Liquid Chromatographic and Mass Spectral Analysis of 1-(3,4-Methylenedioxyphenyl)-3-butanamines, Homologues of 3,4-Methylenedioxyamphetamines

F. Taylor Noggle, Jr.
Alabama Department of Forensic Sciences, Wire Road, Auburn, Alabama 36830

C. Randall Clark* and **Jack DeRuiter**
Department of Pharmacal Sciences, School of Pharmacy, Auburn University, Auburn, Alabama 36849

Abstract

The 1-(3,4-methylenedioxyphenyl)-3-butanamines (HMDAs) are prepared via reductive amination of the corresponding ketone with a series of low molecular weight alkylamines. These amines are homologues of the *N*-substituted 3,4-methylenedioxyamphetamines (MDAs). Compounds of the HMDA series have UV absorption properties similar to the MDAs because both series contain the same 3,4-methylenedioxyphenyl chromophore. The HMDAs are separated via reversed-phase liquid chromatographic methods using a C_{18} stationary phase and an acidic aqueous acetonitrile mobile phase. The mass spectra of these potential designer drugs are very similar to the spectra of the MDA homologues having the same *N*-substituent.

Introduction

The various *N*-substituted derivatives of 3,4-methylenedioxyamphetamine (MDA) have become popular drugs of abuse in recent years (1–3). The *N*-methyl MDA derivative (MDMA), also known as ecstasy, is perhaps the most widely used drug of the series. These drugs are said to have a unique ability to facilitate interpersonal communication by reducing the anxiety or fear that normally accompanies the discussion of emotionally painful events (4). The continued designer-drug exploration of the MDA series has resulted in legislation to upgrade the penalties associated with the clandestine use of these compounds.

Several of the small alkyl group *N*-substituted MDAs have appeared as street drugs (3). These compounds are usually prepared via a one-step reductive amination of 1-(3,4-methylenedioxyphenyl)-2-propanone (3,4-methylenedioxyphenylacetone) with the appropriate amine. This ketone is often referred to as piperonylacetone. Shulgin (5) has pointed out that nomenclature confusion regarding this reagent has resulted in the commercial substitution of 1-(3,4-methylenedioxyphenyl)-3-butanone for 1-(3,4-methylenedioxyphenyl)-2-propanone. This substitution in the synthesis of amines would result in the formation of 1-(3,4-methylenedioxyphenyl)-3-butanamines (homomethylenedioxyamphetamines, HMDAs). This potential for substitution of reagents was emphasized by a recent clandestine purchase of the butanone in the southeastern United States. Davis and Borne (6) have compared the acute toxicity of MDA and MDMA with HMDA and HMDMA. The HMDAs were equal or greater in toxicity than the MDAs in mice, suggesting that the HMDAs constitute no less a hazard for acute toxicity in humans than MDA. Although some qualitative differences in pharmacological activity between the MDAs and HMDAs were observed (6), little is known about the hallucinogenic activity of HMDA and HMDMA.

The popularity of the MDAs and the commercial availability of the homologous 1-(3,4-methylenedioxyphenyl)-3-butanone prompted our synthesis and analytical investigation of the *N*-alkyl HMDAs.

Experimental

Instrumentation

The liquid chromatograph (LC) consisted of a Waters Associates Model 6000A pump, U6K injector, Model 440 UV detector with dual wavelength accessory operated at 254 and 280 nm, and Houston Instruments OmniScribe dual pen recorder. Infrared spectra were recorded on a Perkin-Elmer Model 1710 Fourier transform infrared (FTIR) spectrophotometer. UV spectra were recorded on a Shimadzu Instruments Model UV-160 spectrophotometer. Nuclear magnetic resonance spectra (^1H) were obtained using a Varian T-60A spectrometer.

The electron impact mass spectra were obtained using a Hewlett-Packard 5970B mass selective detector. The ionization voltage was 70 eV and the source temperature was 220°C. The individual samples were dissolved in methanol (1 mg/mL), and 0.5 μL was introduced into the mass spectrometer via the gas chromatograph (GC) equipped with a 12-m × 0.31-mm i.d. fused-silica column with a 0.52-μm thickness of OV-1. The column temperature was programmed from 70°C to 150°C at a rate of 15°C/min and from 150°C to 250°C at a rate of 25°C/min. The split ratio for the GC was 10:1 and all samples eluted in approximately 7 min.

