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Methods for the Analysis of 1-(3,4-Methylenedioxyphenyl)-2-Butanamine and *N*-Methyl-1-(3,4-Methylenedioxyphenyl)-2-Propanamine (MDMA)

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

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

Abstract

The infrared and mass spectra of *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine (MDMA) and 1-(3,4-methylenedioxyphenyl)-2-butanamine are quite similar. These two compounds differ only in the position of substitution of a single methyl group. MDMA is a controlled street drug known as Ecstasy, while the isomeric butanamine is a member of a new class of potential psychotherapeutic agents called entactogens. These two compounds produce similar mass spectral fragmentation patterns including a common base peak at *m/z* 58. Reversed-phase liquid chromatographic (RPLC) methods consisting of a C_{18} stationary phase and an aqueous acidic mobile phase were used to separate these two compounds. Thus, LC methods can be used to differentiate MDMA from the isomeric butanamine for forensic analysis.

Introduction

The various *N*-substituted derivatives of 3,4-methylenedioxyamphetamine (MDA) have become popular drugs of abuse in recent years (1–3). These drugs are claimed 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.

MDA was one of the first class of hallucinogenic amphetamine derivatives to show popularity as a recreational drug. Structurally, MDA is a phenethylamine resembling both amphetamine and mescaline and is reported to act primarily as a central nervous system stimulant that may be hallucinogenic in large doses (5,6).

Although MDA may lack the sensory disruptions commonly recognized with lysergic acid diethylamine (LSD) and mescaline, it has been reported to be more toxic than mescaline in laboratory animals (7). Several of the *N*-substituted derivatives of MDA have appeared as drugs of abuse and the *N*-methyl (MDMA), *N*-ethyl (MDEA), and *N*-hydroxy (NOHMDA) analogs have been reported to have psychotomimetic activity in humans (8). MDMA is perhaps the most popular of the MDA series and is known by the street names Ecstasy or XTC. This drug has been extensively studied in animals via a variety of techniques including drug discrimination (9) and neurochemical methods (10).

In two separate reports, Hayner and McKinney (11) and Dowling (12) document several case studies where MDMA resulted in both tolerance development and death. In addition, several samples of MDMA purchased on the street have been found (11) to vary substantially in MDMA content, from a low of 16 mg to a high of 150 mg. MDMA has been described (11,12) as an unpredictable drug that has the potential to kill at previously tolerated doses.

The α-ethyl phenethylamine, 1-(3,4-methylenedioxyphenyl)-2-butanamine was recently reported by Nichols et al. (13) and its pharmacology compared to the α-methyl homologue, MDA. In rats trained to discriminate between saline and LSD, these effects were generalized by racemic MDA and the racemic butanamine. However, the butanamine did not produce complete generalization and was described as a less potent psychoactive drug. In human studies the *N*-methylated butanamine has been characterized as producing a pleasant state of introspection which facilitates the discussion of emotionally painful issues. Hence, this compound was described as representing a new pharmacological class, the entactogens. The word entactogen is derived from the Greek roots "en" for within and "gen" meaning produce, and the Latin root "tactus" for touch (13). Entactogens produce their unique behavioral effects without causing profound sensory experiences or distortions as observed with the hallucinogens or psychodelics. Thus entactogens continue to be suggested as potential therapeutic agents in facilitating psychotherapy.

The similarity in structure and pharmacology of the butanamines and the MDA series of drugs has prompted the investigation of analytical methods to distinguish between these compounds. The primary amine butanamine and *N*-methyl MDA (MDMA) differ only in the position of the methyl group. These two compounds have the same molecular weight and should show considerable similarity in MS and IR spectral properties. Thus differentiation between these two compounds could represent a considerable challenge in forensic analysis.

* Author to whom correspondence should be addressed.

