Analusis, **1999**, *27*, 523-532

Identification of *N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), an homologue derivative of "ecstasy"

Ph. Baudot[1,*], A. Vicherat[2], M.-L. Viriot[1] and M.-C. Carré[1,3]

[1]*Département de Chimie Physique des Réactions (DCPR), UMR 7630 CNRS-INPL,*
École Nationale Supérieure des Industries Chimiques (ENSIC),
Institut National Polytechnique de Lorraine (INPL),
1 rue Grandville, BP. 451, 54001 Nancy Cedex, France
[2]*Service de RMN, ENSIC-INPL, France*
[3]*INSERM, Plateau de Brabois, 54505 Vandœuvre-les-Nancy, France*

Abstract. Some of the various *N*-substituted derivatives of the MDA have become popular drugs of abuse (MDMA, MDEA) in Europe and in France. With the increasing seizures of MBDB, [*N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine] a new homologue of MDMA and MDEA, forensic analysis of these controlled substances requires the use of powerful techniques to characterize them. Analysis by either high performance liquid chromatography (HPLC) or capillary gas chromatography (CGC) allows the separation of MDMA, MDEA, MBDB and EBDB. The isomers MDEA and MBDB are best differentiated by either nuclear magnetic resonance spectroscopy (^{1}H-NMR) or the combination of mass spectra (MS) and retention time (CGC). These techniques were successfully applied to seized tablets.

Key words. MBDB – EBDB – DRUGS – HPLC – CGC-MS – NMR – tablets.

Introduction

MDMA or "Ecstasy, Adam", [3,4-methylenedioxymethamphetamine] and MDEA (Eve), its ethyl derivative are synthetic drugs derived from MDA or [3,4-methylenedioxyamphetamine] that will be considered as the parent. All of these MDA derivatives used as recreational drugs have come to Europe and France from the United States and are extremely popular with certain young people, particularly in discos and rave-parties.

Some pharmacologists take the view that some psychopharmacological properties of *N*-substituted derivatives of MDA are sufficiently distinctive for them to be considered as a new class of psychoactive compounds, the Entactogens (Greek "en" = within or inside, "gen" = to produce or originate, Latin "tactus" = touch) [1]. There is some disagreement on this point within the scientific community. These compounds are popular with their users because of their stimulant effect on the central nervous system, their power to reduce inhibitions and to enhance empathy, and their mildly hallucinogenic properties. Due to their amphetamine-like structure (Tab. I), these molecules can exert harmful peripheral and central effects, such as hypertension, cardiac arrhythmia and malignant hyperthermia, and because of their hallucinogenic feature, they can give rise to psychic and neuropsychiatric complications [2,3]. Additionally, specific deleterious effects have been demonstrated in non-human primates for MDA and, to a lesser extent, other methylenedioxyamphetamines, consisting of a destruction of serotonin neurones; they are likely in man too. Therefore, though never studied so far, the consequences of long term exposure to these drugs might be severe. Finally, as for most psychotropic drugs, the users of these substances may develop a tolerance which leads them to take increasing doses [3]. Psychic dependence is potential with cyclic users and certain with heavy consumers [4].

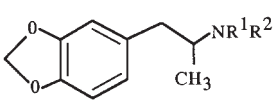
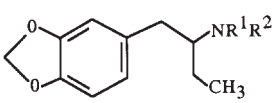
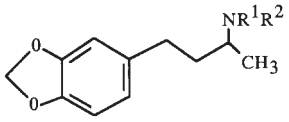
Analogues [1-(3,4-methylenedioxyphenyl)-propanamines, i.e. MDMA, MDEA, MDMMA, NOHMDA], and homologues [1-(3,4-methylenedioxyphenyl)-butanamines, e.g. MBDB] of MDA are regularly synthesized in an effort to evade the law, so that the latter needs to be constantly updated in order to keep pace. Increasing demand has fed to the development of a flourishing illicit market.

Hardly a week goes by without the press reporting large seizures (hundreds or even thousands tablets or capsules) of what is almost always described as "Ecstasy" [5]. MBDB is the latest arrival on the "illicit drugs market" and has only recently been prohibited in France (December 1996).