LC procedures

The analytical column was 30 cm × 3.9 mm i.d. packed with Bondex C_{18} (Phenomonex). The analytical column was preceded by a 7-cm × 2.1-mm i.d. guard column dry packed with CO:Pell ODS (Whatman). The amines (1 mg/mL) were dissolved in HPLC-grade methanol and chromatographed using a mobile phase of pH 3.0 phosphate buffer/HPLC-grade acetonitrile

* Author to whom correspondence should be addressed.

(600:125). The pH 3.0 phosphate buffer was prepared by mixing 9.2 g monobasic NaH_2PO_4 in 1 L 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 0.1 AUFS. A 15-μL aliquot of each amine solution was injected into the LC.

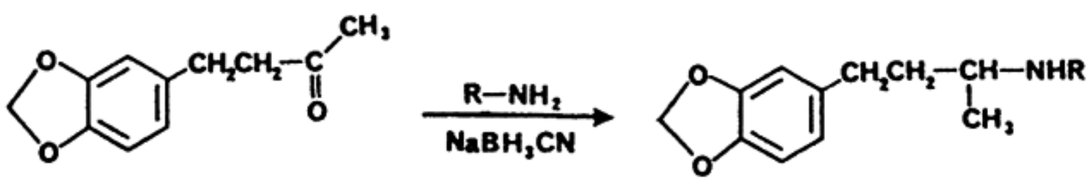
Synthesis of the 1-(3,4-methylenedioxyphenyl)-3-butanamines

A solution of the appropriate ketone (10 mmol), ammonium acetate, or alkylamine (100 mmol) and sodium cyanoborohydride (25 mmol) in methanol (25 mL) was stirred at room temperature for 24 h. The reaction mixture was then evaporated to dryness under reduced pressure, and the remaining residue was suspended in dichloromethane (50 mL). The dichloromethane suspension was extracted with 3 N HCl (2 × 75 mL), and the combined acid extracts were made basic (pH 12) with sodium hydroxide. The basic aqueous suspension was then extracted with dichloromethane (2 × 100 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The dichloromethane was filtered and evaporated to give the product amine as the free base. Treatment of the bases with ethereal HCl (50 mL) afforded the amine hydrochlorides, which were isolated by filtration and recrystallized from mixtures of anhydrous ether and absolute ethanol.

Results and Discussion

The clandestine synthesis of the various *N*-substituted 3,4-methylenedioxyamphetamines most commonly begins with the commercially available 3,4-methylenedioxyphenylacetone. Reductive amination of the ketone with various amines yields the MDAs. The homologous ketone 1-(3,4-methylenedioxyphenyl)-3-butanone is commerically available, and reductive amination gives the corresponding butanamine series HMDAs.

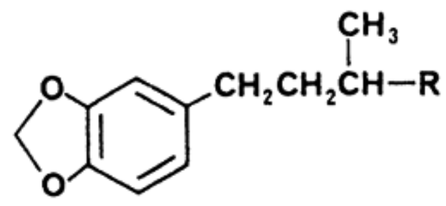
In this study, the small *N*-alkyl and the *N*-hydroxy derivatives of HMDA were prepared in order to compare their analytical profiles to that of the MDA series. Reductive amination of the ketone was accomplished using the appropriate amine in the presence of sodium cyanoborohydride ($NaBH_3CN$) according to the general method of Borch et al. (7).



The *N*-hydroxy isomer was prepared via $NaBH_3CN$ reduction of the oxime of the ketone (8). The chromophoric moiety in the HMDAs is the 3,4-methylenedioxyphenyl group, which is also responsible for the UV absorption in the MDA molecules. Thus, the UV absorption properties of these compounds are similar to those of the MDAs. The HMDAs show two absorption bands (Table I) in the 285-nm and 232-nm ranges with the intermediate absorbance minimum occurring at 255 nm. The absorptivity at the two maximum absorbance bands is essentially equal for all compounds examined. These UV absorption properties, as expected, are quite similar to those of the MDA series.

