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LC and GC–MS Analysis of 4-Bromo-2,5-Dimethoxyphenethylamine (Nexus) and 2-Propanamine and 2-Butanamine Analogues

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Abstract

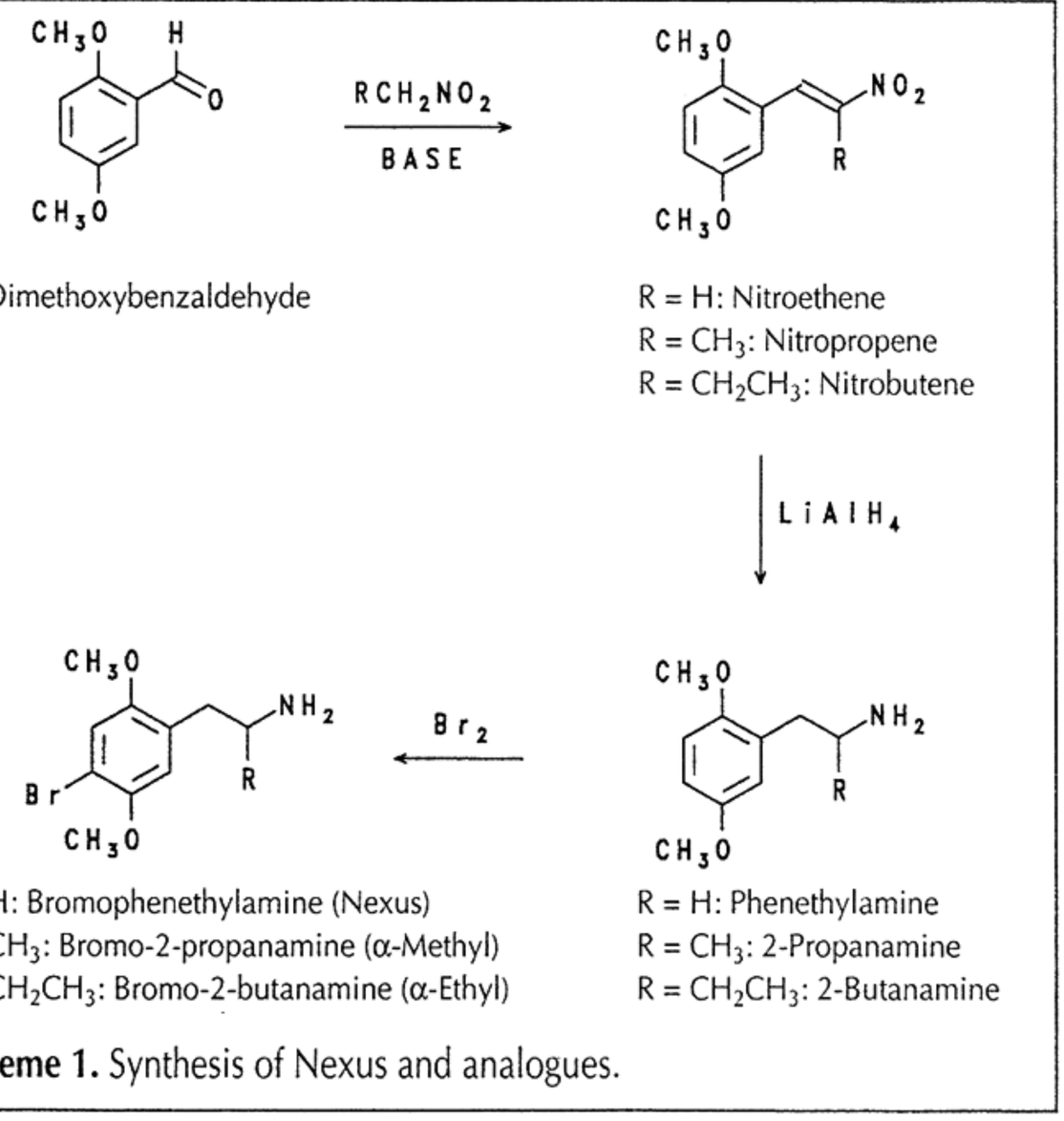
The street drug Nexus (4-bromo-2,5-dimethoxyphenethylamine) has appeared in clandestine samples in recent years. This hallucinogenic phenethylamine is prepared from the commercially available aldehyde, 2,5-dimethoxybenzaldehyde, and other readily available precursor chemicals and reagents. Nexus and some designer analogues are separated by liquid chromatography using a C_{18} stationary phase and an acidic (pH 3) mobile phase. Nexus, a brominated phenethylamine, shows enhanced reversed-phase retention relative to the unbrominated precursor phenethylamine. The mass spectra of these amines show fragment ions consistent with amine-dominated reactions common to phenethylamines and substituted phenethylamines. The gas chromatographic–mass spectrometric analysis of mixtures of the amines and the synthetic precursor nitroethenes show on-column reaction products that complicate the analytical results. These reaction products are identified as the imines that result from condensation of the amine with the substituted benzaldehyde, which is generated from the 2-nitroethene.

Introduction

4-Bromo-2,5-dimethoxyphenethylamine (Nexus) was encountered by the Drug Enforcement Administration in Texas in 1979. Since that time, samples containing this compound were reported in California, Arizona, Louisiana, Pennsylvania, Iowa, Oregon, Georgia, Tennessee, and Florida, and clandestine laboratories producing Nexus were seized in California in 1986 and in Arizona in 1992 (1). Because its use presents a potential hazard to public safety (1), Nexus was placed in Schedule I of the United States Controlled Substances Act in 1993.

Data from human studies (1,2) indicate that Nexus produces intoxication with euphoria and sensory enhancement at doses of 0.1–0.2 mg/kg and intense and frightening hallucinations at higher doses. These effects are likely mediated through the affinity of central serotonin receptors for this compound (1). Nexus is structurally similar to the Schedule I hallucinogens 4-methyl-2,5-dimethoxyamphetamine (DOM) and 4-bromo-2,5-dimethoxyamphetamine (DOB). Although some analytical data on Nexus were reported in 1979 (3), there is very little information available concerning analysis of starting materials and intermediates in its clandestine manufacture and no data comparing Nexus with analogues.

The most likely method for the preparation of Nexus is shown in Scheme 1 and involves use of the commercially available starting material 2,5-dimethoxybenzaldehyde (4). Treatment of the benzaldehyde with an organic base and nitromethane yields the 1-(2,5-dimethoxyphenyl)-2-nitroethene intermediate (R = H) which, upon reduction with lithium aluminum hydride (LAH), yields the corresponding 2,5-dimethoxyphenethylamine (R = H, Scheme 1). Treatment of this intermediate with bromine in glacial acetic acid results in bromination at the 4-position of the ring to yield Nexus (R = H, 4-bromo-2,5-dimethoxyphenethylamine). This same approach can be used to prepare Nexus analogues such as DOB (R = CH_3) or α-ethyl Nexus (R = CH_2CH_3, 4-bromo-2,5-dimethoxyphenyl-2-



Scheme 1. Synthesis of Nexus and analogues.

