383 min; C, mass spectrum of peak eluting at 10.902 min.

dimethcathinone, as expected. Again a minor component is present, and it shows a more abundant molecular ion at *m/z* 181 and a base peak at *m/z* 76. A comparison of the mass spectra in Figures 3C and 4C indicates that the fragments at 181, 152, and 76 in Figure 4C are 6 mass units higher than the corresponding fragments in dimethcathinone (Figure 3C), indicating that these fragments contain all six deuterium atoms. The peak at *m/z* 58 in Figure 4C is 3 mass units higher than the corresponding fragment in Figure 3C, suggesting it contains three deuterium atoms. Although these data strongly suggest the enamine structure involving carbon–carbon double bond formation in the minor component, it could be argued that the *m/z* 76 ion is the loss of one deuterium from a completely different fragmentation pathway. Further structural information regarding the minor component was obtained by GC–MS analysis of a sample of dimethcathinone partially labeled with deuterium at the 2-position. The acidic hydrogen that is in the alpha position relative to the carbonyl moiety in dimethcathinone was allowed to undergo deuterium exchange (11) by dissolving dimethcathinone hydrochloride in D_2O in the presence of potassium carbonate (Scheme 6). The GC–MS of the partially exchanged product (Figure 5) reveals a major peak showing ions at *m/z* 72 and 73 of almost equal abundance. This suggests a dimethcathinone sample in which about 50% of the acidic protons have been replaced by deuterium. The minor component, however, shows a mass spectrum with a base peak at *m/z* 70 with a very low abundance ion at *m/z* 71, suggesting that the ion at *m/z* 70 occurred by loss of 2 mass units (H_2) from unlabeled dimethcathinone and by loss of 3 mass units (H-D) from the α-deuterio dimethcathinone. Thus, these experiments show that the most likely source for the minor decomposition product in these arylaminoketones is the enamine. The actual companion chromatographic peak may be the 2,3-enamine or some rearrangement product of the enamine. The formation of the companion peak, however, appears to be mediated through the 2,3-enamine of methcathinone and analogues via oxidation of the 2,3-carbon–carbon bond under the conditions of the GC analysis.

