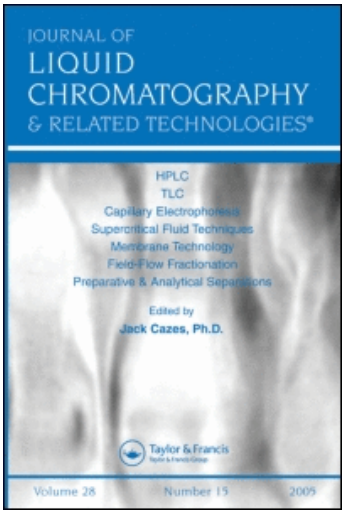

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Liquid Chromatographic and Mass Spectral Analysis of 1-(3,4-Methylenedioxyphenyl)-1-ethanamines: Homologues of 3,4-Methylenedioxyamphetamines

F. Taylor Noggle Jr.[a]; C. Randall Clark[b]; Jack Deruiter[b]
[a] Alabama Department of Forensic Sciences, Auburn, Alabama [b] Department of Pharmacal Sciences, School of Pharmacy Auburn University, Auburn, Alabama

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LIQUID CHROMATOGRAPHIC AND MASS SPECTRAL ANALYSIS OF 1-(3,4-METHYLENEDIOXYPHENYL)-1-ETHANAMINES: HOMOLOGUES OF 3,4-METHYLENEDIOXYAMPHETAMINES

F. TAYLOR NOGGLE, JR.[1], C.RANDALL CLARK[2], AND JACK DERUITER[2]

[1]*Alabama Department of Forensic Sciences*
Wire Road
Auburn, Alabama 36830

[2]*Department of Pharmacal Sciences*
School of Pharmacy
Auburn University
Auburn, Alabama 36849

Abstract

The deletion of a methylene unit from the arylamine side-chain of the 3,4-methylenedioxyamphetamines (MDAs) produces the homologous 1-(3,4-methylenedioxyphenyl)-1-ethanamines. These ethanamines were prepared via reductive amination of the corresponding ketone with a series of N-alkylamines. Analytical methods were developed to distinguish these compounds from the MDA series. The ethanamines were separated under reversed-phase

liquid chromatographic conditions using a C_{18} stationary phase and a mobile phase of aqueous acidic (pH3) acetonitrite containing triethylamine. The electron impact mass spectra of the ethanamines were determined by GC-MS and the fragmentation pattern clearly distinguishes these compounds from those of the MDA series having the same molecular weight.

Introduction

The unique pharmacological effects of 3,4-methylenedioxymethamphetamine ("Ecstasy, XTC"), and related compounds have made these compounds very popular drugs of abuse. The drugs appear to reduce the fear and anxiety that accompanies the discussion of emotionally painful events and have been used in phychotherapy (1). Several of the small alky group N-substituted MDAs have appeared as street drugs in recent years (2-4). These compounds are usually prepared from the commercially available 1-(3,4-methylenedioxyphenyl)-2-propanone via reductive amination (5). The continued designer-drug interest in the MDA series suggests the possibility of the appearance of other homologues when starting materials are readily available. One such commercially available starting material is 3,4-methylenedioxyacetophenone which upon reductive amination would yield the 1-(3,4-methylenedioxyphenyl)-1-ethanamines. The MDA series of amines are simply the methylene

homologues of the ethanamines. The absence of this methylene-unit in the side chain would be expected to produce compounds of less phenethylamine-type CNS activity. However, no specific activity data relative to the MDAs appears to be available.

Experimental

INSTRUMENTATION. The liquid chromatograph consisted of a Waters Associates Model 6000 A pump, μ6K injector, Model 440 UV detector with dual wavelength accessory operated at 254 and 280nm, and 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 spectra (1H) were determined 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 280°C. The individual samples were dissolved in methanol (1mg/mL) and 0.5 μL introduced into the mass spectrometer via the gas chromatograph equipped with a 12m x 0.31mm i.d. fused silica column with a 0.52μm 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 had eluted in approximately 7 minutes.