The LC separation of the *N*-substituted HMDAs prepared in this study is shown in Figure 1. The compounds were separated using reversed-phase chromatographic conditions consisting of a C_{18} Bondex stationary phase and a mobile phase of pH 3 phosphate buffer and methanol (600:125). Dual wavelength detection at 280 nm and 254 nm is very close to the absorption maximum and minimum, respectively, for the HMDAs; thus, the A280/A254 is quite a high ratio. The primary amine HMDA has the lowest capacity factor in this chromatographic system

Table I. UV Absorption Properties of the 1-(3,4-Methylenedioxyphenyl)-3-butanamines*



R	λ_1	E_1	λ_2	E_2
NH_2	285	1.6×10^3	232	1.6×10^3
NHMe	285	2.2×10^3	232	2.2×10^3
$NHMe_2$	282	2.1×10^3	232	2.1×10^3
NHEt	284	2.0×10^3	232	2.0×10^3
NHnPr	285	2.0×10^3	232	2.0×10^3
NHiPr	285	2.1×10^3	233	2.1×10^3

* Determined in 0.1 N H_2SO_4 solution.

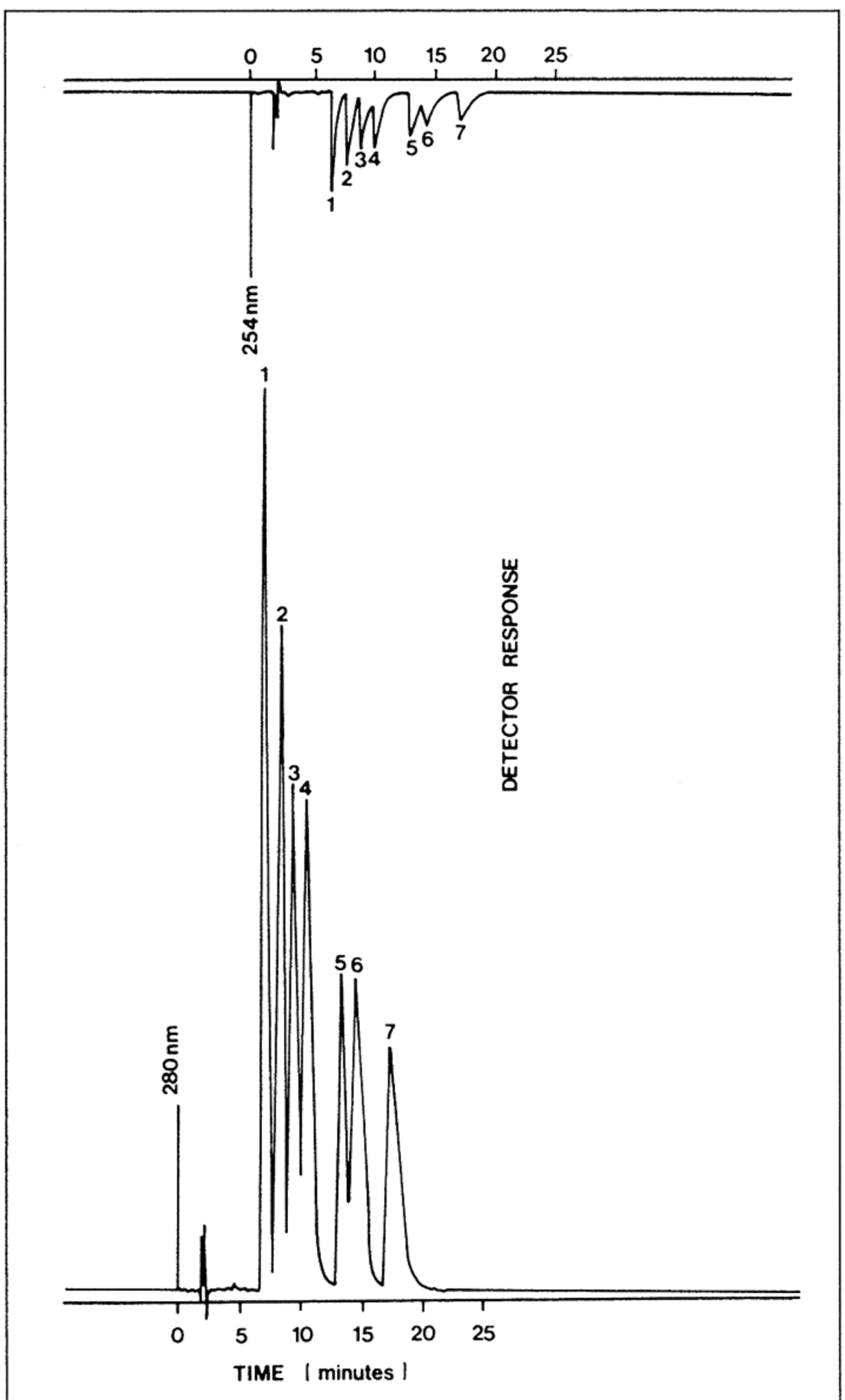


Figure 1. LC separation of the *N*-substituted 1-(3,4-methylenedioxyphenyl)-3-butanamines. Peaks: 1=HMDA; 2=*N*-methyl; 3=*N,N*-dimethyl; 4=*N*-ethyl; 5=*N*-hydroxy; 6=*N*-isopropyl; 7=*N*-*n*-propyl.

followed by the *N*-methyl derivative HMDMA. The *N,N*-dimethyl HMDA elutes before the *N*-ethyl derivative similar to the elution order observed in other series of substituted *N*-alkylamines. The final three peaks in Figure 1 are the *N*-hydroxy-, isopropyl-, and *n*-propyl HMDAs, respectively. The branched chain isopropyl group eluting before its straight chain isomer *n*-propyl is consistent with hydrophobicity measurements. The *N*-hydroxy HMDA should be more polar than the *N*-alkyl derivatives; however, its capacity factor in this chromatographic system places its polarity between that of the *N*-ethyl and *N*-isopropyl isomers. The acidic mobile phase, pH 3, would be sufficient to protonate the *N*-alkyl HMDA derivatives, which should have pK_a values in the 9 to 11 range. The pK_a value for the *N*-hydroxy isomer could be sufficiently low that an equilibrium between the free base and the protonated species can exist under the conditions of the chromatography. This variation in chromatographic species could account for the relatively high capacity factor for the *N*-hydroxy HMDA.

The LC separation of the primary amine, the *N*-methyl, and the *N*-ethyl derivatives of MDA and HMDA is shown in Figure 2. All three MDA derivatives elute before any of the HMDAs,