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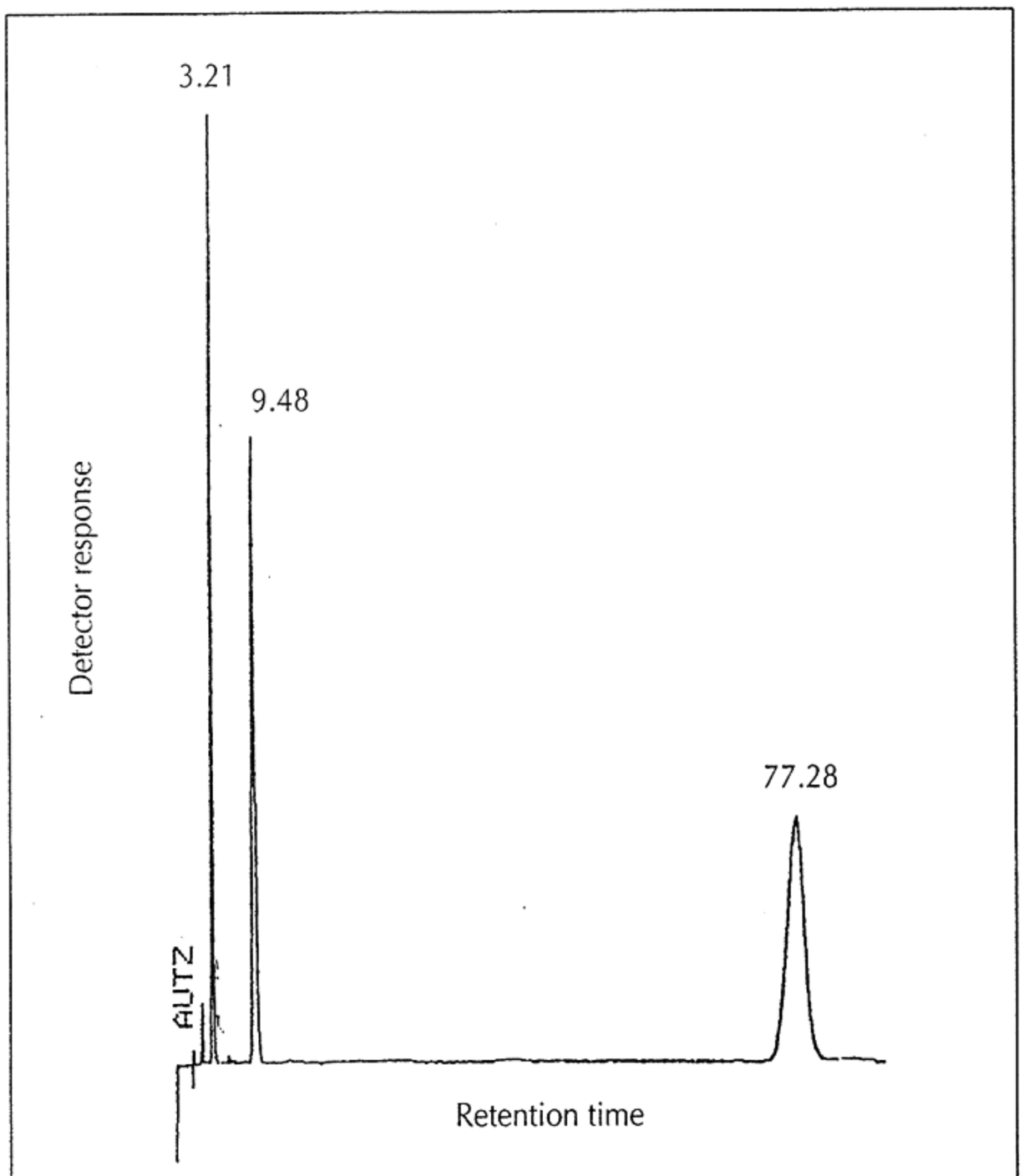


Figure 1. HPLC separation of 2,5-dimethoxyphenethylamine (3.21 min), 4-bromo-2,5-dimethoxyphenethylamine (9.48 min), and 1-(2,5-dimethoxyphenyl)-2-nitroethene (77.28 min) at a flow rate of 1.5 mL/min.

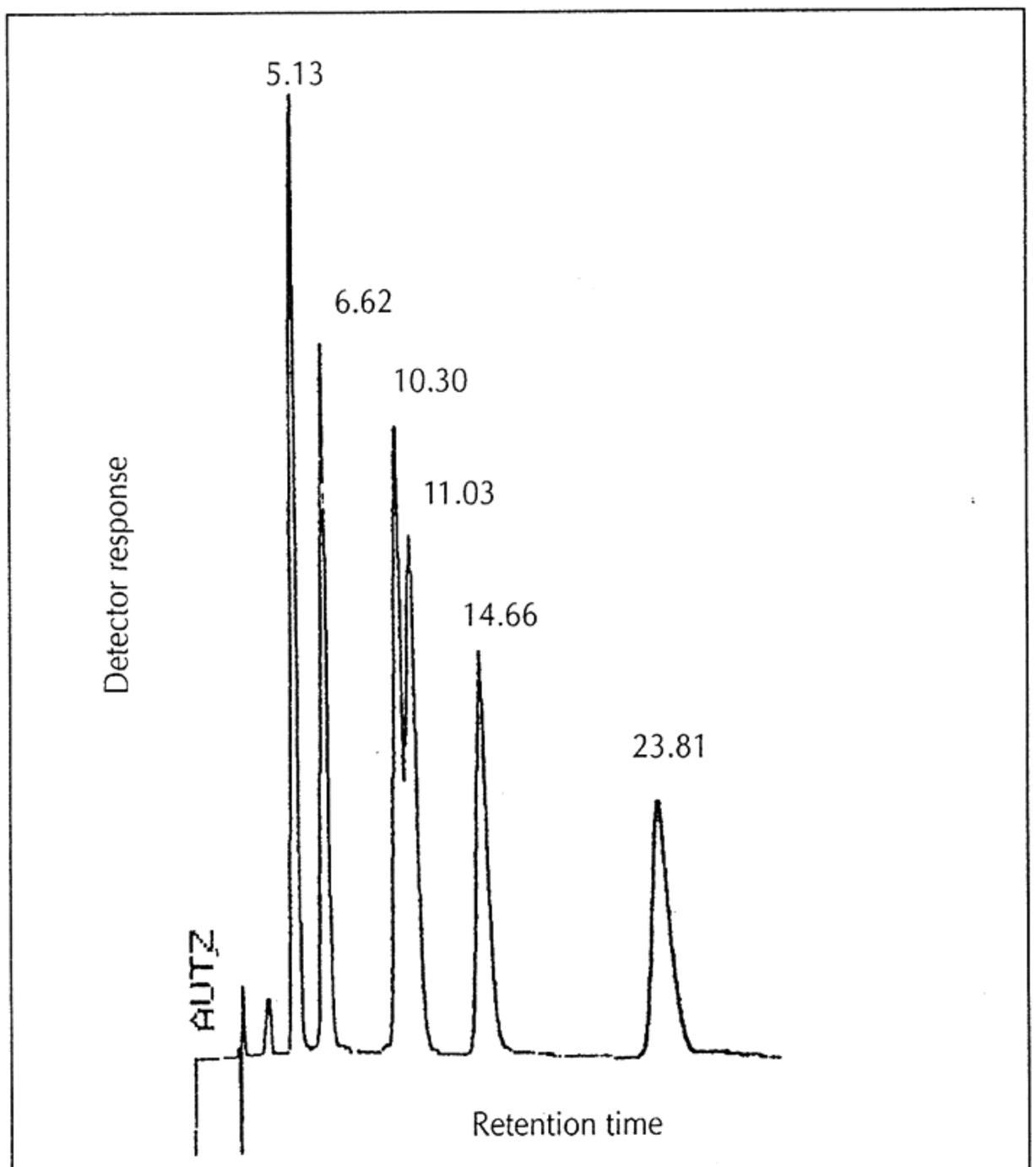


Figure 2. HPLC separation of 2,5-dimethoxyphenethylamine (5.13 min), 1-(2,5-dimethoxyphenyl)-2-propanamine (6.62 min), 1-(2,5-dimethoxyphenyl)-2-butanamine (10.30 min), 4-bromo-2,5-dimethoxyphenethylamine (11.03 min), 1-(4-bromo-2,5-dimethoxyphenyl)-2-propanamine (14.66 min), and 1-(4-bromo-2,5-dimethoxyphenyl)-2-butanamine (23.81 min) at a flow rate of 1.25 mL/min.

butanamine) by substituting nitroethane or nitropropane for nitromethane. In this paper, the analytical profiles of the intermediate 1-(2,5-dimethoxyphenyl)-2-nitroalkenes, 2,5-dimethoxyphenylalkylamines, and brominated final products are described and compared.