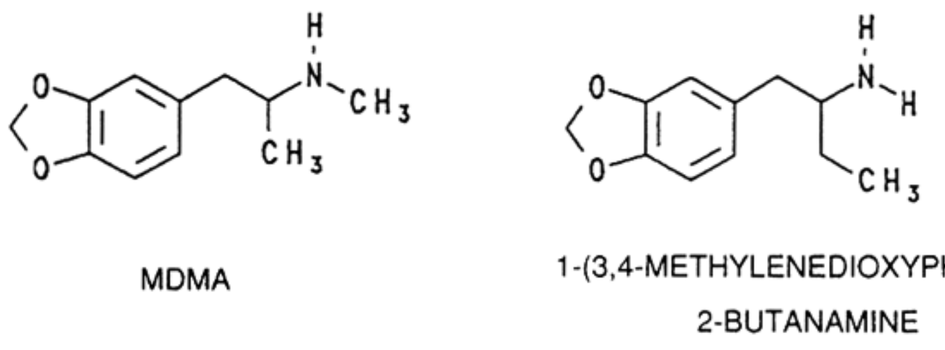
Experimental

Instrumentation. The liquid chromatograph consisted of a Waters Associates Model 6000A pump, U6K injector, Model 440UV detector with a dual wavelength accessory operated at 254 and 280 nm, and a Houston Instruments Omniscribe dual pen recorder. Infrared spectra were recorded on a Perkin-Elmer Model 1710 Fourier transform infrared (FTIR) spectrophotometer. Ultraviolet spectra were recorded on a Shimadzu Instruments Model UV-160 spectrophotometer. Nuclear magnetic resonance (NMR) spectra (^1H) were recorded using a Varian EM-360 spectrometer.

The electron impact (EI) 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 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° to 150°C at a rate of 15°/min and from 150° to 250°C at a rate of 25°/min. The split ratio for the GC was 10:1 and the samples eluted in approximately 7 min.

Liquid chromatographic procedures. The analytical column was a 30 cm × 3.9 mm i.d. packed with µBondapak C_{18} (Waters Associates). The analytical column was preceded by a 7-cm × 2.1-mm i.d. guard column 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, methanol, and triethylamine (600:75:25:1.5). The pH 3.0 phosphate buffer was prepared by mixing 9.2 g monobasic (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 0.2 AUFS. A 15-µL aliquot of each amine solution was injected into the liquid chromatograph.

Synthesis of 1-(3,4-methylenedioxyphenyl)-2-butanamine. A solution of piperonal (10.0 g, 67 mMol) and *n*-butylamine (19.4 g, 267 mMol) in benzene (100 mL) was stirred at reflux for 6 h. The water generated (1.2 mL) during imine formation was removed with a Dean–Stark trap. The reaction mixture was cooled to room temperature and the solvent evaporated in vacuo to yield the intermediate imine as a yellow oil. The imine was dissolved in a solution of nitropropane (6.2 g, 70 mMol) and glacial acetic acid (20 mL) and stirred at reflux for 30 min. The reaction mixture was then poured over crushed ice and acidified with concentrated HCl to pH 2 to yield the nitrostyrene as a dark green solid. The solid was isolated by filtration and recrystallized from 2-propanol (8.4 g, 63%). A solution of the nitrostyrene (2.0 g) in ethanol (100 mL) containing 5% palladium on carbon (1 g) was shaken under a hydrogen atmosphere (initial psi = 42) for 18 h using a Parr hydrogenator. The reaction mixture was then filtered and the filtrate solvent evaporated under reduced pressure to yield a yellow oil. The oil was dissolved in aqueous acid and washed with ether. The acidic solution was then made alkaline and extracted with ether. The combined ether extracts were dried and evaporated under reduced pressure to afford the free base. Treatment of the base with ethereal HCl provided the hydrochloride salt as a white powder which was isolated by filtration and washed with dry acetone, mp 153–154°C. Analysis: Theory C, 57.46;, H, 7.02; N, 6.09. Found: C, 57.50; H, 7.06; N, 6.04.