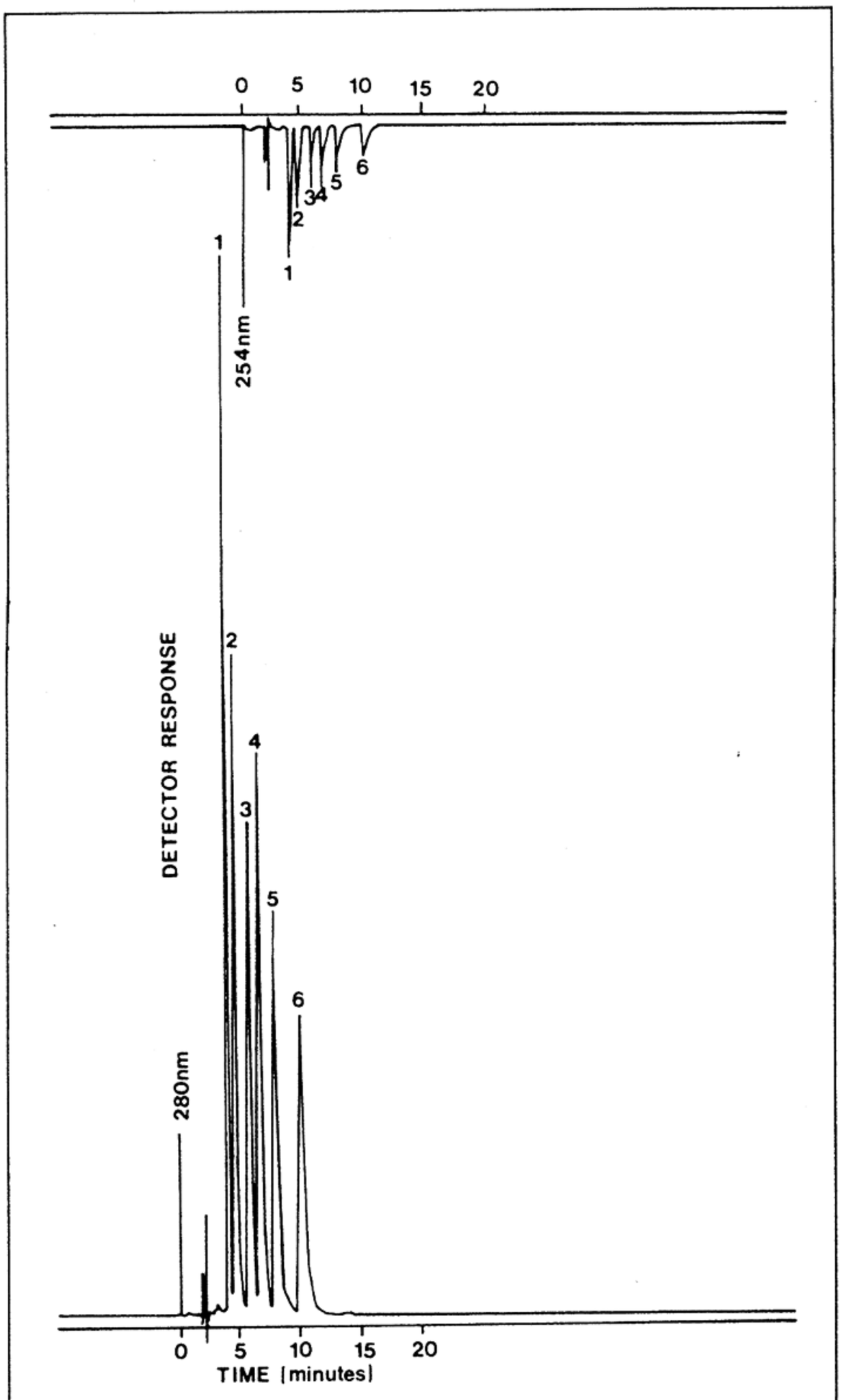


Figure 2. LC separation of some *N*-substituted MDAs and HMDAs. Peaks: 1=MDA; 2=*N*-methyl MDA; 3=*N*-ethyl MDA; 4=HMDA; 5=*N*-methyl HMDA; 6=*N*-ethyl HMDA.