To combat clandestine synthesis, the starting materials such as 3,4-methylenedioxyphenyl-2-propanone, safrole, isosafrole and piperonal have been placed in Europe in the

*Correspondence and reprints.
Received December 29, 1998; revised March 03, 1999; accepted March 03, 1999.

Table I. Principal derivatives of MDA.

1-(3,4-methylene-dioxyphenyl)-2-propanamines 		*1-(3,4-methylene-dioxyphenyl)-2-butanamines* 		*1-(3,4-methylene-dioxyphenyl)-3-butanamines* 		*molar Mass (g/mol)*
MDA	$R^1 = R^2 = H$					179
MDMA	$R^1 = H$, $R^2 = CH_3$	MDP-2-B	$R^1 = R^2 = H$	MDP-3-B	$R^1 = R^2 = H$	193
NOHMDA	$R^1 = H$, $R^2 = OH$					195
MDEA	$R^1 = H$, $R^2 = C_2H_5$	MDP-2-MB = *MBDB*	$R^1 = H$, $R^2 = CH_3$	MDP-3-MB	$R^1 = H$, $R^2 = CH_3$	207
MDMMA	$R^1 = R^2 = CH_3$					207
		MDP-2-OHB	$R^1 = H$, $R^2 = OH$	MDP-3-OHB	$R^1 = H$, $R^2 = OH$	209
		MDP-2-EB = *EBDB*	$R^1 = H$, $R^2 = C_2H_5$	MDP-3-EB	R^1 H, $R^2 = C_2H_5$	221
		MDP-2-MMB	$R^1 = R^2 = CH_3$	MDP-3-MMB	$R^1 = R^2 = CH_3$	221

***Nomenclature and abbreviations** - For the designation of these compounds in the literature, two systems are found: (i) the first one, called trivial or common nomenclature (CN), based on the amphetamine moiety in their structure is obviously employed by physicians and toxicologists, because it recalls the psychoactive power of these drugs in man; (ii) the second one, based on the rules of the organic systematic nomenclature is used by chemists (SN).

Common and systematic nomenclatures are in *italic* and in roman types respectively:
MDMA: 3,4-methylenedioxymethamphetamine or N-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine or N-methyl-1-(1,3-benzodioxol-5-yl)-2-propanamine.
MDEA: 3,4-methylenedioxyethamphetamine or N-ethyl-1-(3,4-methylenedioxyphenyl)-2-propanamine or N-ethyl-1-(1,3-benzodioxol-5yl)-2-propanamine.
MDMMA: N-methyl-1-(3,4-methylenedioxymethamphetamine) or N-dimethyl-1-(3,4-methylenedioxyphenyl)-2-propanamine or N-dimethyl-1-(1,3-benzodioxol-5-yl)-2-propanamine.
NOHMDA: N-hydroxy-1-(3,4-methylenedioxyamphetamine) or N-hydroxy-1-(1,3-benzodioxol-5-yl)-2-propanamine.
MDP-2-MB: N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine or (MBDB) N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine.
MDP-2-EB: N-ethyl-1-(3,4-methylenedioxyphenyl)-2-butanamine or (EBDB) N-ethyl-1-(1,3-benzodioxol-5yl)-2-butanamine.

first category of "chemical precursors of narcotics or psychotropic substances" [6a-c]. Nevertheless, these common substances (used notably in perfume manufacture) can arrive illicitly from inside and outside the EEC, from Asia and elsewhere.

Analytical methods used for the screening and confirmation of methylenedioxyamphetamines include radioimmunoassays [7,8], fluorescence polarization immunoassays [8-11], enzyme immunoassays [8-10,12-14], thin-layer chromatography [8,15,16]. And the toxicologist is called upon, therefore, to put to work the most powerful analytical techniques to separate by high performance liquid chromatography [8,16-27,29,30], or gas chromatography [8,11,19,21,23-27,29-34] and identify by mass spectrometry [8,11,19,21,23-34], or nuclear magnetic resonance [17,19,32,35] these various "designer amphetamines". In this article, we shall present the results we have obtained using pure MBDB or EBDB, in the presence of MDMA and MDEA. These latter two substances (on which we have already worked [32]) are those which are the most frequently met with in the illicit drugs market. We shall also give results obtained on confiscated tablets. We investigated the ethyl derivative of MBDB, EBDB, which is a likely target of "drug designers" in France since its use is not yet prohibited. Its effects and toxic properties are unknown and its physico-chemical properties have been little studied [24].