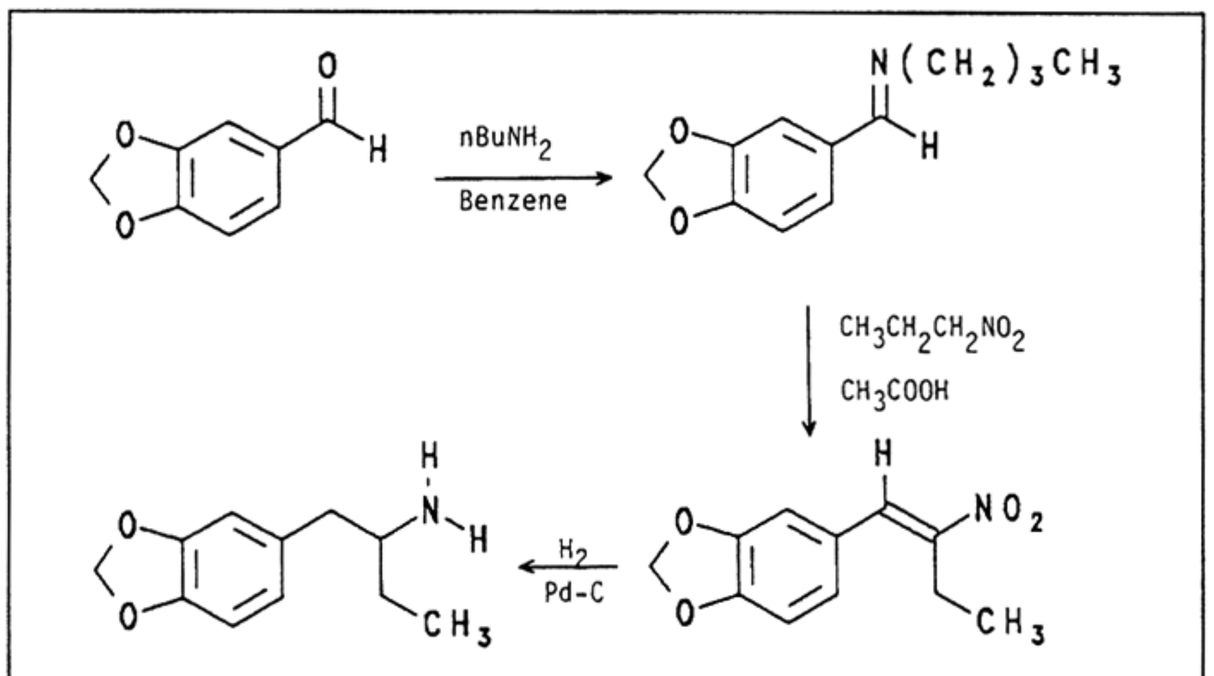


Scheme 1. Structures of *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine and 1-(3,4-methylenedioxyphenyl)-2-butanamine.

Results and Discussion

The synthesis and unique pharmacological properties of 1-(3,4-methylenedioxyphenyl)-2-butanamine were first reported by Nichols et al. in 1986 (13). They prepared this compound by reductive amination of the corresponding ketone, 1-(3,4-methylenedioxyphenyl)-2-butanone. The requisite ketone was prepared in a three step sequence involving treatment of piperonal with propyl magnesium bromide, dehydration of the resulting alcohol and finally oxidation of the 1-(3,4-methylenedioxyphenyl)-2-butene intermediate. In this paper, Nichols and coworkers also report that attempts to synthesize 1-(3,4-methylenedioxyphenyl)-2-butanamine by the more direct nitrostyrene method were unsuccessful because of difficulties encountered in the condensation between piperonal and nitropropane. We have found that modification of the initial condensation reaction can provide the key nitrostyrene in good yield, and this intermediate can be reduced to 1-(3,4-methylenedioxyphenyl)-2-butanamine directly. For example, treatment of piperonal with butylamine in benzene at reflux affords the intermediate imine in quantitative yield (Scheme 2). Reaction of the imine with nitropropane in acetic acid then provides the nitrostyrene intermediate in yields exceeding 60%. Catalytic reduction of the nitrostyrene with palladium on carbon in ethanol affords the desired amine which is purified by acid–base extraction and converted to the hydrochloride salt.

