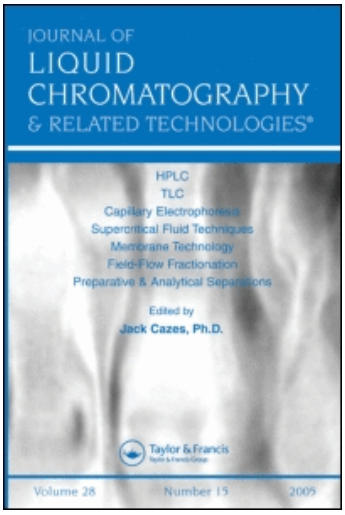

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LIQUID CHROMATOGRAPHIC ANALYSIS OF SOME N-ALKYL-3,4-METHYLENEDIOXY-AMPHETAMINES

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Abstract

The liquid chromatographic separation of a series of low molecular weight N-alkyl derivatives of 3,4-methylenedioxyamphetamine (MDA) is reported. The N-methyl-, N-ethyl- and N,N-dimethyl-derivatives of MDA have appeared as street drugs in recent years. These compounds are becoming significant forensic problems due to their unique pharmacological properties and relative ease of chemical synthesis. These amines were synthesized via reductive amination of the corresponding ketone with alkylamines. The UV absorption spectra for these compounds produced almost equally intense absorbance at 234 and 285 nm. The compounds were separated by reversed-phase (C_{18}) HPLC procedures using a mobile phase of aqueous methanol at low pH.

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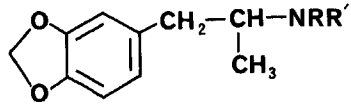
Introduction

The pharmacological actions of 3,4-methylenedioxyamphetamine (MDA) allow for its classification as an hallucinogen.[1] Although it has other atypical effects such as enhancing empathy and a low potential to produce severe sensory disruption, MDA became a popular street drug primarily because of its enhancing effect on empathy.[2] Methylation to yield the secondary amine, MDMA, produces significant changes in the pharmacological properties. Methylation results in a shorter duration of effect, a general decrease in potency and elimination of the hallucinogenic properties. However, the empathy enhancing properties are retained and appear to be more pronounced in MDMA.[3] This compound, MDMA, is claimed to have unique properties in psychotherapy, reducing the anxiety that normally accompanies the discussion of emotionally unpleasant events.[4] The recent appearance of this drug on the street market as "Ecstasy" indicates the popularity and potential for abuse of this drug. Its popularity is probably due to its mild effects and its ability to facilitate interpersonal communication.[5]

The increased availability of MDMA on the street and its potential to function as a neurotoxin in serotonergic pathways led to its inclusion as a Schedule I drug in 1984[6]. More recently, "designer drug" modifications of MDMA have produced the N-ethyl- and N,N-dimethyl-derivatives of MDA. These latter compounds have now appeared on the clandestine drug market.



MDA	R = R' = H
N-Methyl-MDA	R = H, R' = CH_3
N-Ethyl-MDA	R = H, R' = CH_2CH_3
N,N-Dimethyl-MDA	R = R' = CH_3

Based upon these facts, we have prepared reference samples of these low molecular weight N-alkyl derivatives of MDA and developed HPLC methods for their analysis in pharmaceutical samples.

Experimental

General: Melting points were determined in open glass capillaries using a Thomas-Hoover melting point apparatus and are uncorrected. All ^1H NMR spectra were measured in DMSO on a Varian T-60A spectrometer with an internal standard of tetramethylsilane. IR spectra were recorded on a Perkin-Elmer model 1500 Fourier transform infrared spectrophotometer. The UV absorption spectra were determined using a Shimadzu 160 spectrophotometer. Solutions for UV studies were prepared in 0.1N H_2SO_4 at a concentration of 1×10^{-4}M. The N-methyl- and N-ethyl-MDA derivatives were prepared as previously described.[7]