The techniques used were high performance liquid chromatography (HPLC), capillary gas chromatography (CGC) coupled with mass spectrometry (MS) or nuclear magnetic resonance (NMR).

Experimental

Standards and chemicals used

MDMA hydrochloride (Sigma-Aldrich®).

MDEA hydrochloride obtained by extraction [19a] of a batch of seized tablets which had been previously analyzed [32].

MBDB hydrochloride synthesized in our laboratory (with ministerial permission).

EBDB hydrochloride synthesized in our laboratory.

Acetonitrile gradient grade LIChrosolv® Merck.

Methanol spectrosol sds®.

Chloroform D, CEA France.

All other reagents were analytical grade.

Seized sample: batch M; round, slightly biconvex tablets [diameter = 0.8 cm; thickness = 0.57 cm; average weight = 282.4 mg (275–289 mg)]. Appearance: off white with a few small grey speckles and no distinguishing marks nor inscription.

Standard and working solutions

For HPLC - A quaternary mixed standard working solution was prepared by adding the four compounds as hydrochloride (MDMA: 4.2 mg/mL; MDEA: 3.7 mg/mL; MBDB: 4.1 mg/mL; and EBDB: 2.7 mg/mL) in methanol. Further, this solution was diluted by one fifteenth in methanol, degassed by ultrasonication and used for carrying out the chromatographic separation of the derivatives.

For each compound (i.e. respectively MDMA, MDEA, MBDB and EBDB hydrochloride), a working standard solutions (≅ 2 mg/mL in methanol) was prepared, and its corresponding daughter solution was obtained by a one fifteenth dilution in methanol and finally degassed by ultrasonication and injected into the chromatograph for peak identification.

Solid samples (batch M): solid tablets were ground to a powder and dissolved in hydrochloric acid. Any insoluble materials were removed by filtration and the aqueous solution was then extracted by a classical toxicological procedure [19,36] and the base converted into hydrochloride form [19]. This purification of "street samples" is useful to protect the HPLC column, but not necessary when a system such a precolumn is employed.

For CGC-MS - S*tandard and working solutions* were prepared with the same protocol as for the HPLC, except that the new quaternary mixed standard working solution was prepared with the following concentrations (MDMA: 4 mg/mL; MDEA: 3.8 mg/mL; MBDB: 4.5 mg/mL; and EBDB: 3.5 mg/mL).

Solid samples (batch M): solid tablets were ground to a powder and an aliquot dissolved in 1 mL methanol. After filtration, 0.5 µL was injected and analyzed by CGC-MS using the same procedure as the standards.

For NMR - Stock solutions: deuterochloroform ($CDCl_3$) solutions (≅ 10^{-2}mol L^{-1}) of each compound (MDMA, MDEA, MBDB or EBDB hydrochlorides) were prepared.

Solid samples (batch M): solid tablets were ground to a powder and a few mg were dissolved and sonicated for 5 seconds in 500 µL deuterochloroform. After filtration through a cotton plug in the mouth of a Pasteur pipette, the deuterated filtrate was collected directly in the usual 5 mm i.d. NMR tube (the concentration of the active principle should be about 10^{-2}mol L^{-1}).

High Performance Liquid Chromatography (HPLC)

The Liquid Chromatograph consisted of a Shimadzu® LC-10AS pump, a Shimadzu® SPD-10A ultraviolet (UV) detector, a Chromjet Spectra-Physics® integrator, and an IPC Intellscan® computer running the BOREAL software for analysis of HPLC data.