The goal of this project was to compare the analytical properties of MDMA and the butanamine because these amines should produce the same major fragments by mass spectrometry as well as having identical molecular weights. These compounds differ simply in the location of a methyl group which, in both cases, is positioned within the amine portion of the major electron impact (EI) fragmentation pattern. Gas chromatography–mass spectrometry (GC–MS) showed these two compounds to be base-line resolved using an OV-1 capillary column and a temperature programming technique (Figure 1). The MDMA eluted first followed by the butanamine. The mass spectra obtained for these two peaks are shown in Figure 2, and as expected they are quite similar. The major dif-



Scheme 2. Synthesis of 1-(3,4-methylenedioxyphenyl)-2-butanamine.

ferences are the relative abundances for a few of the ions. The major fragmentation product is the *m/z* 58 ion in each compound as shown in Scheme 3. These two *m/z* 58 ions are positional isomers differing only in the location of the methyl group. The 135 and 136 ions result from the 3,4-methylenedioxybenzyl fragment ion. Thus, without an analytical sample for comparison, it would be difficult to differentiate between MDMA and the butanamine by mass spectrometry alone.

The FTIR spectra of the two compounds are shown in Figure 3, again indicating some interesting similarities. The major absorption bands in the 2000–500 cm^{-1} region are very similar. For MDMA the bands labeled A–E occur at 1491, 1246, 1039, 931, and 798 cm^{-1}, respectively, while for the butanamine bands A–E correspond to 1504, 1248, 1040, 930, and 803 cm^{-1}, respectively. Thus a library search based on the spectrum obtained for the butanamine could produce a good match for MDMA.

The liquid chromatographic separation of MDMA and the butanamine is shown in Figure 4. The separation was achieved using a reversed-phase system consisting of a C_{18} stationary phase and a ternary mobile phase of pH 3 phosphate buffer, methanol, and acetonitrile containing triethylamine (600:100:25:1). The amines should exist predominantly in the protonated form under these conditions and the role of the protonated triethylamine additive is to mask active silanol sites on the stationary phase which produce peak tailing with the amines (14). The detection in this system was UV spectrophotometric at 280 nm. This wavelength is very near the absorption maxima for the 3,4-methylenedioxyphenyl chromophore in these compounds. The resolution of the two compounds is excellent under these conditions with the butanamine having the higher capacity factor. In reversed-phase chromatography on hydrocarbon stationary phases, retention is associated with molecular hydrophobic surface area (15). The enhanced retention of the bu

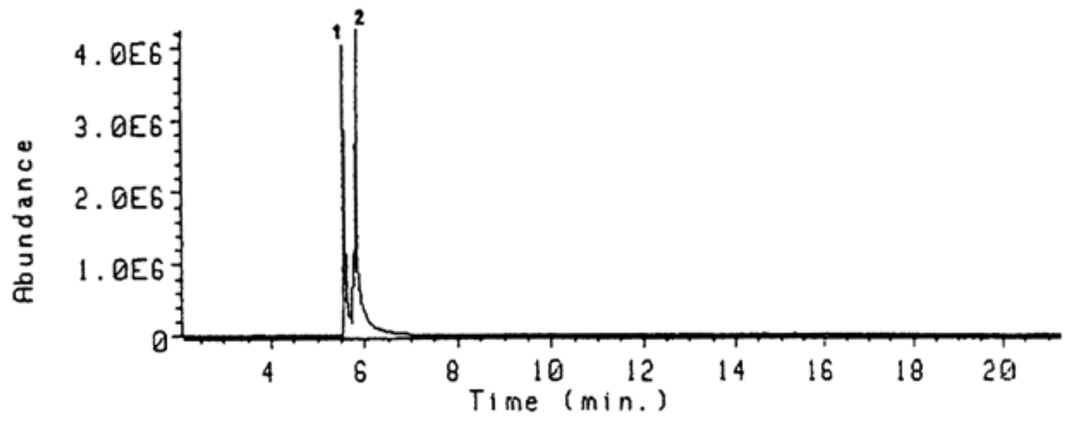


Figure 1. Gas chromatographic separation of (1) *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine and (2) 1-(3,4-methylenedioxyphenyl)-2-butanamine using an OV-1-stationary phase and a temperature programming technique.