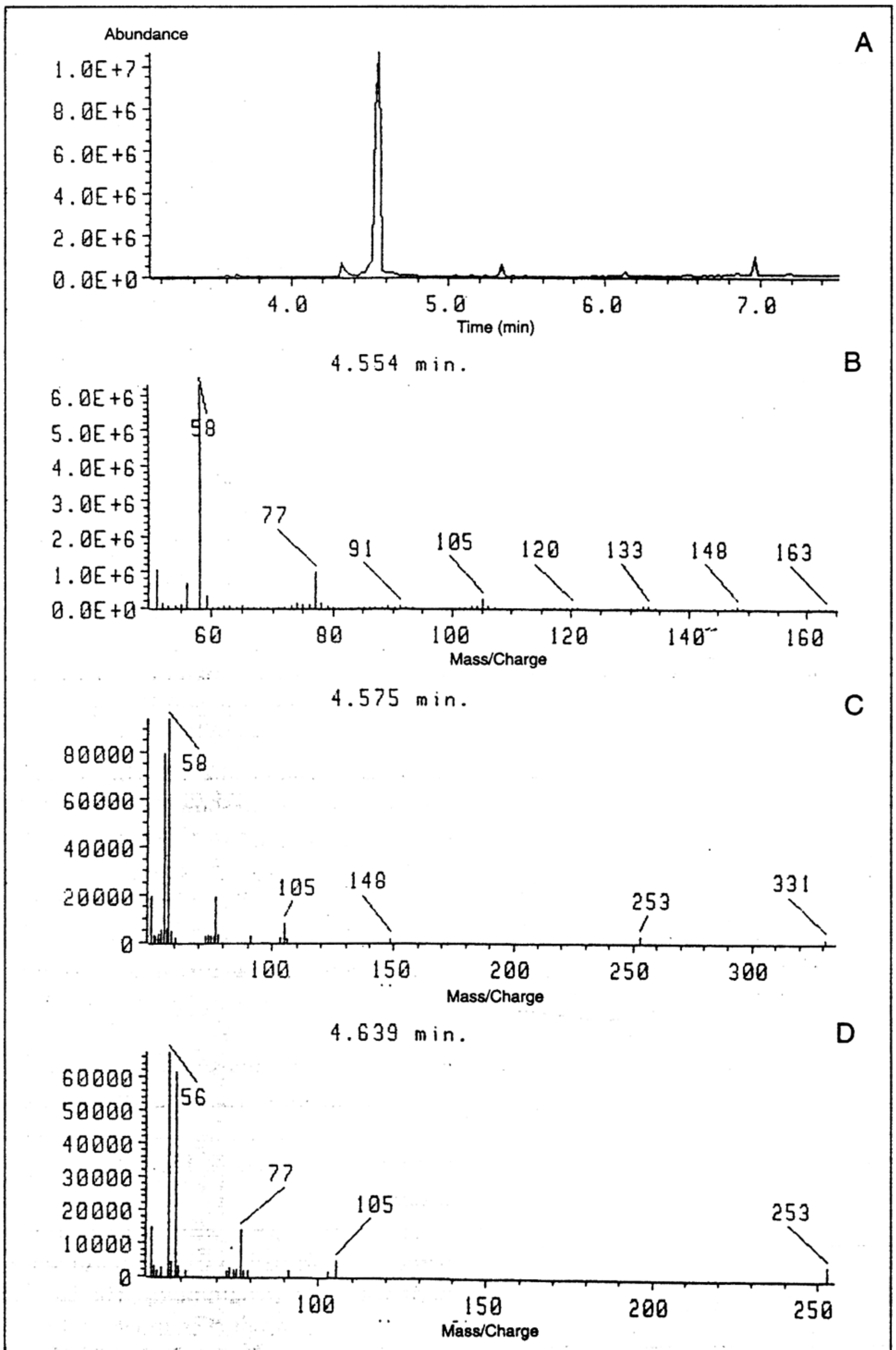


Figure 7. Gas chromatographic and mass spectral analysis of methcathinone under GC conditions in which the parent amine and enamine oxidation product coelute: A, chromatogram; B, initial mass spectrum for the front side of the peak; C, mass spectrum obtained near the apex of the peak; D, mass spectrum for the back side of the peak.

The drug used for treatment of anorexia, diethylpropion, which is available from commercial sources, is a compound similar in structure to methcathinone and dimethcathinone. The GC–MS analysis of a sample of pharmaceutical-grade diethylpropion is shown in Figure 6. The major peak elutes at 10.383 min and shows the expected mass spectrum with a molecular ion at *m/z* 205 and a base peak at *m/z* 100 from the loss of C_6H_5CO from the parent molecule. A significant chromatographic peak for the minor component shows a mass spectrum yielding a more abundant molecular ion at *m/z* 203 and a fragmentation pattern remarkably similar to that of dimethcathinone. The major difference in the spectra is the relative abundance of the *m/z* 98 and 42 ions. This is not unexpected because the enamine fragment from diethylpropion at *m/z* 98 contains the two *N*-ethyl groups that can rearrange to eliminate ethylene from each group, resulting in the *m/z* 42 ion.

Figure 7 illustrates a potential analytical problem that the enamine decomposition product can generate. The parent amine and its enamine oxidation product may coelute under some chromatographic conditions, producing a hybrid mass spectrum. Figure 7 was obtained using a 10-m × 0.20-mm i.d. fused-silica column with 0.33-µm thickness of phenylmethylsilicone (DB-5). The oven temperature was held at 40°C for 1 min then raised to 150°C at 15°C/min and from 150 to 250°C at 25°C/min. This program is commonly used by drug abuse screening laboratories in the confirmation protocols for amines such as methamphetamine, amphetamine, and others. The methcathinone peak eluting in the 4.5-min range gives the appearance of a symmetrical peak; however, mass spectra obtained at different times across the eluting band show the presence of the enamine decomposition product. The initial MS scan (Figure 7B) on the front side of the peak shows only one major fragment at *m/z* 58 and a mass spectrum for methcathinone. The mass spectrum obtained near the apex (Figure 7C) of the peak and on the back side (Figure 7D) of the peak show significant *m/z* 56 fragments from the coeluting enamine oxidation product. These hybrid mass spectra produced by a mixture of the parent amine and the product enamine are significantly different from the standard methcathinone spectrum.