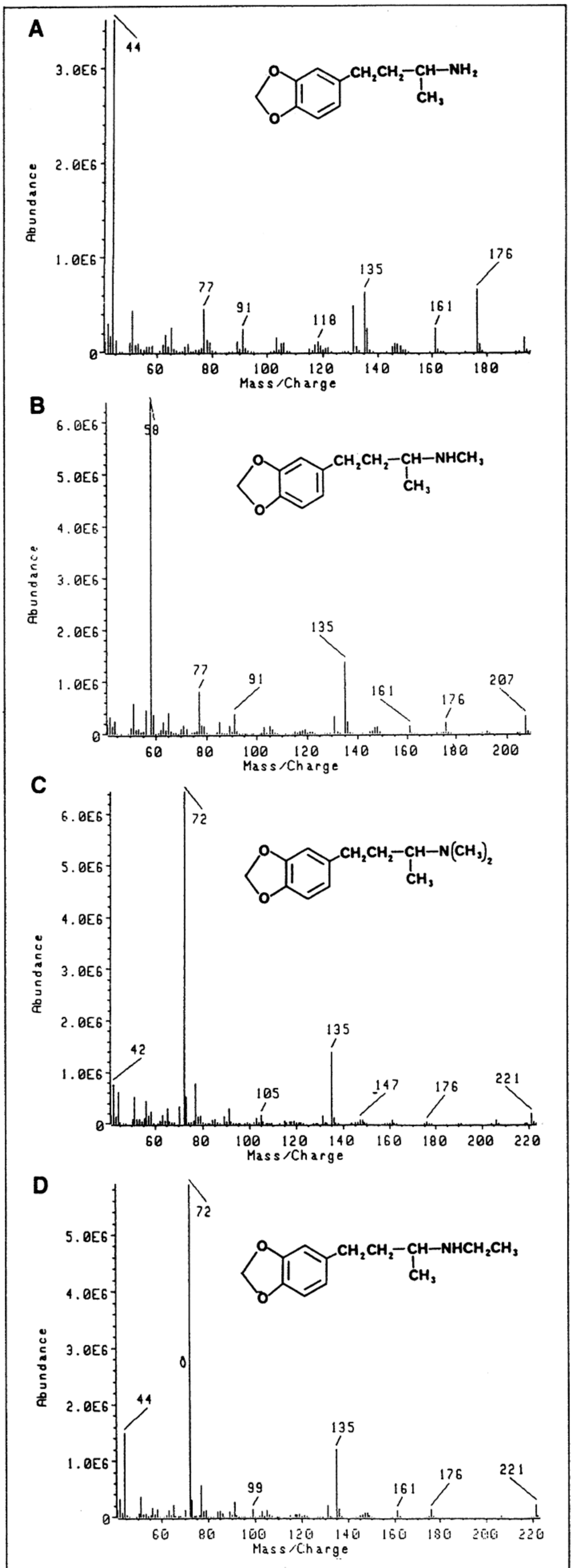


Figure 3. Electron impact mass spectra of HMDA and *N*-substituted HMDAs. Spectra: A=HMDA; B=*N*-methyl HMDA; C=*N,N*-dimethyl HMDA; D=*N*-ethyl HMDA.

indicating the increased lipophilicity of the butanamine series. For *N*-substituents larger than ethyl, the substituted MDAs whould overlap the HMDAs in this isocratic chromatographic system. It is interesting to compare the chromatographic effects of homologation in the *N*-substitutent and in the arylamine portion of these molecules. For example, the separation of the *N*-methyl and *N*-ethyl MDAs (peaks 2 and 3) and HMDAs (peaks 5 and 6) illustrates the effect of *N*-substituent homologation. The separation of *N*-methyl MDA and HMDA (peaks 2 and 5) as well as *N*-ethyl MDA and HMDA (peaks 3 and 6) illustrates the chromatographic effects of homologation on the arylamine chain. The arylamine homologation produces α-values higher than those resulting from the corresponding methylene insertion in the *N*-substituent.

The electron impact mass spectra of these HMDA derivatives were determined at 70 eV using a capillary GC/mass spectrometric (MS) system. The spectra in Figure 3 show that the fragmentation is extensive in these compounds, and very little molecular ion is observed. The compounds undergo the typical amine-dominated fragmentation with the base peak resulting from cleavage of the bond α to the amine nitrogen, as is the case in the MDA series (3). The resulting ammonium species can rearrange to yield the *m/z* 44 ion when the *N*-alkyl substituent is an ethyl group or larger. For example, the spectra of the *N*,*N*-dimethyl and *N*-ethyl derivatives (Figure 3,C and D) are very similar with the exception of the much higher relative abundance of the *m/z* 44 ion in the *N*-ethyl HMDA. Furthermore, the low mass portion of the spectra in Figure 3 is essentially the same as the low mass portion of the MDA series having the same *N*-substituent. Thus, without the molecular ion, it would be very difficult to distinguish between the two series based on the mass spectra.

Conclusion

In summary, the HMDAs are a potential series of designer drugs related to the MDA group of compounds. The analytical profiles of these compounds have been compared to the MDAs, and methods were developed for their identification.

References

1. F.T. Noggle, Jr., J. DeRuiter, S.T. Coker, and C.R. Clark. *J. Assoc. Off. Anal. Chem.* **70:** 981 (1987).
2. F.T. Noggle, Jr., J. DeRuiter, C.L. McMillian, and C.R. Clark. *J. Liq. Chromatogr.* **10:** 2497 (1987).
3. F.T. Noggle, Jr., C.R. Clark, A.K. Valaer, and J. DeRuiter. Liquid chromatographic and mass spectral analysis of *N*-substituted analogues of 3,4-methylenedioxyamphetamine. *J. Chromatogr. Sci.*, **26:** 410–17 (1988).
4. A.T. Shulgin and D.E. Nichols. In, *The Psychopharmacology of Hallucinogens,* R.C. Stillman and R.E. Willette, Eds. Pergamon Press, New York, 1978, p. 74.
5. A.T. Shulgin. *J. Psychoactive Drug* **18:** 291 (1986).
6. W.M. Davis and R.F. Borne. *Substance and Alcohol Actions/Misuse* **5:** 105 (1984).
7. R.F. Borch, M.D. Bernstein, and H.D. Durst. *J. Am. Chem. Soc.* **93:** 12 (1971).
8. U. Braun, A.T. Shulgin, and G. Braun. *J. Pharm. Sci.*, **69:** 192 (1980).

Manuscript received September 27, 1988;
revision received December 2, 1988.