Experimental

Instrumentation and methods

Gas chromatographic–mass spectrometric (GC–MS) analyses were performed using a Hewlett-Packard 5970B mass selective detector (Palo Alto, CA). The mass spectrometer was operated in the electron impact mode, and an ionization voltage of 70 eV and a source temperature of 220°C were used. The samples were dissolved in methanol (1 mg/mL), and 0.5 µL was introduced into the mass spectrometer via a gas chromatograph equipped with an HP-1 methylsilicone fused-silica column (12 m × 0.20-mm i.d., 0.33-µm film thickness). The column temperature was held at 70°C for 2.5 min, then it was programmed to 170°C at a rate of 25°C/min and from 170°C to 275°C at a rate of 12°C/min with a hold time of 6 min. The split ratio for the GC was 10:1, and the injector port temperature was 230°C. The carrier gas was ultra-pure helium.

Liquid chromatographic analyses were conducted using a

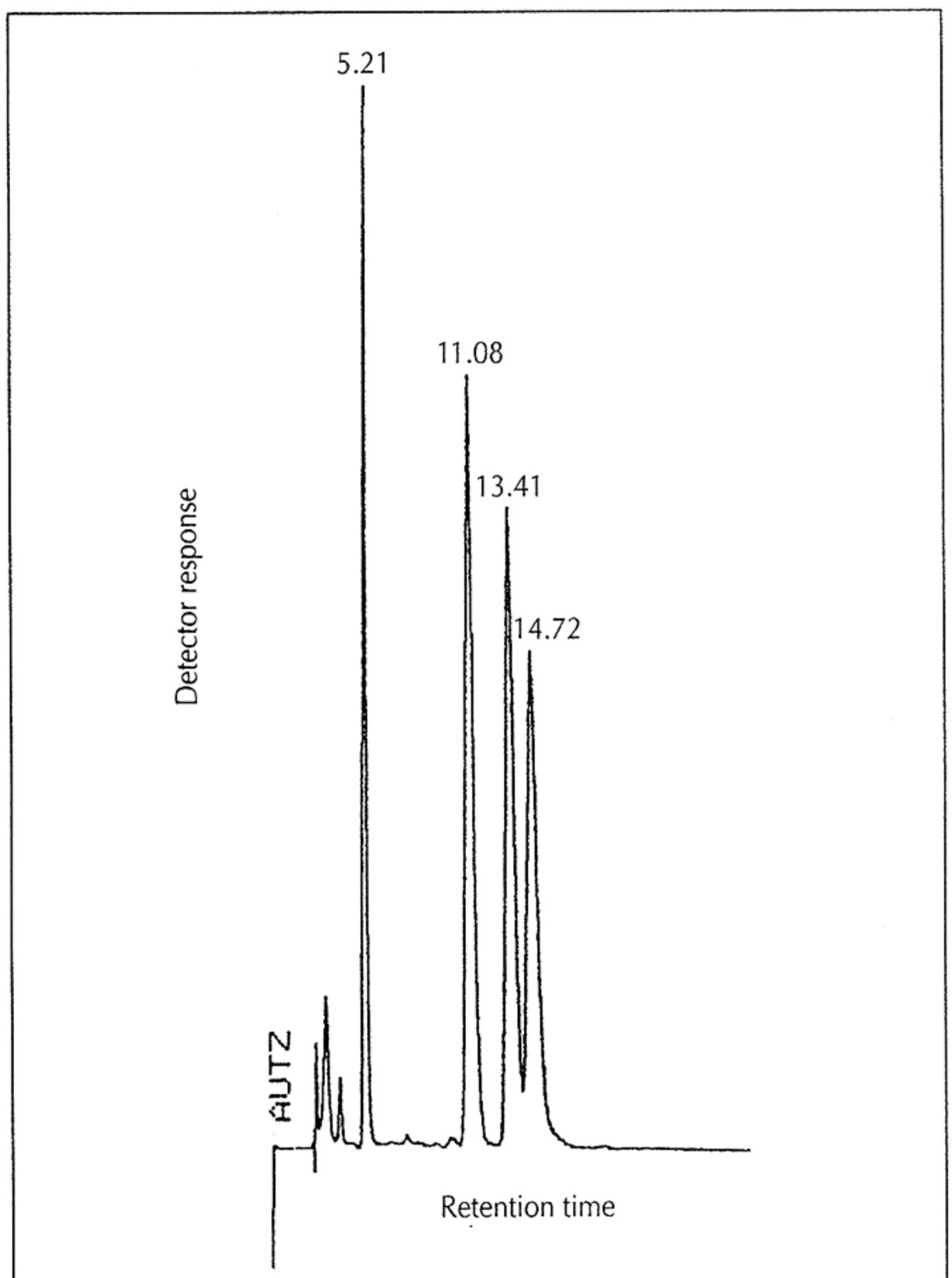


Figure 3. HPLC separation of 2,5-dimethoxyphenethylamine (5.21 min), 4-bromo-2,5-dimethoxyphenethylamine (11.08 min), 1-(4-methyl-2,5-dimethoxyphenyl)-2-propanamine (13.41 min), and 1-(4-bromo-2,5-dimethoxyphenyl)-2-propanamine (14.72 min) at a flow rate of 1.25 mL/min.