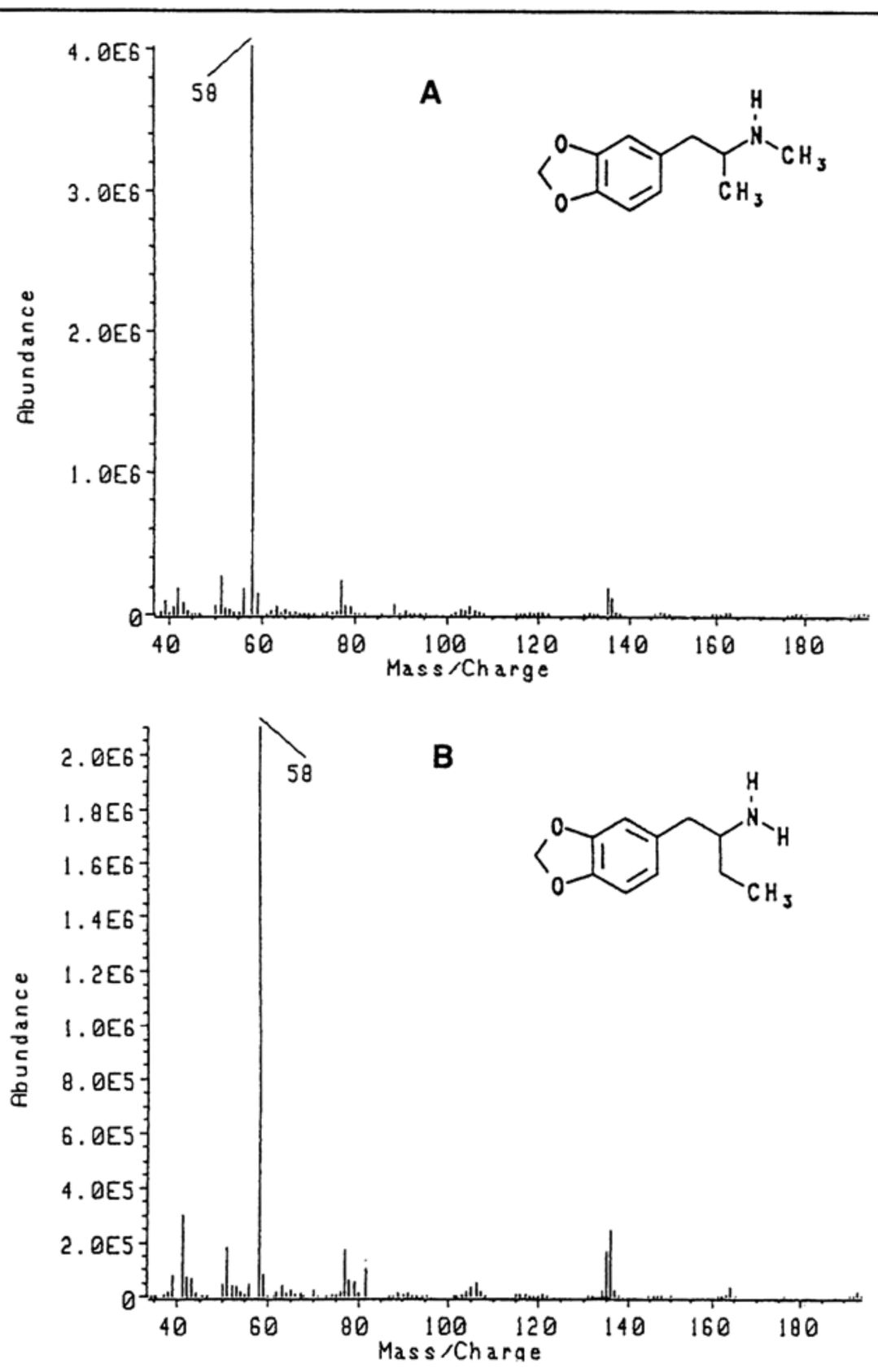