In the course of conducting these studies, several designer analogues of methcathinone were prepared (Chart 1). The GC separation of a mixture of these compounds is complicated by their decomposition products. However, LC separation of the series of arylaminoketones was accomplished using a reversed-phase system. Figure 8 shows the separation of these compounds on a 5-µm Spherisorb phenyl column (250 × 4.6 mm) using a mobile phase of pH 3 phosphate buffer, methanol, and triethylamine (600:100:1). The pH 3 phosphate buffer is sufficiently acidic to protonate the amino group of methcathinone and analogues (pK_a values of about 8). Thus the compounds are eluted as the more hydrophilic cationic ammonium species. Triethylamine is also protonated under these conditions and serves as a silanol masking agent to prevent the severe peak tailing often observed for amines in reversed-phase systems. Triethylamine is a very useful mobile phase additive for silanol masking because it is transparent in detection systems based on UV spectrophotometry. The compounds elute according to increasing hydrophobic surface area, as expected, with the primary amine (cathinone) eluting first, followed by methcathinone, then dimethcathinone, ethcathinone (*N*-ethylcathinone), and diethylpropion, eluting at 28.36 min in this system.

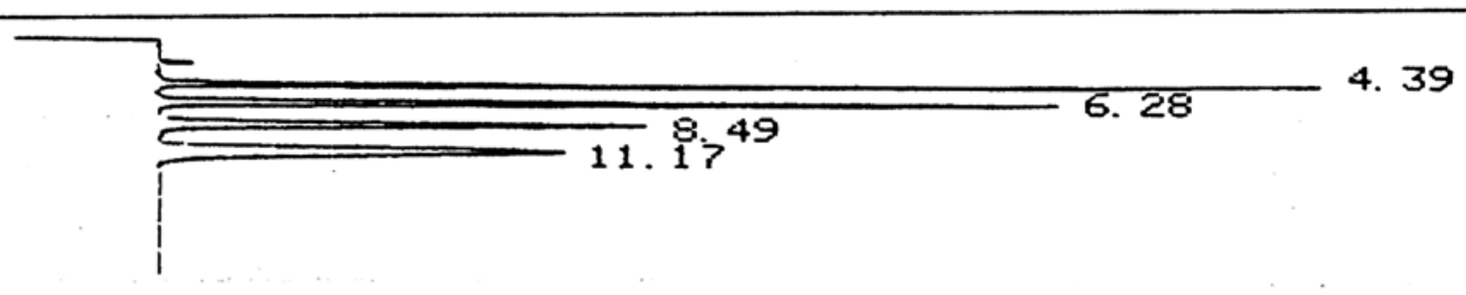


Figure 8. LC separation of cathinone (4.39 min), methcathinone (6.28 min), dimethcathinone (8.49 min), and ethcathinone (11.17 min).

Table I. Toxi-Lab Analysis of Methcathinone, Cathinone, and Related Phenethylamine Drugs of Abuse*

Compound	R_f	Stage I	Stage II	Stage III	Stage IV
Ephedrine	0.14	Yellow/Green	Green	Brt Fluores†	Brown
Pseudoephedrine	0.14	Yellow/Green	Green	Brt Fluores	Brown
Methamphetamine	0.22	Yellow/Brown	Fade	Brt Fluores	Brown
Phenylpropanolamine	0.25	Yellow/Green	Green	Brt Fluores	Brown
Amphetamine	0.32	Yellow/Brown	Fade	Fluores†	Tan/Brown
(+)-Methcathinone	0.52	Blanch	Fade	Not Detected	Brown
(–)-Methcathinone	0.52	Blanch	Fade	Not Detected	Brown
(+/–)-Cathinone	0.54	Blanch	Fade	Fnt Fluores†	Brown
Diethylpropion	0.92	Blanch	Blanch	Fluores	Brown

* Stage I: concentrated sulfuric acid; Stage II: water rinse; Stage III: UV light; Stage IV: Dragendorf's reagent.
† Abbreviations: Brt Fluores, bright fluorescence; Fluores, fluorescence; Fnt Fluores, faint fluorescence.