Synthesis of N,N-dimethyl-MDA: Sodium cyanoborohydride (1.9 g, 30 mmol) was added portionwise to a solution of 3,4-methylenedioxyphenyl-2-propanone (1.78 g, 10 mmol) and dimethyl amine (5.0 ml) in acetonitrile (50 ml). This mixture was stirred at room temperature and glacial acetic acid (1.0 ml) added. After stirring for 2 h, more glacial acetic acid was added (1.0 ml) and the mixture stirred an additional 30 min. The reaction mixture was then extracted with ether (2 X 100 ml) and the combined ether extracts washed successively with 1N NaOH (100 ml), sat'd $NaHCO_3$ (100 ml) and H_2O (100 ml). The ether solution was then extracted with 3N HCl (2 X 100 ml) and the combined HCl extracts washed with $CHCl_3$ (100 ml). The aqueous acid solution was then made basic (pH 12) with 2N NaOH, and this suspension extracted with $CHCl_3$ (3 X 150 ml). The combined $CHCl_3$ extracts were washed with H_2O (200 ml) and dried (Na_2SO_4). Filtration, followed by evaporation of the filtrate gave the product base as an oil. The base was converted to the corresponding salt upon treatment with ethereal HCl and recrystallized from mixtures of ethanol and ether.

Chromatographic Procedures: The liquid chromatograph consisted of a Waters Associates (Milford, MA) Model 6000A pump, U6K injector, 440 UV detector with

dual wavelength accessory operated at 254 and 280 nm, and Houston Instruments (Austin, TX) Omniscribe dual pen recorder. The column was 30 cm X 3.9 mm id packed with u Bondapak C_{18} (Waters Associates) and the mobile phase consisted of pH 3.0 phosphate buffer: methanol: triethylamine (650:100:0.5) (solvent system I) or pH 3.0 phosphate buffer and methanol (6:1) (solvent system II). The mobile phase flow rate was 1.5 ml/min and the UV absorbance detector was operated at 0.2 AUFS. Sample solutions for analysis were prepared in methanol and separations were accomplished at ambient temperature.

Results and Discussion

3,4-Methylenedioxymethamphetamine (MDMA) has been used since the mid 1970s in counciling sessions as an adjunct to psychotherapy. The drug is reported to ease psychic trauma and break down barriers to communication between people involved in a significant emotional relationship. In recent years, the increased recreational use of the drug has resulted in its inclusion as a Schedule I controlled substance. To many recreational users, MDMA possesses the positive features of LSD without LSD's hallucinogenic properties.

The control of MDMA has led to designer drug type molecular modifications of the basic structure which retain the biological activity profile yet differ chemically from MDMA. The N-ethyl analog of MDA, "Eve," was one of the first such designer drugs to appear on the street followed more recently by the N,N-dimethyl MDA derivative.

In this study we have obtained reference standard samples of MDA, MDMA, N-ethyl and N,N-dimethyl-MDA and developed an HPLC procedure for their identification in clandestine drug samples. The amines were prepared via condensation of 3,4-methylenedioxyphenyl-2-propanone with the appropriate amine to yield the imine followed by in situ reduction to the desired amine using sodium cyanoborohydride.[8] Synthesis of the monoalkyl-MDA derivatives has been described in other recent reports.[7] The preparation of the tertiary amine N,N-dimethyl-MDA was accomplished using the same procedure. The ultraviolet absorption characteristics for N,N-dimethyl-MDA were quite similar to the secondary