The analytical reversed phase column (250 mm × 4.6 mm i.d.) was packed with a C_{18}, 5 µm particle size stationary phase Kromasil 100 (Touzart & Matignon® Ref. 18651255).

The mobile phase consisted of a linear gradient of acetonitrile (from 5% to 80% in 25 min) in 0.1 M aqueous triethylammonium acetate pH 7.3. The UV absorbance detector was operated at 280 nm and 0.05 absorbance units full scale (AUFS). The separations were accomplished at a flow rate of 1 mL/min and at ambient temperature.

Capillary Gas Chromatography-Mass Spectrometry (CGC-MS)

The CGC-MS analysis was carried out using a Hewlett-Packard® HP G1800A GCD system which consists of a gas chromatograph and an electron ionization detector (EID). The instrument is controlled by a data system that consists of an HP Vectra 486 personal computer. Chromatographic separation was achieved on a 60 m × 0.323 mm i.d. fused silica capillary column Alltech AT-1 (100% dimethylpolysiloxane; film thickness 0.25 µm; Ref. 13668). The injector was used in the splitless mode at 250 °C and the gas-chromatograph oven temperature was programmed as follows: initial temperature 100 °C for 1 min; temperature program rate 30 °C/min to 300 °C; and this temperature was maintained for 12 min. Helium was used as the carrier gas at a flow rate of 2 mL/min. The detector (EID) operated in the electron impact mode with the ion source temperature set at 250 °C, the ionization voltage at 70 eV and the mass spectrometer (quadrupole) used in the scan mode.

Nuclear Magnetic Resonance (NMR)

Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded as the hydrochloride salts using a Bruker® DRX 400 Fourier Transform (400 MHz NMR) equipped with a 5 mm probe and running in pulse mode (with a 15 ppm spectral width and 16 K data size). A zero filling of 2 allows to obtain a 0.18 Hz/point for digital resolution. A 30° flip angle (pulse width ≅ 3 µs) and a 4 s relaxation time allow the integration of bands for a relative value quantification.

Samples were dissolved in deuterochloroform (99.8 %), and tetramethylsilane served as the reference.

Results and discussion

High Performance Liquid Chromatography

For the qualitative analysis, a sample loop of 20 µL is used for each injection. The mobile phase is composed of pH 7.3 acetate buffer/acetonitrile (linear gradient of CH_3CN). We chose a mobile phase about that of Rop to separate MDMA and MDEA [25]. Moreover, the presence of triethylamine in our solvent avoids the peak tailing of amines. The separation of the quaternary standard solution (MDMA, MDEA, MBDB and EBDB) is very efficient (Fig. 1), and the retention times ($t_{R\ MDMA}$ = 12.26 min; $t_{R\ MDEA}$ = 13.13 min; $t_{R\ MBDB}$ = 14.07 min; $t_{R\ EBDB}$ = 15.40 min) are next to the results of Rop [25]. UV detection wavelength was set at 280 nm for all these amines, because the 3,4-methylenedioxyphenyl group is the major common chromophoric unit with high absorptivity. Finally, our method gave good results, the separation of amines was well resolved with good symetrical peak shape and the retention times were quite similar to those obtained by other authors with an acidic mobile phase and deactivated C_{18} column [16,17,21,26,34].

The analysis of seized tablets (batch M) using High Performance Liquid Chromatography shows a single peak having the same elution time as pure MBDB. This result was confirmed by CGC-MS analysis.