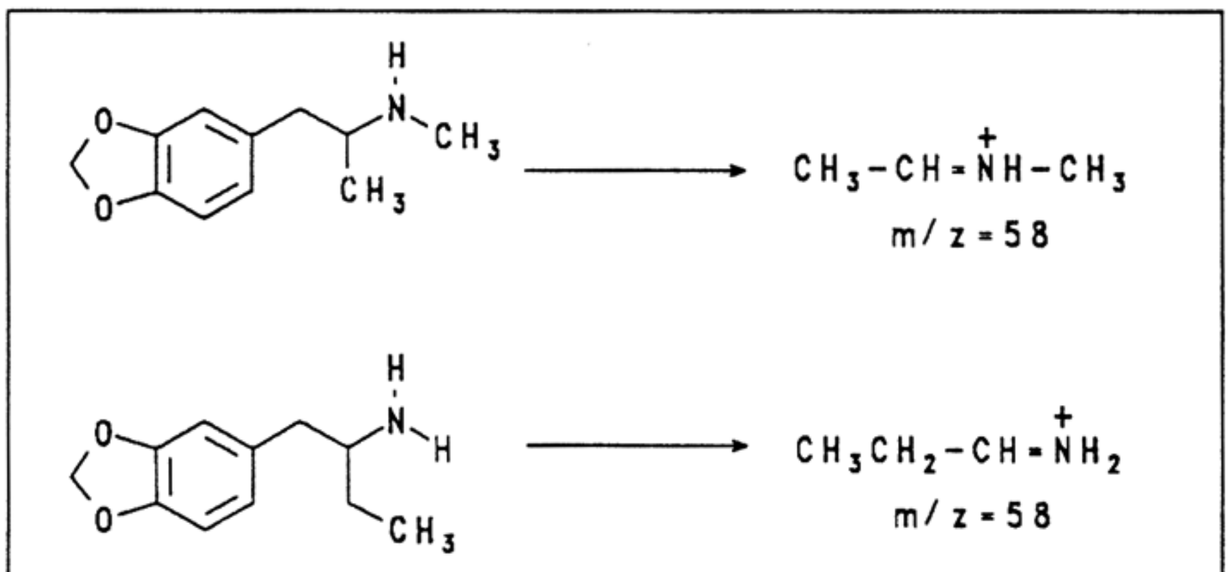