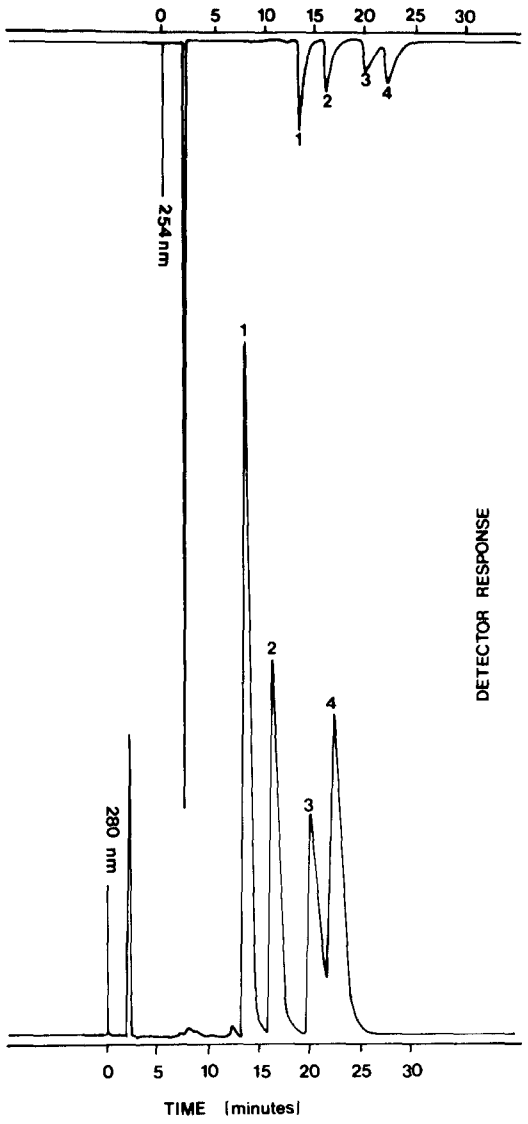


Figure 1. Reversed-phase liquid chromatographic separation of MDA and MDA-derivatives. a) 254 nm, b) 280 nm. Peaks: 1 = MDA; 2 = N-methyl-MDA; 3 = N,N-dimethyl-MDA; 4 = N-ethyl-MDA. Solvent system I.

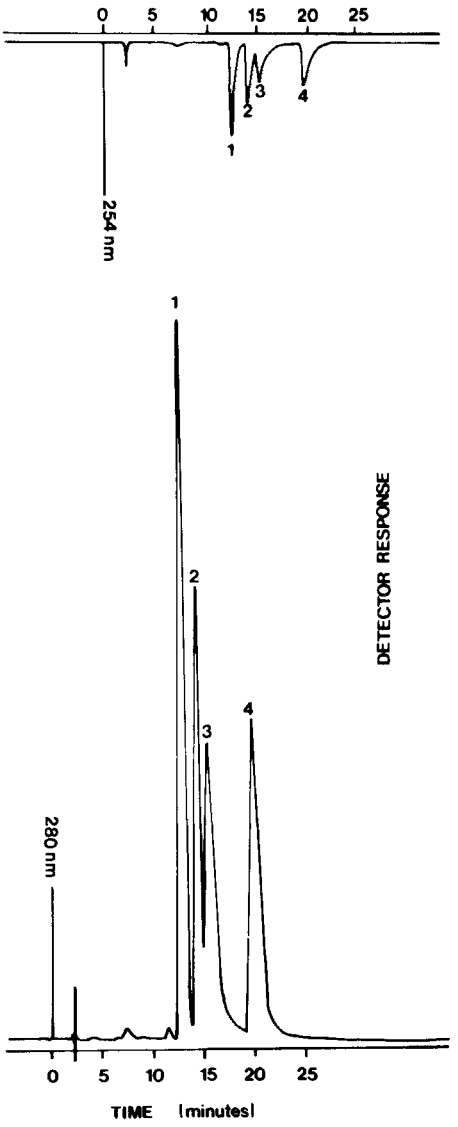


Figure 2. Reversed-phase liquid chromatographic separation of MDA and MDA-derivatives. a) 254 nm, b) 280 nm. Peaks: 1 = MDA; 2 = N-methyl-MDA; 3 = N,N-dimethyl-MDA; 4 = N-ethyl-MDA. Solvent system II.

amines with the major absorption bands occurring at 285 and 233 nm with the absorptivity slightly higher at the lower wavelength.

The liquid chromatographic separation of the MDA-derivatives was accomplished using reversed-phase techniques consisting of a C_{18} stationary phase with aqueous methanol mobile phases. Figure 1 shows the separation of the four amines using a mobile phase of pH 3 phosphate buffer, methanol and a low concentration of triethylamine (solvent system I). The low pH produces good peak shape and the resolution factor is less than one for only N,N-dimethyl and N-ethyl MDA (peaks 3 and 4). Figure 2 shows the chromatogram obtained for these compounds in a binary solvent system of pH 3 phosphate buffer and methanol (solvent system II). The major difference between the chromatograms in Figures 1 and 2 is the enhanced resolution of peaks 3 and 4 in Figure 2. These chromatograms were obtained using dual wavelength UV detection at 254 and 280 nm producing large peak area ratios (absorbance ratios) since these wavelengths are very close to the absorbance minimum and maximum respectively. These amines display similar UV absorption characteristics since the 3,4-methylenedioxyphenyl group is the major chromophoric moiety common to all these compounds.

In summary, the reported methods allow for the analysis of small N-alkyl derivatives of MDA in pharmaceutical samples.

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