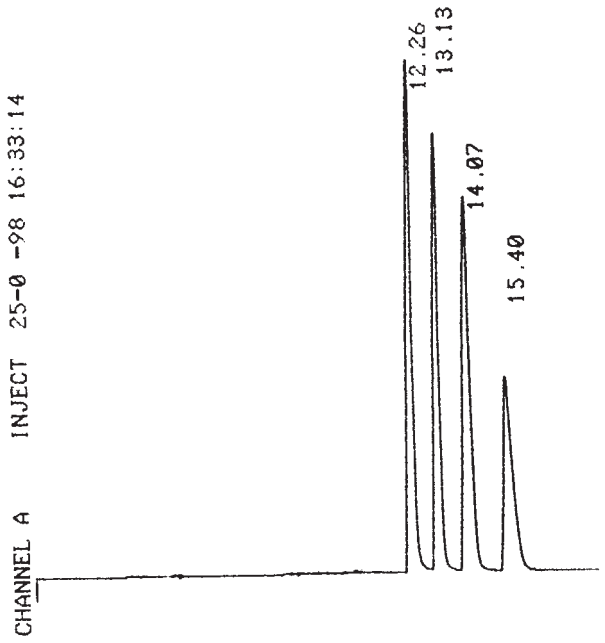


Fig 1. HPLC separation for a quaternary mixed solution in methanol of MDMA/MDEA/MBDB/EBDB hydrochloride salts.

CGC-MS procedure

The selectivity of the procedure was tested by injecting 0.5 µL of the pure solution of each compound at first and then the quaternary standard solution (MDMA, MDEA, MBDB and EBDB). A typical chromatogram is shown in figure 2 and presents rapid separation and good resolution. Figures 3A, 3B and 3C show the corresponding electron impact mass spectra of MDEA, MBDB and EBDB. The electron impact mass spectra obtained for MDMA and MDEA fit those described in a previous report on the one hand [32], and in the literature on the other hand [19a,21,25,31].

Table II gives a summary analysis of the mass spectral fragmentation of these derivatives. For MDMA and EBDB (Fig. 3C), the base peak and some other fragments are sufficient to easily characterize these two molecules which are

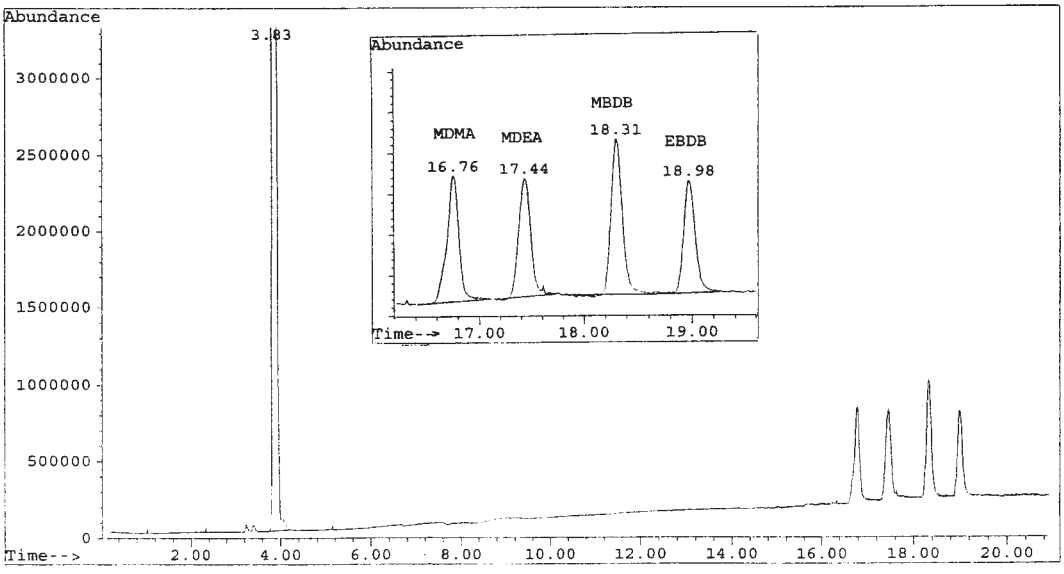
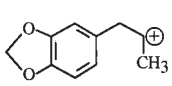
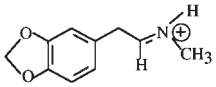
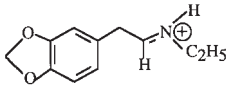
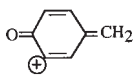
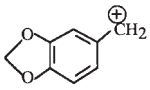
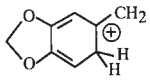


Fig 2. Gas chromatogram for a quaternary mixed solution in methanol of MDMA/MDEA/MBDB/EBDB hydrochloride salts.