Table II. EMIT* Screening Analysis of Methcathinone, Cathinone, and Related Phenethylamine Drugs of Abuse

Compound	Conc. giving a positive response (ng/mL)
S-Amphetamine	1000
S-Methamphetamine	1000
1*R*,2*S*-Ephedrine	150,000
1*S*,2*S*-Pseudoephedrine	300,000
Phenylpropanolamine	250,000
R-(+)-Methcathinone	200,000
S-(–)-Methcathinone	400,000
(+/–)-Cathinone	300,000

* SYVA's amphetamine/methamphetamine monoclonal reagent.

In the course of conducting these studies, several designer analogues of methcathinone were prepared (Chart 1). The GC separation of a mixture of these compounds is complicated by their decomposition products. However, LC separation of the series of arylaminoketones was accomplished using a reversed-phase system. Figure 8 shows the separation of these compounds on a 5-µm Spherisorb phenyl column (250 × 4.6 mm) using a mobile phase of pH 3 phosphate buffer, methanol, and triethylamine (600:100:1). The pH 3 phosphate buffer is sufficiently acidic to protonate the amino group of methcathinone and analogues (pK_a values of about 8). Thus the compounds are eluted as the more hydrophilic cationic ammonium species. Triethylamine is also protonated under these conditions and serves as a silanol masking agent to prevent the severe peak tailing often observed for amines in reversed-phase systems. Triethylamine is a very useful mobile phase additive for silanol masking because it is transparent in detection systems based on UV spectrophotometry. The compounds elute according to increasing hydrophobic surface area, as expected, with the primary amine (cathinone) eluting first, followed by methcathinone, then dimethcathinone, ethcathinone (*N*-ethylcathinone), and diethylpropion, eluting at 28.36 min in this system.

The properties of methcathinone and cathinone were examined by procedures used for drug screening in urine. The TLC properties of these compounds were compared with those of phenethylamine drugs of abuse in the Toxi-Lab commercial system. Table I shows the R_f value for methcathinone and cathinone to be in the 0.5 range; it has a much higher migration rate than the ephedrines, amphetamine, or methamphetamine. The visualization of the chromatographic zones in Stage I suggests that the additional carbonyl group in these aminoketones is responsible for a considerable color change. The colors in Stages II and III are not significant for these compounds, and Stage IV produces the usual brown color characteristic of amines. These results indicate that methcathinone and cathinone are not likely to interfere with TLC procedures for screening the amphetamine-type stimulants.

The individual enantiomers of methcathinone and racemic cathinone were screened in an enzyme multiplied immunoassay technique (EMIT) for screening amphetamine and related amines. Table II lists the drugs tested against the methamphetamine antibodies and the concentrations required to give a positive response. A positive response equivalent to

1000 ng/mL of *s*-amphetamine required a concentration of methcathinone or cathinone in the 200,000 to 400,000 ng/mL range. Thus, these aminoketones show a 200- to 400-fold lower affinity for the amphetamine antibodies. The relative affinities for methcathinone and cathinone are similar to those for ephedrine or pseudoephedrine.

Conclusion

In summary, the oxidation of ephedrine and pseudoephedrine to methcathinone using dichromate or permanganate proceeds with retention of stereochemical integrity at the 2-position common to both the reactant and the product. Thus 1*R*,2*S*-ephedrine and 1*S*,2*S*-pseudoephedrine yield *S*-methcathinone, and 1*S*,2*R*-ephedrine and 1*R*,2*R*-pseudoephedrine yield *R*-methcathinone. GC–MS analysis of underivatized methcathinone showed a companion peak at a slightly higher retention time and a molecular ion 2 mass units lower than methcathinone. This pattern was observed for designer compounds similar to methcathinone including dimethcathinone and diethylpropion (diethylcathinone). Deuterium labeling experiments indicate that the companion peak is a result of further oxidation (loss of H_2) to produce the 2,3-enamine of methcathinone or its designer analogues. Methcathinone and cathinone do not show any appreciable interferences in standard urine drug screening procedures involving TLC or immunoassay procedures.

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