LIQUID CHROMATOGRAPHIC PROCEDURES. The analytical column was 30cm x 3.9mm i.d. packed with Bondex C_{18} (Phenomonex, Rancho Palos Verdes, California). The analytical column was preceded by a 7cm x 2.1mm i.d. guard column dry packed with CO:Pell ODS (Whatman). The amines (1mg/mL) were dissolved in HPLC grade methanol and chromatographed using a mobile phase of pH 3.0 phosphate buffer, HPLC grade acetonitrile and triethylamine (600:75:2). The pH 3.0 phosphate buffer was prepared by mixing 9.2g 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 1.5mL/min and the detector was operated at 0.1 AUFS. A 15 μL aliquot of each amine solution was injected into the liquid chromatograph.

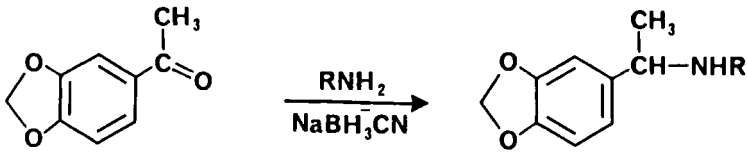
SYNTHESIS OF THE 1-(3,4-methylenedioxyphenyl)-1-ethanamines. A solution of the appropriate ketone (10 mmol), ammonium acetate or alkylamine (100 mmol) and sodium cyanoborohydride (25 mmol) in methanol (25 mL) was stirred at room temp for 24 h. The reaction mixture was then evaporated to dryness under reduced pressure and the remaining residue suspended in dichloromethane (50 mL). The dichloromethane suspension was extracted with 3N HCl (2 x 75 mL) and the combined acid extracts made basic (pH 12) with sodium hydroxide. The basic aqueous suspension was then extracted with dichloromethane (2 x 100 mL) and the combined organic extracts dried over anhydrous sodium sulfate. Filtration followed by evaporation of the filtrate solvent gave 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 various designer drug modifications of 3,4-methylenedioxyamphetamine (MDA) have become very popular drugs of abuse. In recent years several N-substituted derivatives including N-methyl, N,N-dimethyl, N-ethyl and N-hydroxy MDA have appeared as street drugs. The growing popularity of these drugs has generated interest in related compounds. One such related series of compounds are the N-substituted 1-(3,4-methylenedioxyphenyl)-1-ethanamines, homologues of the MDAs. In this study the ethanamines were prepared (Scheme I) via reductive amination of 3,4-methylenedioxyacetophenone with the appropriate amine in the presence of sodium cyanoborohydride (6). The amines were isolated as the free bases and converted to the hydrochlorides using ethereal HCl.

The ultraviolet absorption properties of these compounds are essentially equivalent to those of the MDA series. The 3,4-methylenedioxyphenyl chromophore is a feature both series have in common. The ethanamines show good UV absorbance in both the 284nm and 237nm ranges, with almost equal molar absorptivities at the two wavelengths (Table 1). The minimum between the two absorption bands is in the 256nm region.

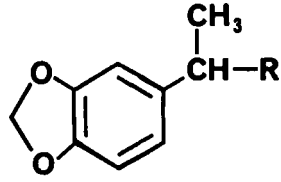


Scheme 1

Table 1

Ultraviolet Absorption Properties[a]

of 1-(3,4-Methylenedioxyphenyl)-1-ethanamines



R	λ_1	E_1	λ_2	E_2
NH_2	283.6()	$2.3x10^3$	235.0	$2.3x10^3$
NHMe	284.0	$1.9x10^3$	235.0	$2.3x10^3$
NMe2	284.4	$1.8x10^3$	237.4	$1.9x10^3$
NHEt	283.4	$1.9x10^3$	236.4	$2.0x10^3$
NHnPr	283.4	$1.7x10^3$	237.4	$1.8x10^3$
NHiPr	284.4	$1.9x10^3$	237.4	$1.9x10^3$