Table II. Main fragments resulting from electron-impact mass fragmentation of MDMA, MDEA, MBDB and EBDB (by CG coupling SM).

	[1-(3,4-methylene-dioxyphenyl)-2-propanamine] derivatives		*[1-(3,4-methylene-dioxyphenyl)-2-butanamine] derivatives*	
molecular peak*	MDMA 193	MDEA 207	MBDB 207	EBDB 221
base peak	58 CH_3-CH=$\overset{+}{N}$H-CH_3	72 CH_3-CH=$\overset{+}{N}$H-C_2H_5	72 CH_3-CH_2-CH=$\overset{+}{N}$H-CH_3	86 CH_3-CH_2-CH=$\overset{+}{N}$H-C
other peaks	42 163  178	44 163  192	57 178 	192
common peaks	77 	105# 	135 	136 

*The molecular peak can be small.
Structure for this peak proposed by Dal Cason [19a].

already well-separated by gas-chromatography ($t_{R\ MDMA}$ = 16.76 min; $t_{R\ EBDB}$ = 18.98 min). The mass spectrum of the MBDB (Fig. 3B) is similar to that of the isomeric propanamine MDEA (Fig. 3A). The molecular ion occurs at *m/z* 207 and is of very low abundance. The base peaks of the two compounds are the cleavage products at *m/z* 72, resulting from amine dominated loss of the 3,4-methylene-dioxybenzyl radical. These base peaks appearing at $(M - 135)^+$ are the isomeric immonium ions 72, the structure of which varies among the molecules. A further characteristic of this class of compounds is a peak at *m/z* 135, which corresponds to a methylenedioxybenzyl cation and the hydrogen-rearranged radical cation at 136. Nevertheless some differences in their mass spectra allow differentiation. The MDEA spectrum shows a peak at *m/z* 44, by the well-known rearrangement loss of ethylene at quaternary nitrogen atom of the immonium ion 72 (base peak). For MBDB a peak at *m/z* 57 appears, caused by a single methyl loss. Some other small peaks at *m/z* 163 and 192 appear in the MDEA mass spectrum (Fig. 3A). In contrast to MDEA, the mass spectrum of MBDB shows a $(M - 29)^+$ peak at *m/z* 178 which can be explained by an alternative cleavage reaction with loss of the ethyl group (Fig. 3B and Tab. II) [24]. Despite everything, their differentiation poses no problem because their CGC retention times provide the additional distinguishing parameter (Fig. 2: $t_{R\ MDEA}$ = 17.44 min and $t_{R\ MBDB}$ = 18.31 min).

We found finally that the extract from the seized tablets was indeed MBDB (the retention time and mass spectrum of the only peak are the same as standard MBDB: figure not shown).

Nuclear magnetic resonance

For forensic drug analysis, results must be confirmed by a completely different technique. We chose nuclear magnetic resonance (NMR) which is (i) a powerful tool for structural analysis, (ii) very useful for identifying variations in molecular structure from a parent molecule (designer drugs) and (iii) very useful for isomeric differentiation [37]. The methodology is very simple, rapid, and becomes more and more used in the analysis of pharmaceutical and illicit drug preparations [35]. MDA and its *N*-substituted analogues and homologues can be easily and unequivocally differentiated by NMR [19,32,35].

The 400 MHz FT-^{1}H-NMR spectra of MBDB and EBDB hydrochlorides and an extract of powdered seized tablet (batch M) were recorded. All are of good quality and the