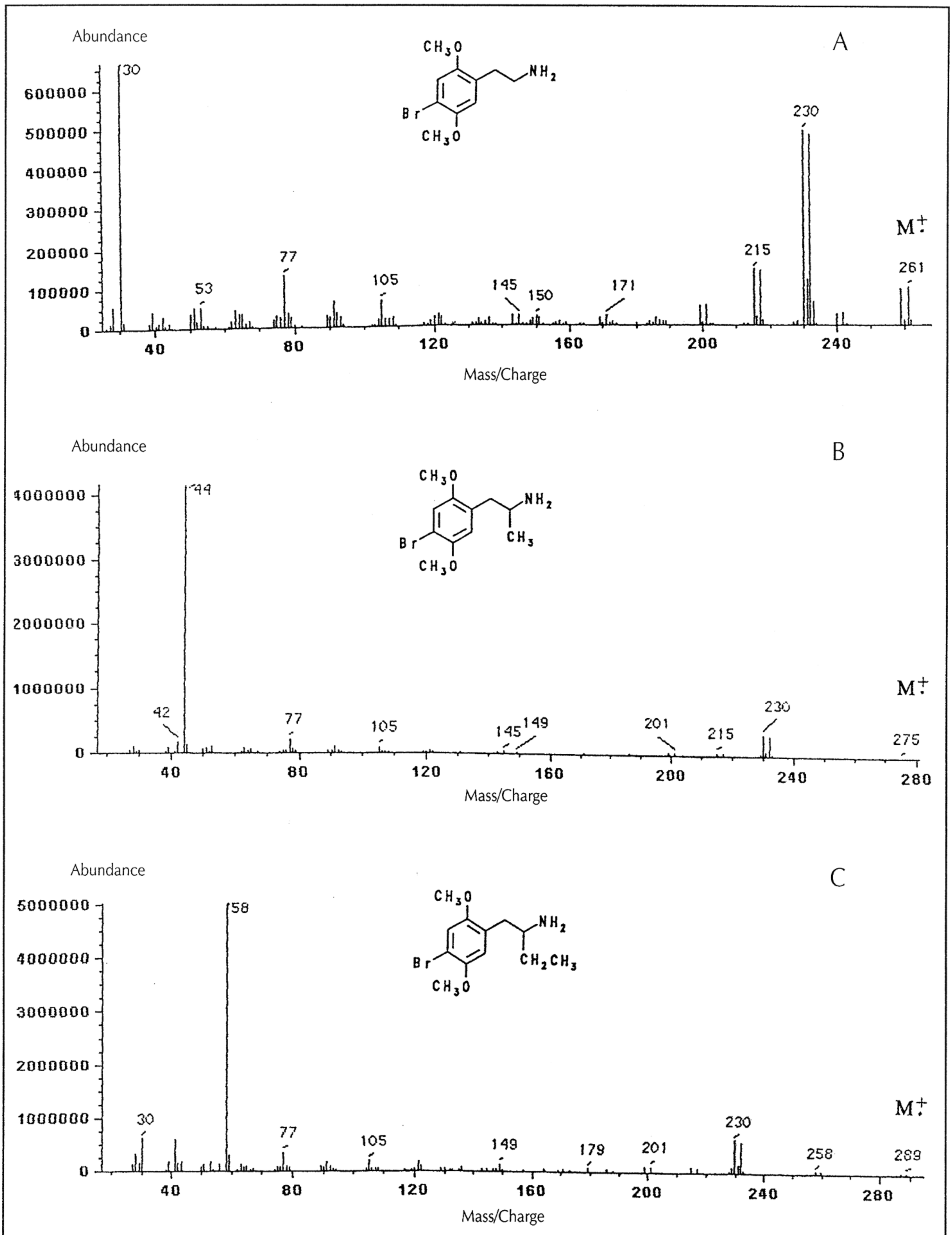


Figure 4. Mass spectra of 4-bromo-2,5-dimethoxyphenethylamine (A), 1-(4-bromo-2,5-dimethoxyphenyl)-2-propanamine (B), and 1-(4-bromo-2,5-dimethoxyphenyl)-2-butanamine (C).

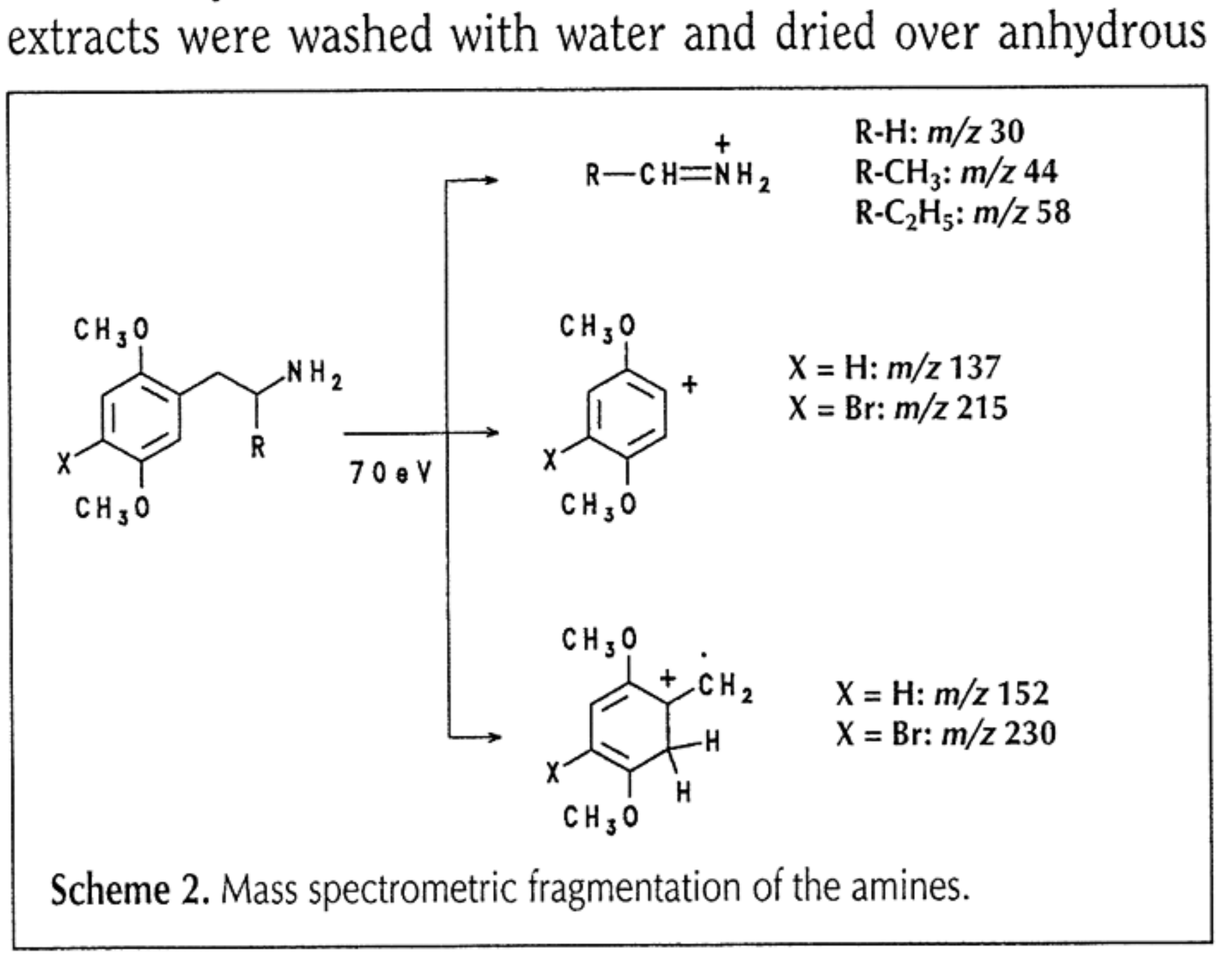
Laboratory Data Control Constametric 3000 pump (Riviera Beach, FL), a Model 3100 Spectromonitor ultraviolet detector, a CI 4100 integrator, and a Rheodyne Model 7125 injector (Cotati, CA). The analytical column (25 cm × 4.6-mm i.d.) was packed with Bondclone C_{18} (Phenomenex; Torrance, CA). The analytical column was preceded by a Direct Connect guard column (Alltech; State College, PA) packed with CO:Pell ODS (Whatman; Clifton, NJ). The mobile phase consisted of pH 3.0 phosphate buffer–methanol–triethylamine (500:250:1) at flow rates of 1.25 or 1.50 mL/min. The pH 3.0 phosphate buffer was prepared by mixing 9.2 g monobasic sodium phosphate in 1 L of double-distilled water and adjusting the pH to 3.0 with H_3PO_4. The ultraviolet absorbance detector was operated at 280 nm and 0.2 AUFS. The compounds were prepared as methanol solutions (1 mg/mL), and 1 µL was injected.

Synthesis of 1-(2,5-dimethoxyphenyl)-2-nitroalkenes

A mixture of 2,5-dimethoxybenzaldehyde, butylamine, and benzene was stirred at reflux for several hours using a Dean–Starke trap to remove water. The reaction mixture was evaporated under reduced pressure, and the remaining oil was dissolved in a mixture of glacial acetic acid and the appropriate nitroalkane. After this solution was stirred at reflux for several hours, it was cooled, and ice was added to precipitate the product. Concentrated HCl was added to adjust the pH to 2. The product was isolated by filtration, washed with water, and recrystallized from 2-propanol to yield the nitroalkenes as highly colored needles.