Figure 2. Electron impact mass spectra for (2a) *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine and (2b) 1-(3,4-methylenedioxyphenyl)-2-butanamine.



Scheme 3. The primary mass spectral fragmentation pathways for *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine and 1-(3,4-methylenedioxyphenyl)-2-butanamine.

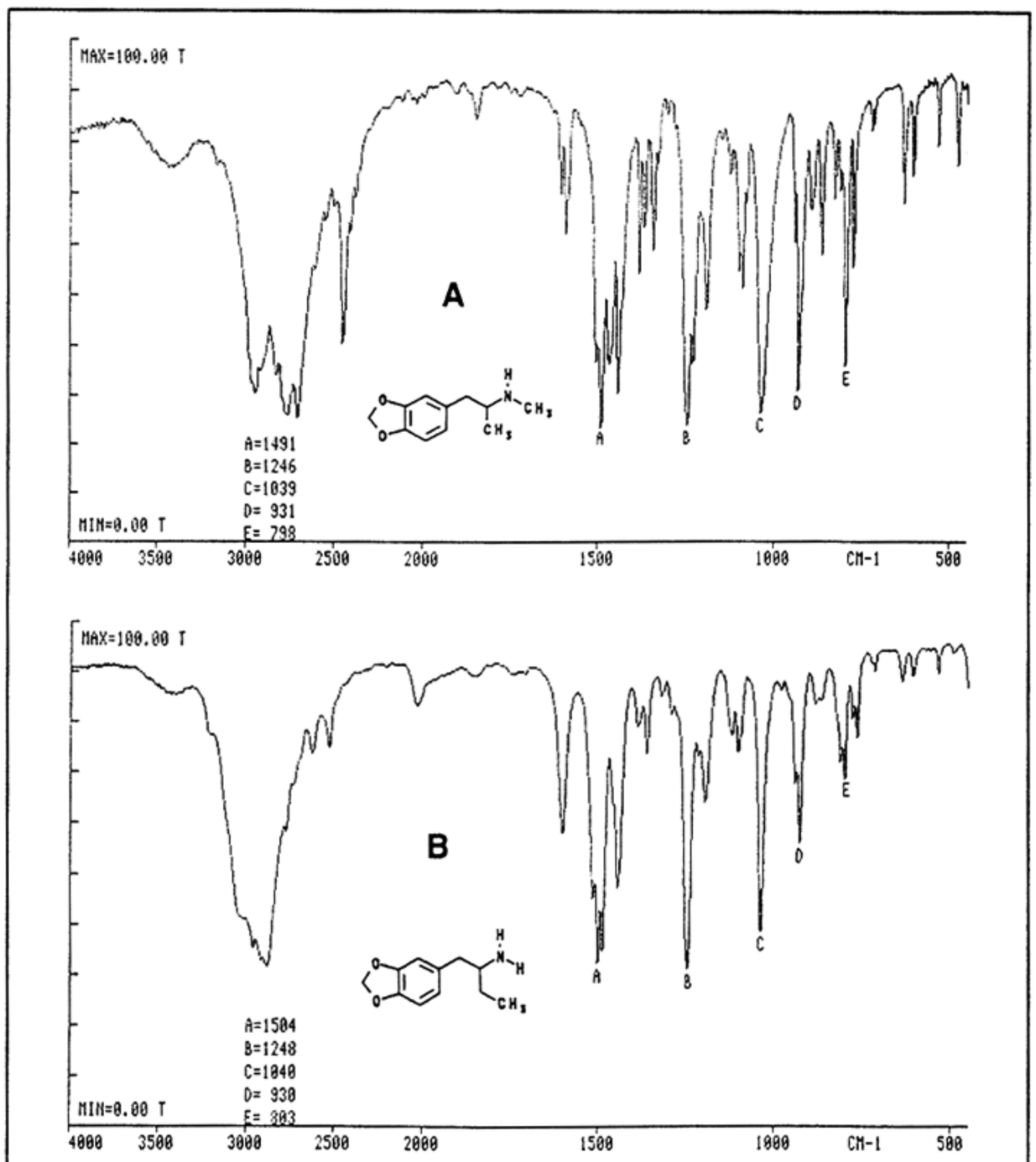


Figure 3. FTIR spectra for the free bases of (3a) *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine and (3b) 1-(3,4-methylenedioxyphenyl)-2-butanamine.

tanamine side chain suggests a more efficient hydrophobic interaction with the stationary phase ligands.

In summary, the potential for clandestine use of the butanamines as designer drug substitutes for the MDA-type drugs provides an interesting challenge for forensic analytical chemistry. While MDMA and the butanamine have subtle differences in their IR and MS spectra, the major methods for differentiation are chromatographic and this requires an analytical standard of the compounds in question. The liquid chromatographic separation of the isomeric MDMA and butanamine was achieved under reversed-phase conditions.