a determined in 0.1N H_2SO_4 solution

The liquid chromatographic separation of the 1-(3,4-methylenedioxyphenyl)-1-ethanamines was accomplished using reversed-phase conditions. The stationary phase was Bondex C_{18} shows the separation of the seven 1-(3,4-methylenedioxyphenyl)-1-ethanamines prepared in this study. The primary amine has the lowest capacity factor followed by the N-methyl, N-ethyl and N,N-dimethyl derivatives. Peaks 5 and 6 in Figure 1 are for the larger N-propyl substituents and the isopropyl group displays the lower capacity factor. This elution order is consistent with other series of N-alkylamines and roughly parallels the contact surface area for solute-stationary phase association (7). The N-hydroxy derivative has the highest capacity factor of the seven compounds separated in Figure 1. This unusually high k'-value may reflect the difference in basicity between the N-alkyl compounds and the N-hydroxy isomer. At pH3 the N-alkyls should exist exclusively as the protonated species while the less basic N-hydroxy isomer may exist partially in the more lipophilic nonprotonated species. The mobile phase for the separation of this series of amines required a small quantity of triethylamine in order to improve peak shape and resolution. Such mobile phase additives improve peak shape by competition with the solutes of interest for strong adsorption sites on the stationary phase.

The chromatogram in Figure 2 shows the separation of some ethanamines prepared in this work from the homologous 3,4-methylenedioxyamphetamines. The primary, N-methyl and N-

Figure 1. Reversed-phase liquid chromatographic separation of 1-(3,4-methylenedioxyphenyl)-1-ethanamines. Peaks: 1 = primary amine (NH_2); 2 = N-methyl; 3 = N-ethyl; 4 = N,N-dimethyl; 5 = N-isopropyl; 6 = N-n-propyl; 7 = N-hydroxy.

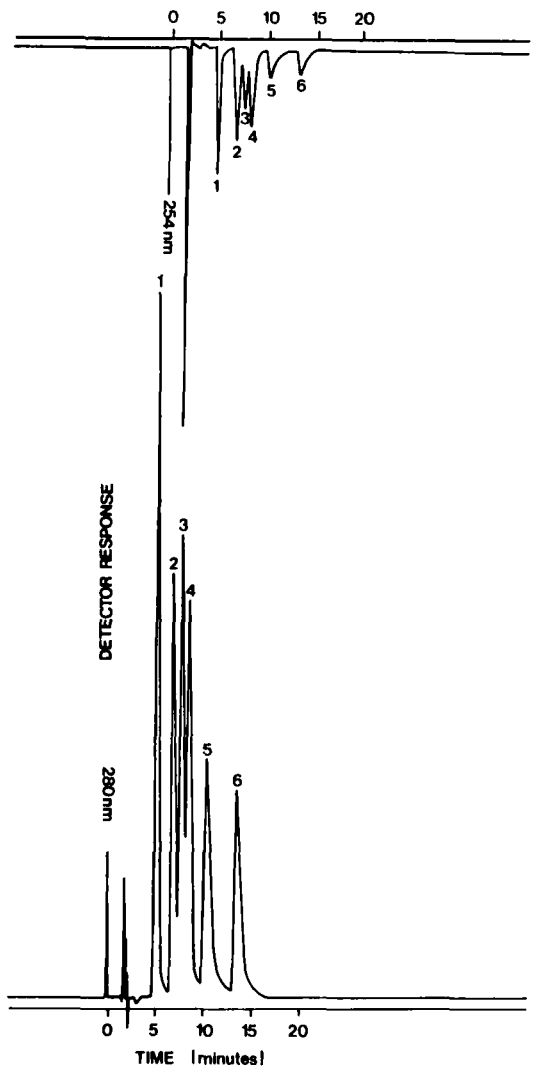


Figure 2. Liquid chromatographic separation of 1-(3,4-methylenedioxyphenyl)-1-ethanamines and the homologous 3,4-methylenedioxyamphetamines. Peaks: 1 = primary ethanamine (NH_2); 2 = N-methylethanamine; 3 = MDA; 4 = N-ethylethanamine; 5 = N-methyl MDA; 6 = N-ethyl MDA.