Synthesis of 2,5-dimethoxyphenalkylamines

A solution of the nitroalkene intermediate in dry tetrahydrofuran (THF) was added to a suspension of LAH in THF stirred at room temperature. After the addition was complete, the reaction mixture was stirred at reflux for several hours and then cooled in an ice bath. The excess LAH and LAH salts were decomposed by the addition of water, 2N NaOH, and additional water successively. The mixture was then filtered, and the filtrate was evaporated under reduced pressure. The remaining oil was suspended in water and acidified to pH 1. The resulting aqueous solution was washed with benzene, after which it was made basic by the addition of NaOH pellets and extracted twice with methylene chloride. The combined methylene chloride extracts were washed with water and dried over anhydrous sodium sulfate. Filtration followed by evaporation of the filtrate solvent yielded the product amines as oils. The amines were converted to their corresponding hydrochloride salts by treatment with ethereal HCl.



Scheme 2. Mass spectrometric fragmentation of the amines.

Synthesis of 4-bromo-2,5-dimethoxyphenalkylamines

A solution of bromine in glacial acetic acid was added over a few minutes to a solution of the amine hydrochloride in glacial acetic acid. After the addition was complete the reaction mixture was stirred at room temperature for an hour, which resulted in the formation of a yellow precipitate. The precipitate was isolated by filtration and suspended in aqueous NaOH. The aqueous basic suspension was extracted with methylene chloride, and the combined organic extracts were washed with water and dried over potassium carbonate. Filtration followed by evaporation of the filtrate solvent yielded the product amines as oils. The amines were converted to their corresponding hydrochloride salts by treatment with ethereal HCl.

Results and Discussion

The synthesis of substituted phenethylamines can be accomplished by several methods. Many of the common methods begin with precursor chemicals that are now controlled under the U.S. Precursor and Essential Chemical Act of 1989. A significant exception involves the use of readily available and uncontrolled substituted benzaldehydes. These compounds are converted to the versatile β-nitroalkenes, which are reduced to the corresponding primary amines, or subjected to reductive–hydrolysis to the ketones. This general method of preparing phenethylamines is illustrated in Scheme 1, which shows the synthesis of the substituted phenethylamine, 2,5-dimethoxy-4-bromophenethylamine, and chain homologues. Commercially available 2,5-dimethoxybenzaldehyde is treated with butylamine and nitromethane to yield the β-nitroethene intermediate (R = H). Upon reduction with LAH, the phenethylamine is obtained in high yield. Bromination of the amine hydrochloride produces the 4-bromo-substituted phenethylamine, which has the street name Nexus (R = H). This analogous procedure can be used to prepare α-methyl ($R = CH_3$), α-ethyl ($R = CH_2CH_3$), and other substituted phenethylamines by condensation of the substituted benzaldehyde with nitroethane, nitropropane, and others. The structures of all products were confirmed by standard spectroscopic techniques (i.e., nuclear magnetic resonance, infrared, and mass spectrometric techniques).

The reversed-phase liquid chromatographic separation of Nexus from its synthetic precursors is shown in Figure 1. The chromatographic conditions consisted of a C_{18} stationary phase and a mobile phase of pH 3 phosphate buffer, methanol, and triethylamine (500:250:1) at a flow rate of 1.5 mL/min. The acidic mobile phase allows the amines to exist primarily in the more hydrophilic protonated form, thus displaying vastly different retention properties compared with the less polar nitroethene. The triethylamine in the mobile phase serves as a dynamic competitor for silanol sites on the stationary phase and prevents the peak tailing commonly observed for amines in reversed-phase liquid chromatography. A comparison of the elution properties of

the two amines in Figure 1 shows the enhanced retention properties of the 4-brominated species (9.48 min) compared with the hydrogen-substituted precursor (3.21 min). The nitroethene precursor is not protonated by the acidic mobile phase and displays a much greater capacity factor under these chromatographic conditions (77.28 min). The multisubstituted aromatic ring system is a strong chromophore in the ultraviolet range and has a wavelength of maximum absorbance at 293 nm; detection at 280 nm allows adequate sensitivity for these compounds.

Figure 2 shows the high-performance liquid chromatographic (HPLC) separation of a series of designer compounds including the unbrominated and 4-brominated derivatives of 2,5-dimethoxyphenethylamine (Nexus series), 2,5-dimethoxyphenyl-2-propanamine (R = CH_3, amphetamine series), and 2,5-dimethoxyphenyl-2-butanamine (R = CH_2CH_3). The chromatographic conditions were the same as those used for the separation in Figure 1 except for the lower mobile phase flow rate (1.25 mL/min). These compounds were prepared according to the method shown in Scheme 1 using nitroalkanes of varying chain length (e.g., methyl, ethyl, and propyl). The three unbrominated amines elute before the three brominated amines, and the length of the alkyl side chain determines the elution order in each group. The unbranched phenethylamine (5.13 min) elutes before the α-methyl side chain (2-propanamine, 6.62 min), and the α-ethyl side chain (2-butanamine, 10.30 min) displays the highest capacity factor. Bromination of these aromatic amines has a significant impact on reversed-phase retention as illustrated in Figure 2. The brominated phenethylamine Nexus (11.03 min) has a higher capacity factor than the unbrominated 2-butanamine derivative (10.30 min), indicating that, in this case, the aromatic bromine has a greater effect on reversed-phase retention than the two carbons of the α-ethyl side chain.

Figure 3 shows the liquid chromatographic separation of Nexus and its precursor from other similar drugs of abuse including DOM and DOB. The elution properties of DOM (13.41 min) indicate increased retention compared with Nexus (11.08 min) and show that the additional two carbons, one at the α-position of the side chain and one on aromatic ring at the 4-posi-