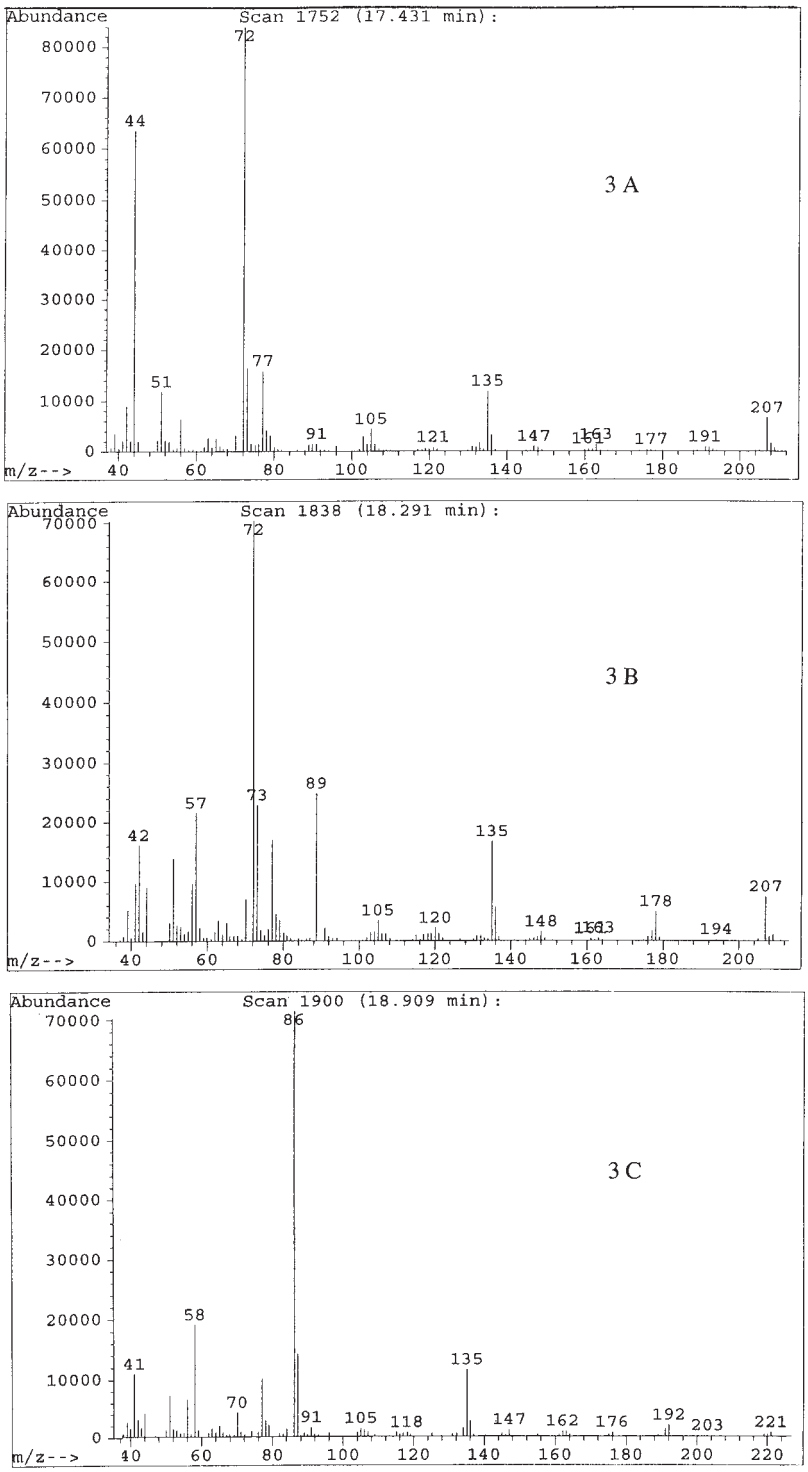
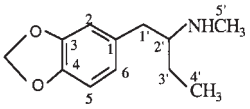
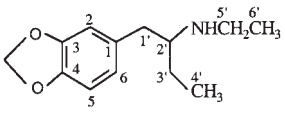


Fig 3. Corresponding electron-impact mass spectra (GC-MS) for MDEA (3A), MBDB (3B) and EBDB (3C).

splitting patterns of MBDB and EBDB NMR spectra are typical:

- the spectra of the MDA derivatives remain essentially the same from analogue to analogue or homologue in the lower field resonances, and show a complex signal in the 6.6 to 6.8 ppm range resulting from three aromatic protons (**H**-2, **H**-5, **H**-6) and a singlet at 5.90 to 5.95 ppm characteristic of methylenedioxy protons (O-C**H**$_2$-O); The protonated amine group forms a broad singlet at 9.45–9.50 ppm (this broadening is due to the fast chemical exchange between the "acidic" proton and water). The singlet at 7.3 ppm is the residual signal of chloroform because $CDCl_3$ is only 99.8% deuterated;

Table III. Chemical shifts (ppm), splitting patterns and coupling constants from 400-MHz FT-1H-NMR spectra of MBDB and EBDB hydrochlorides in $CDCl_3$.