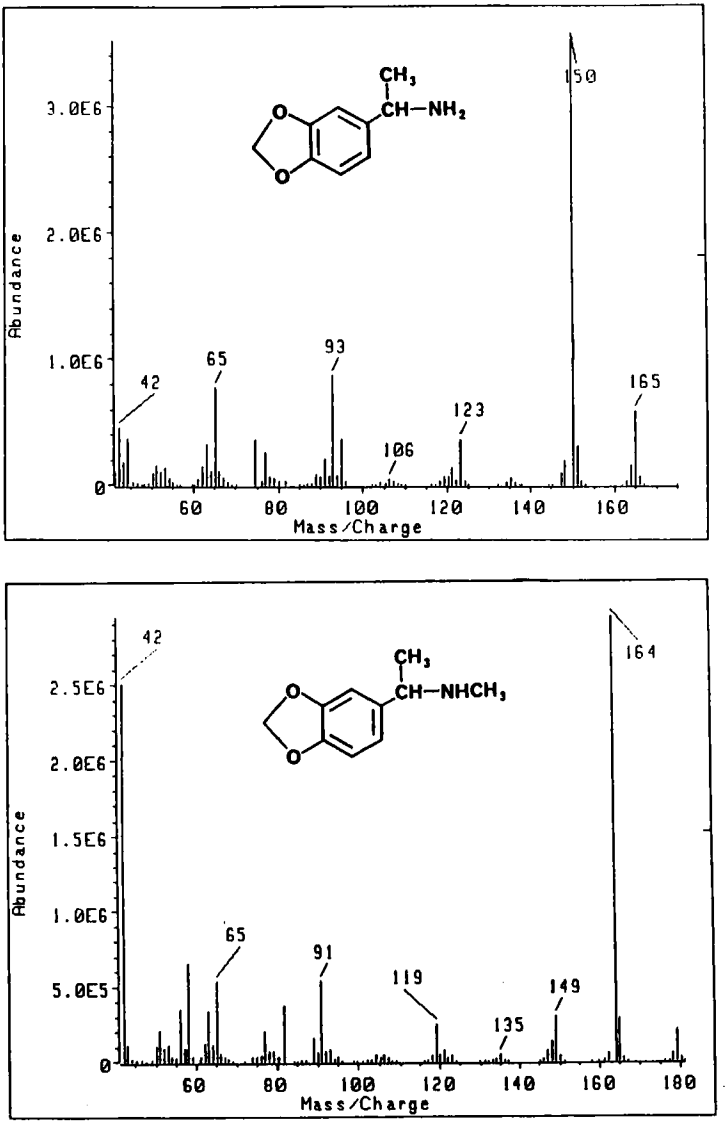


Figure 3. Electron impact mass spectra of 1-(3,4-methylenedioxyphenyl)-1-ethanamines. 3a = primary ethanamine (NH_2); 3b = N-methylethanamine; 3c = N-ethylethanamine.

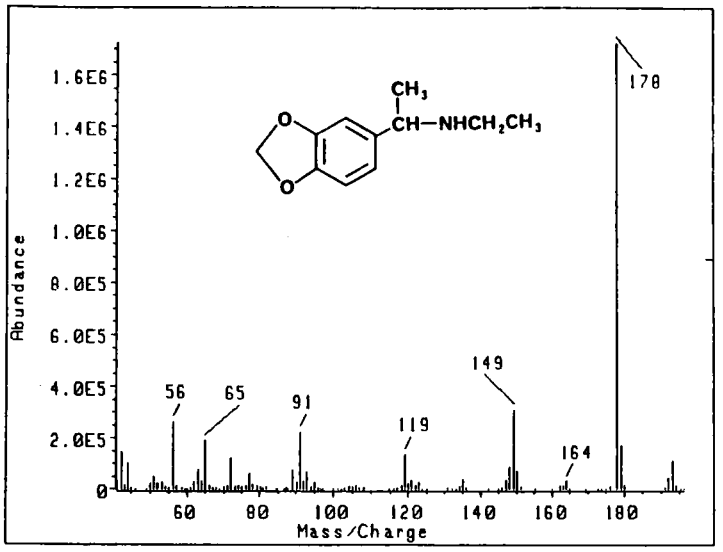


Figure 3c

ethylamines in each series were separated in about 15 minutes using the same chromatographic conditions described for Figure 1. The primary and N-methyl ethanamines elute first, followed by MDA then the N-ethyl ethanamine and finally N-methyl MDA and N-ethyl MDA, respectively. Some overlap of peaks would occur with the higher N-alkyl substituents of each series under these isocratic chromatographic conditions.