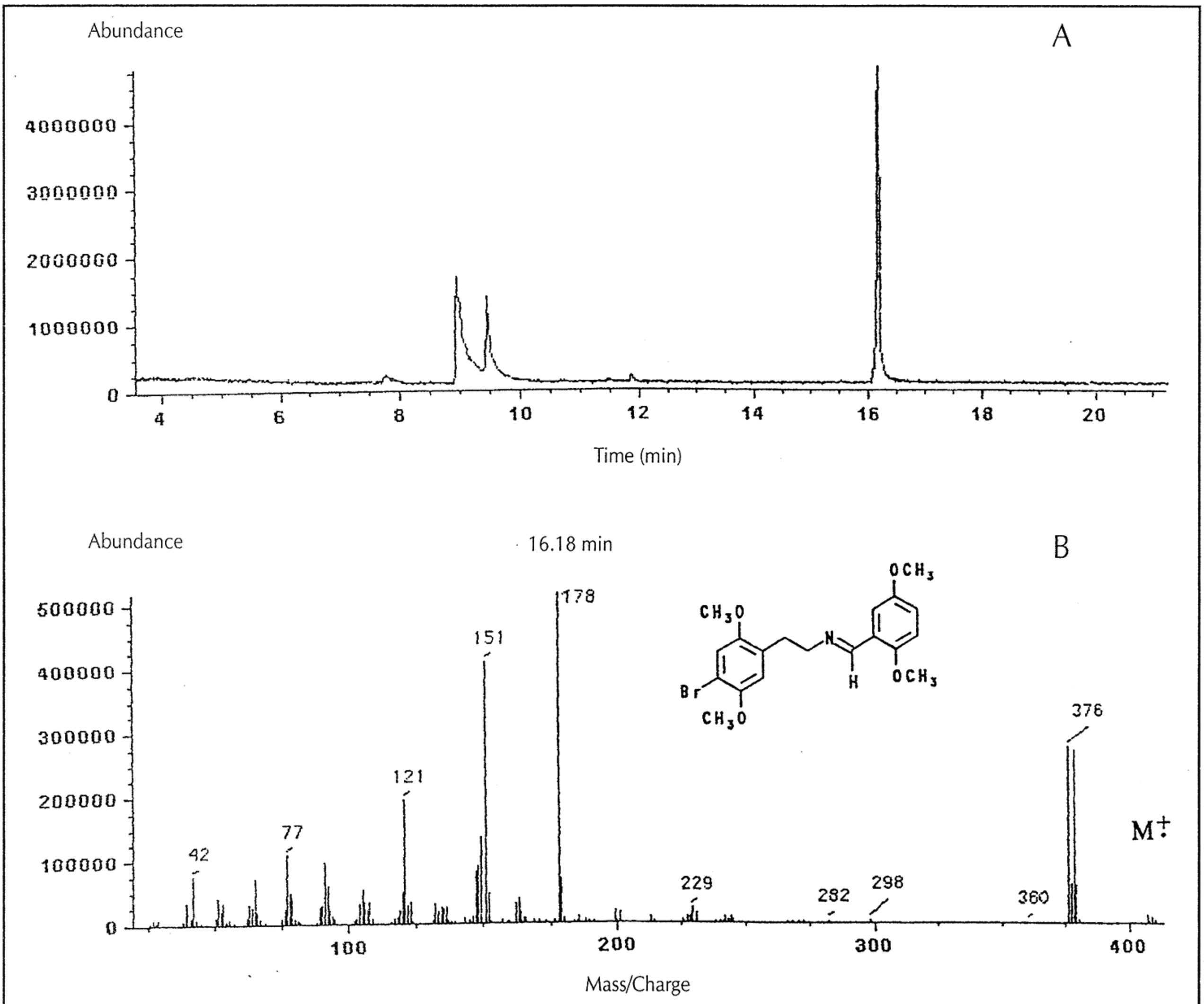
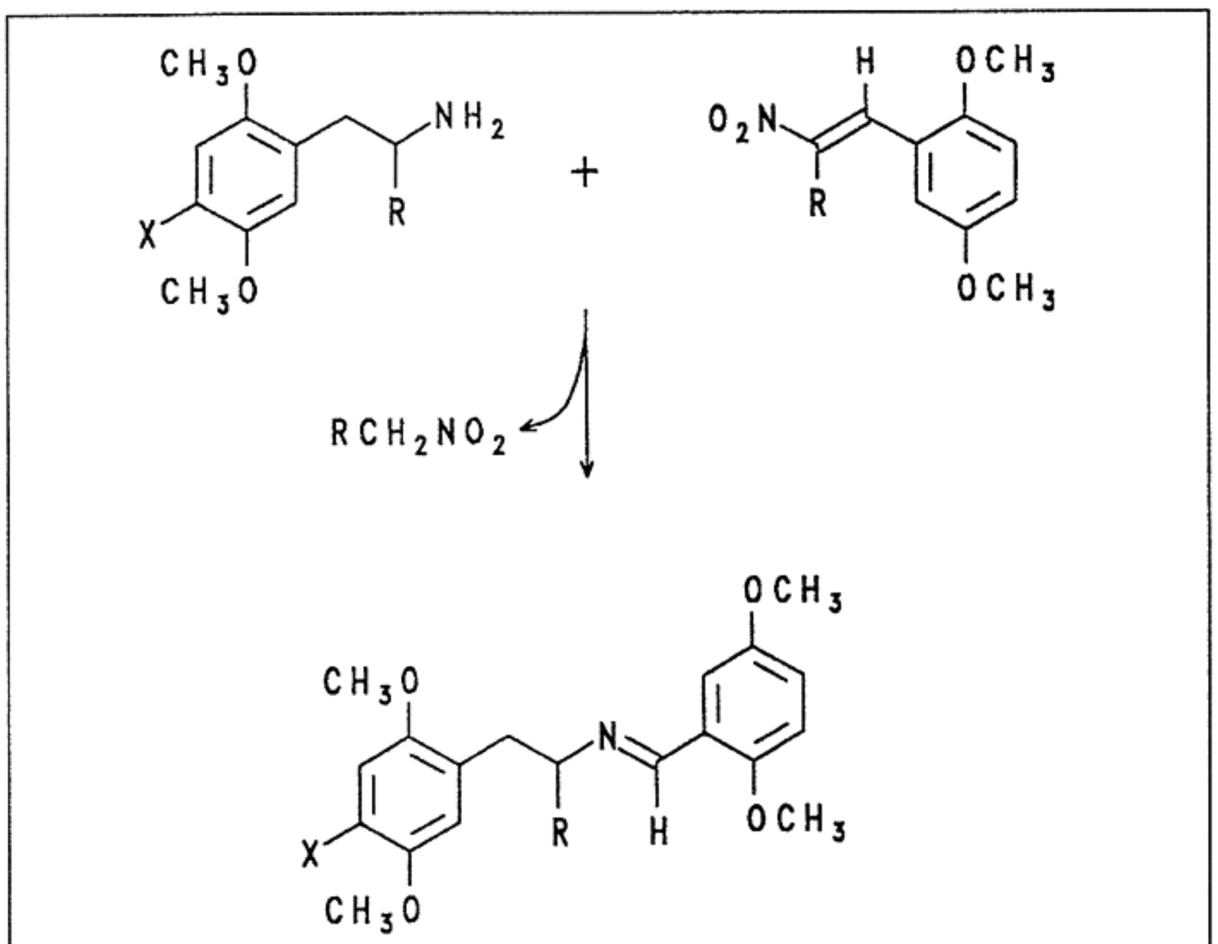


Figure 5. GC–MS analysis of a mixture of 4-bromo-2,5-dimethoxyphenethylamine and 1-(2,5-dimethoxyphenyl)-2-nitroethene: A, chromatogram and B, mass spectrum of the imine peak eluting at 16.18 min.



Scheme 3. Proposed condensation of the amines with nitroalkenes.

tion, produce enhanced retention relative to the aromatic 4-bromo substituent. Comparing Figures 2 and 3 and using the retention of Nexus as a point of reference showed that the α-ethyl group in 2,5-dimethoxyphenyl-2-butanamine produced a capacity factor slightly lower than that of Nexus. However, the additional two carbon atoms in DOM produce greater retention than Nexus in the same chromatographic system. These observations illustrate the sensitivity of reversed-phase chromatography to slight changes in the hydrophobic character of the solute molecules.

The mass spectra for the three brominated amines are shown in Figure 4, and the major fragmentation ions for all six amines are summarized in Scheme 2. The amines show a major low mass fragment produced by the loss of the substituted benzyl radical from the molecular ion. The resulting cationic imine occurs at *m/z* 30, 44, or 58 depending on the substituent at the α-carbon of the parent amine. Other major fragments occur at the high mass end of the spectrum and result from loss of the