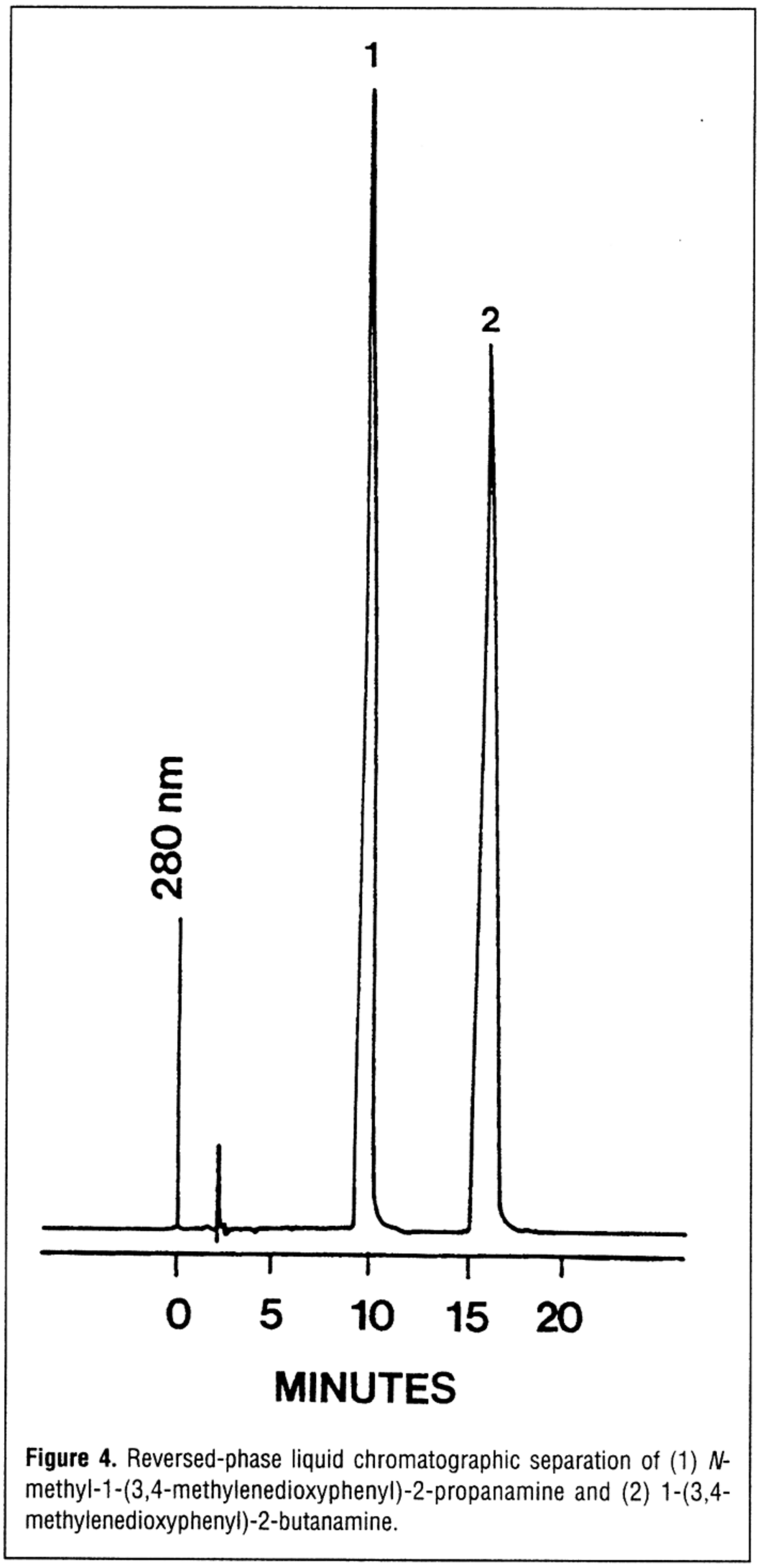


Figure 4. Reversed-phase liquid chromatographic separation of (1) *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine and (2) 1-(3,4-methylenedioxyphenyl)-2-butanamine.

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