The mass spectra of the ethanamines are distinctly different from the homologous methylenedioxyamphetamines. Figure 3 shows the mass spectra for the primary amine, the N-methyl and N-ethyl ethanamines. The base peak in all these spectra is a relatively high-mass ion resulting from the loss of 15 mass units from the

molecular ion. This fragmentation is likely the loss of the alpha-methyl group (C-methyl) of the side chain yielding the N-substituted pipernal imine species. In this series, the formation of the low mass imine species resulting from the loss of the aryl radical does not occur. In the MDA series the loss of the benzyl-type radical yields the low mass imine as the base peak (4). The other major peak in the high mass region of the spectra is the m/z 149 ion resulting from the arylethyl-carbonium ion. These mass spectral characteristics allow for compounds of this series to be easily distinguished from compounds of the MDA series having the same molecular weight. For example, Figure 4 shows the mass spectra of MDA and MDMA and these compounds have the same molecular weight as the N-methyl and N-ethyl ethanamines, respectively. Comparison of Figures 3b and 4a, as well as 3c and 4b, shows the clear difference in the fragmentation of these two homologous series.

In summary, the N-substituted 1-(3,4-methylenedioxyphenyl)-1-ethanamines, were prepared and their analytical profiles compared to the homologous 3,4-methylenedioxyamphetamines. The compounds were separated by liquid chromatographic methods using a C_{18} stationary phase and an acidic (pH3) aqueous acetonitrile mobile phase. The mass spectra of the ethanamines are characterized by fragmentation products which differ significantly from those obtained from the homologous MDA series.

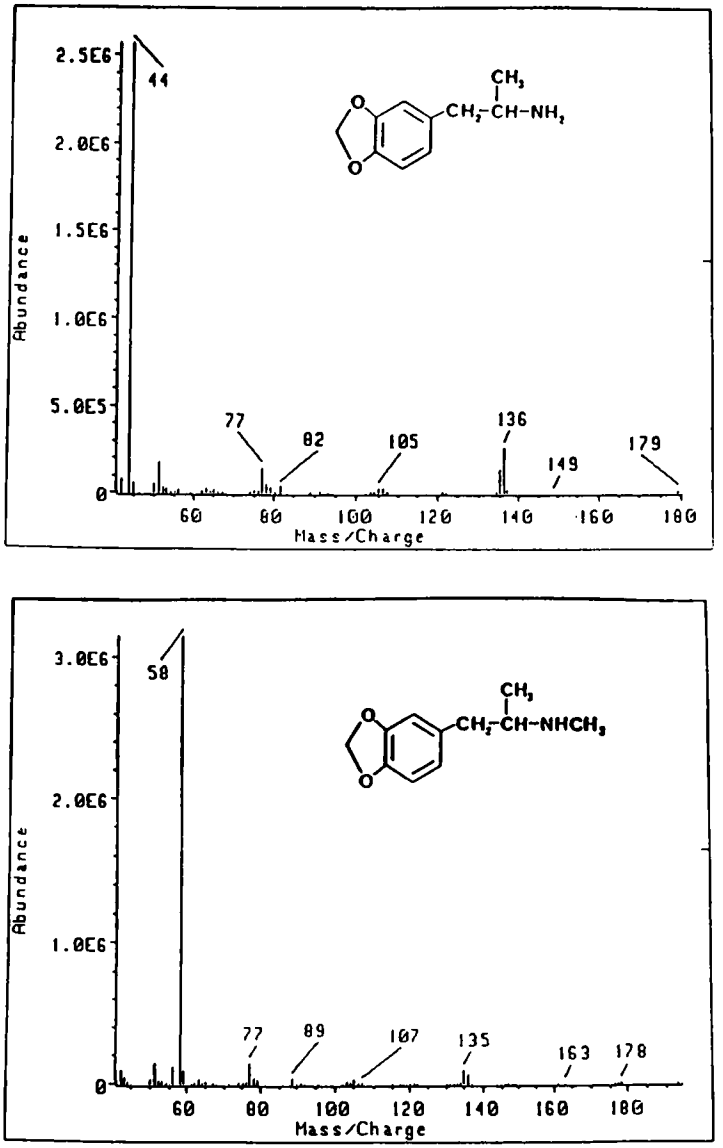


Figure 4. Electron impact mass spectra of MDA (4a) and N-methyl MDA (4b).

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