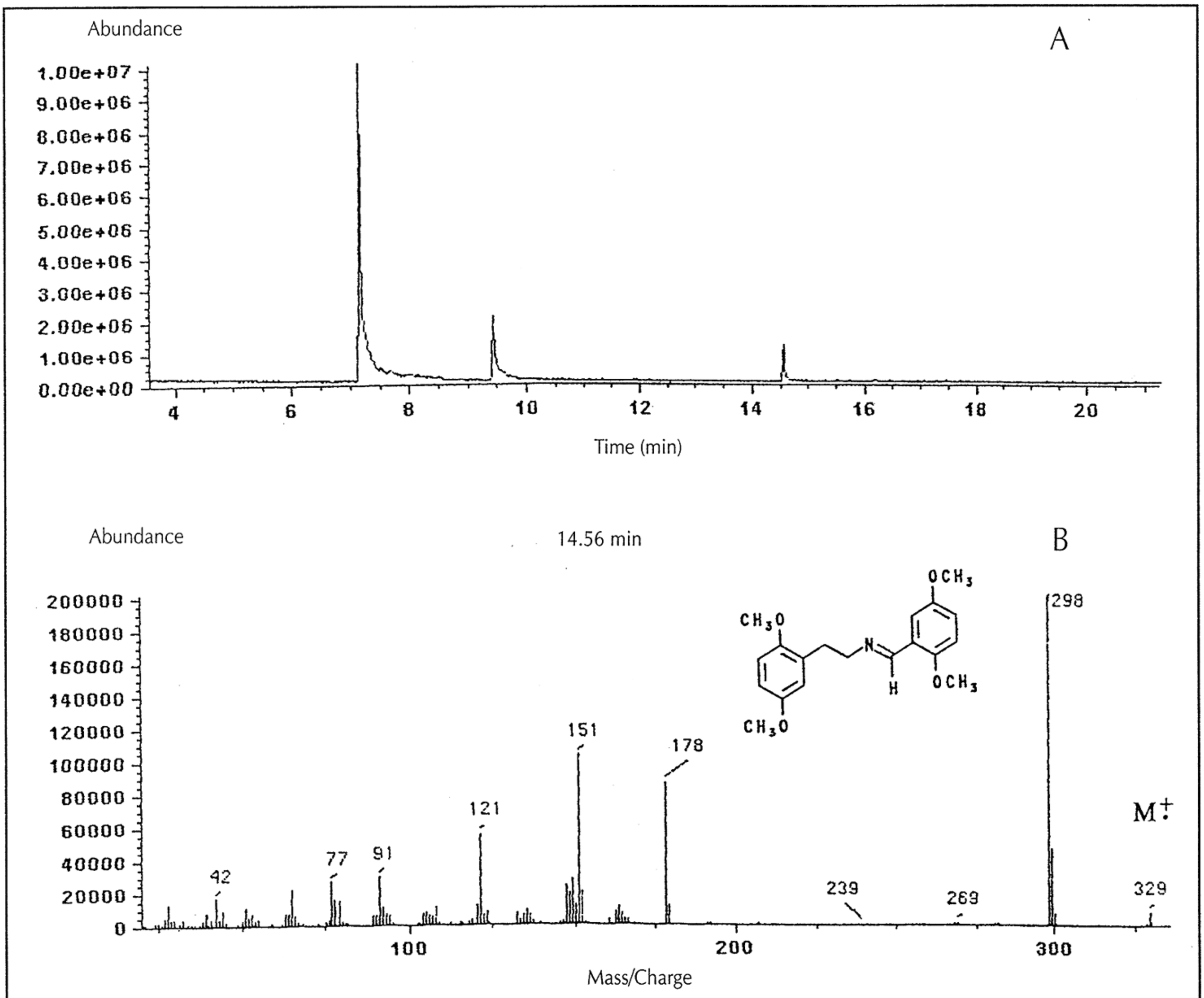


Figure 6. GC–MS analysis of a mixture of 2,5-dimethoxyphenethylamine and 1-(2,5-dimethoxyphenyl)-2-nitroethene: A, chromatogram and B, mass spectrum of the imine peak eluting at 14.56 min.

alkylamine side chain. Two primary side chain fragmentation processes produce ions separated by 15 mass units, the cationic aromatic ring, and the benzyl radical cation. These ions occur at different masses depending on the nature of the 4-substituent (Scheme 2). The bromine isotope effect clearly shows which ions in the mass spectrum contain bromine.

The GC–MS analysis of the individual β-nitroethene, phenethylamine, and brominated phenethylamine (Nexus) showed retention for the individual compounds in the 8- to 10-min range on an HP-1 methylsilicone fused-silica column (0.33-µm thickness). However, injection of a mixture of the three compounds produced additional peaks not present in any of the individual components and not observed in the HPLC separation of the same mixture (Figure 1). Additional experiments identified the presence of the β-nitroethene–phenethylamine combination as the source for the new compounds observed in the GC analysis. Injection of the two amines in combination or injection of the β-nitroethene alone did not produce any additional peaks; however, the β-nitroethene in combination with either amine produced additional compounds in the 14- to 16-min range. Figure 5 shows the results of GC–MS analysis of a mixture of 1-(2,5-dimethoxyphenyl)-2-nitroethene and 4-bromo-2,5-dimethoxyphenethylamine. The peak eluting at 8.93 min in the chromatogram (Figure 5A) is the amine, and the nitroethene elutes at 9.44 min. These peaks appear to show more tailing when injected in combination than when injected individually. The new compound eluting at 16.18 min, which was not present when either the nitroethene or phenethylamine were analyzed individually, produced the mass spectrum in Figure 5B. This new component of significant concentration shows major low mass fragment ions in the mass spectrum at *m/z* 121, 151, and 178 and major high mass fragments at *m/z* 376 and 407.

The results of the GC–MS analysis of a mixture of 2,5-dimethoxyphenethylamine and 1-(2,5-dimethoxyphenyl)-2-nitroethene are shown in Figure 6. The chromatogram shows a peak for the amine eluting at 7.16 min, the nitroethene at 9.43 min, and the new component at 14.56 min. The mass spectrum (Figure 6B) for the peak at 14.56 min shows low mass ions at *m/z* 121, 151, and 178, identical to those seen in Figure 5B. The high mass fragments, however, occur at *m/z* 298 and 329. The high mass ions in Figures 5B and 6B differ by the mass difference in atomic weight between hydrogen and bromine, which supports a common mechanism for the formation of the new, later-eluting compounds. These mass spectra suggest amine condensation at the carbon–carbon double bond of the nitroethene to form the diaryl imine (Scheme 3). The imines have molecular weights of 329 (R = H) and 408 (R = Br), and the loss of one methoxy group would yield the major high mass fragment at $(M–31)^+$, *m/z* 298 (R = H) and *m/z* 376 and 378 (R = Br). The postulated structures in Scheme 3 for the imine products would be the same as those formed from the amine and the substituted benzaldehyde. Figure 7 shows the chromatogram obtained from the GC–MS analysis of a mixture composed of the two amines and 2,5-dimethoxybenzaldehyde. The chromatogram shows excess benzaldehyde and both imine products found in the samples analyzed in Figures 5 and 6. The mass spectra for the peaks eluting at 14.56 and 16.15 min are identical to those in Figures 6B and 5B, respectively. Thus, the new peaks may originate from direct reaction of amine and nitroethene in the injection port. Alternatively, the nitroethene may decompose to yield the benzaldehyde, which then condenses with the amine to form the imine.

In both experiments the condensation product from the brominated amine appears to form in preference to that from the unbrominated amine. This trend holds true for the α-branched amines and their precursor branched 2-nitroethenes. Figure 8 shows the GC–MS analysis of the α-ethyl mixture of the unbrominated amine (7.88 min), the brominated amine (9.73 min), and the nitrobutene (consumed in the reaction). The only imine produced when the quantity of nitrobutene is limited is the brominated imine eluting at 15.83 min. The mass spectrum of the imine is shown in Figure 8B and indicates that the branched imines show less fragmentation

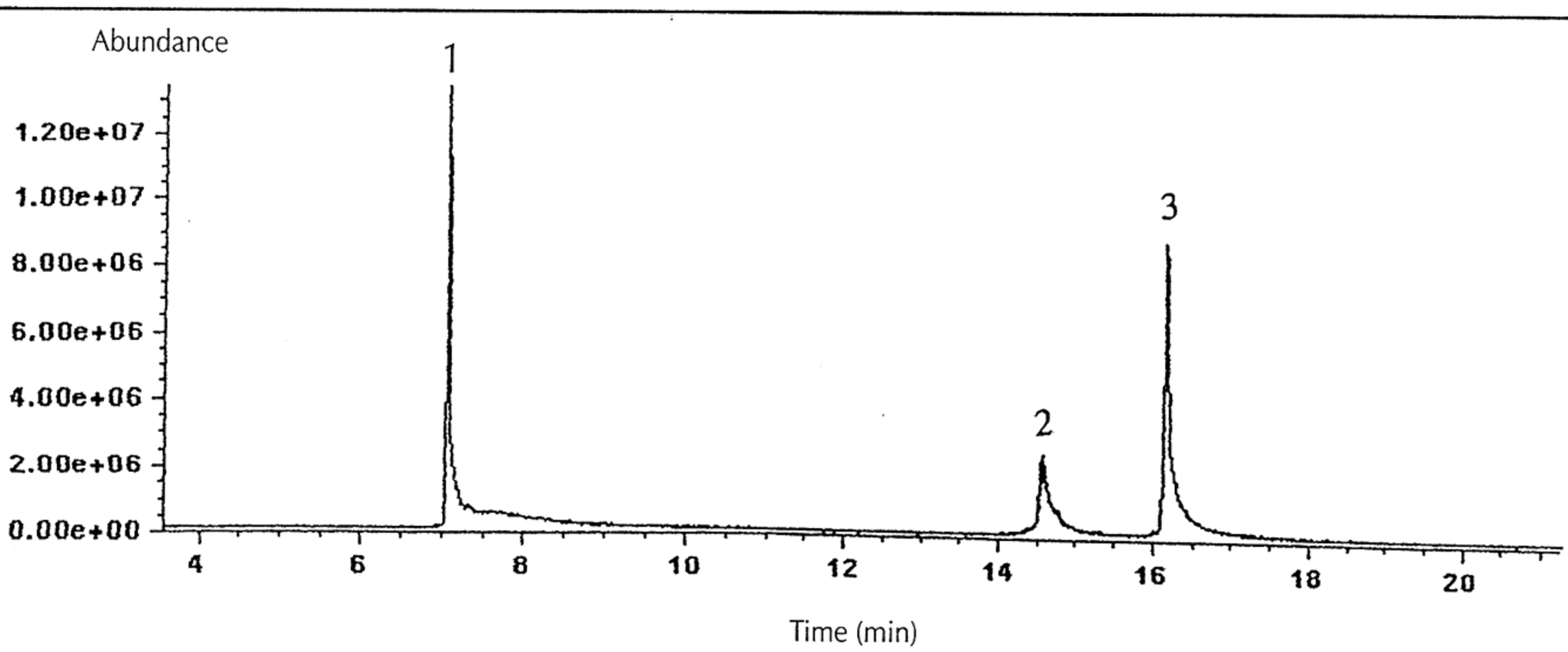


Figure 7. GC analysis of a mixture of 2,5-dimethoxyphenethylamine, 4-bromo-2,5-dimethoxyphenethylamine, and 2,5-dimethoxybenzaldehyde. Peaks: 1, 2,5-dimethoxybenzaldehyde; 2, imine formed from 2,5-dimethoxybenzaldehyde and 2,5-dimethoxyphenethylamine; 3, imine formed from 2,5-dimethoxybenzaldehyde and 4-bromo-2,5-dimethoxyphenethylamine.

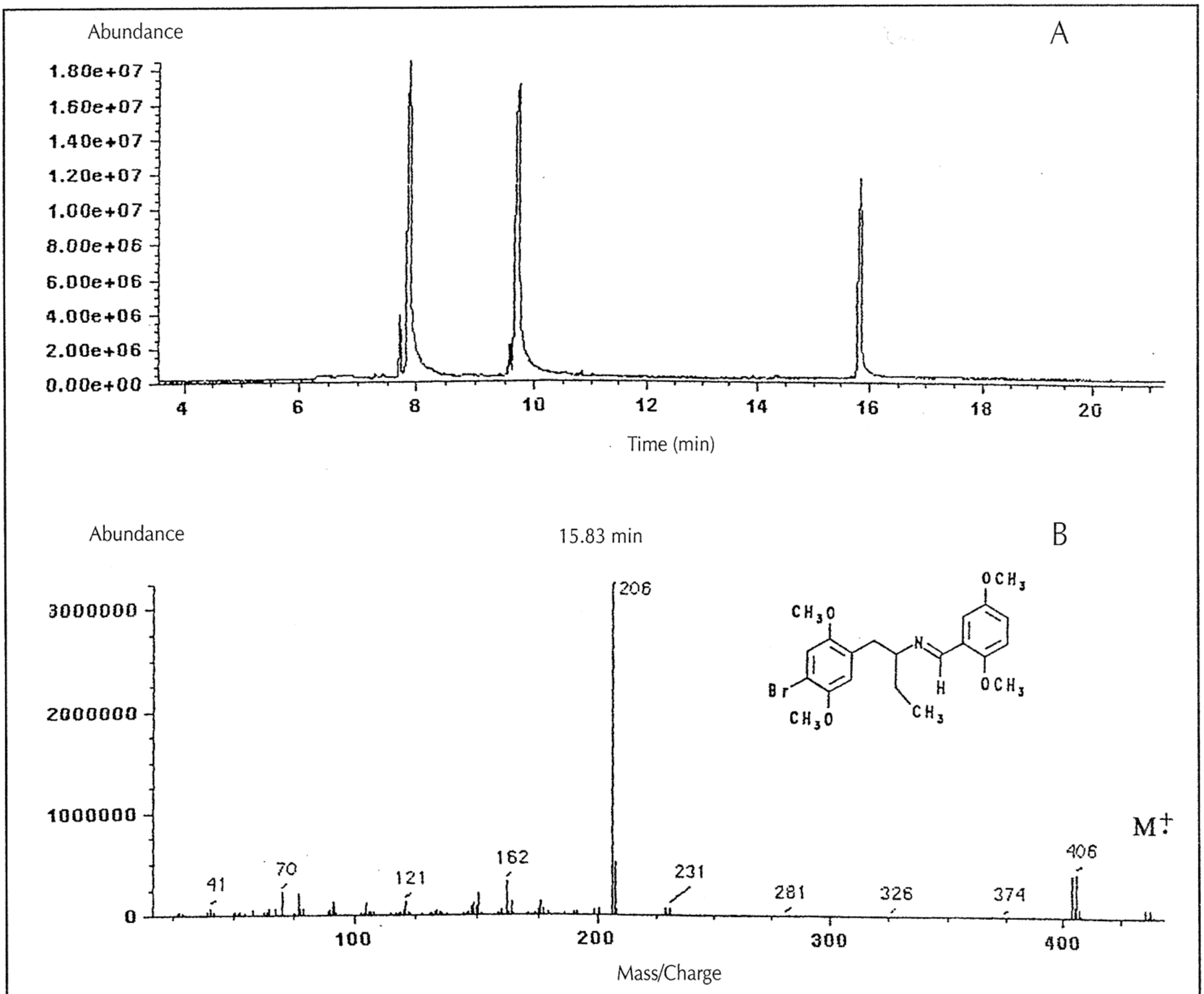


Figure 8. GC–MS analysis of a mixture of 1-(2,5-dimethoxyphenyl)-2-butanamine, 1-(4-bromo-2,5-dimethoxyphenyl)-2-butanamine, and 1-(2,5-dimethoxyphenyl)-2-nitrobutene: A, chromatogram and B, mass spectrum of the imine peak eluting at 15.83 min.

and yield primarily the $(M–31)^+$ ion and the positively charged nitrogen-containing fragment produced by loss of the bromine-containing substituted benzyl radical.

Conclusion

Precursor aldehydes are readily available for preparation of the street drug Nexus and designer analogues. The phenethylamine, Nexus, can be separated from α-substituted analogues by reversed-phase liquid chromatography using an acidic mobile phase. The bromine-substituted compounds show enhanced retention on C_{18} phases relative to the unbrominated compounds. The mass spectra for these compounds show characteristic fragmentation and can be used for specific identification. GC–MS analyses of mixtures of the amines and their precursor nitroalkenes yield imine condensation products not present when the compounds are analyzed individually.

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