MBDB			*EBDB*		
					
Proton(s)	δ (ppm)	*J* (Hz)	Proton(s)	δ (ppm)	*J* (Hz)
NH^+	9.50 bs		NH^+	9.45 bs*	3.9 = $^3J_{NH^+5'}$
H5	6.75 d (ABC)	7.6 = $^3J_{H_5H_6}$	H5 H2		
H2	6.73 d (ABC)	1.5 = $^4J_{H_2H_6}$	H6	6.74 s**	
H6	6.72 dd (ABC)	7.6 and 1.5			
O-CH^2-O	5.94 s		O-CH^2-O	5.94 s	
1'a	3.23 dd	13.5 = $^2J_{1'a1'b}$ 5.1 = $^3J_{1'a2'}$	1'a	3.32 dd	13.7 = $^2J_{1'a1'b}$ 4.9 = $^3J_{1'a2'}$
2'	3.16 tdd	8.8 = $^3J_{2'1'b}$ 5.5 = $^3J_{2'3'}$ 5.1 = $^3J_{2'1'a}$	2'	3.20 tdd	9.0 = $^3J_{2'1'b}$ 5.2 = $^3J_{2'3'}$ 4.9 = $^3J_{2'1'a}$
			5'	3.00 dq	7.1 = $^3J_{5'6'}$ 3.9 = $^3J_{5'NH^+}$
1'b	2.87 dd	13.5 8.8	1'b	2.91 dd	13.7 = $^2J_{1'b1'a}$ 9.0 = $^3J_{1'b2'}$
5'	2.64 s				
3'	1.77 dq	7.6 = $^3J_{3'4'}$ 5.5 = $^3J_{3'2'}$	3'	1.79 dq	7.4 = $^3J_{3'4'}$ 5.2 = $^3J_{3'2'}$
			6'	1.49 t	7.1 = $^3J_{6'5'}$
4'	1.08 t	7.6 = $^3J_{4'3'}$	4'	1.07 t	7.4 = $^3J_{4'3'}$

Legend: s=singlet, bs=broad singlet, t=triplet, q=quadruplet.
* NH^+ reduces the rate of exchanges and induces a coupling.
** singlet apparently (cf. p. 165 in Ref. [37]), but second order spectrum (ABC) with J/ν_o δ >> 1.

- for the other peaks, table III gives proton assignments according to chemical shifts (δ) for each of the ecstasy analogues (the integrated proton numbers are not shown, but they are in agreement with the expected values).

- Due to their common structure, there are certain likenesses between the 400 MHz FT-^{1}H-NMR spectra of MBDB (Fig. 4) and EBDB (Fig. 5), but also some characteristic differences due to *N*-substitutions: for MBDB, the singlet of N-C**H$_3$** at 2.64 ppm and for EBDB the triplet of N-CH_2-**CH_3** at 1.49 ppm and the multiplet of N-**CH_2**-CH_3 at 3.00 ppm.

- It is also interesting to compare the FT-^{1}H-NMR spectrum of MBDB to its isomeric compound MDEA (previously published [32]). They share some common points linked to their molecular structure (cf. table I), but also some fundamental differences related to the position of the ethyl group. A characteristic (N-CH_2-C**H$_3$**) triplet appears at 1.54 ppm when the ethyl group is positioned on the N atom in MDEA [32], and another triplet (CH-CH_2-C**H$_3$**) at 1.08 ppm when the ethyl group is attached to the carbon chain in MBDB.

- Finally, the 400 MHz FT-^{1}H-NMR spectrum of the extract from the batch M is identical with that of the standard

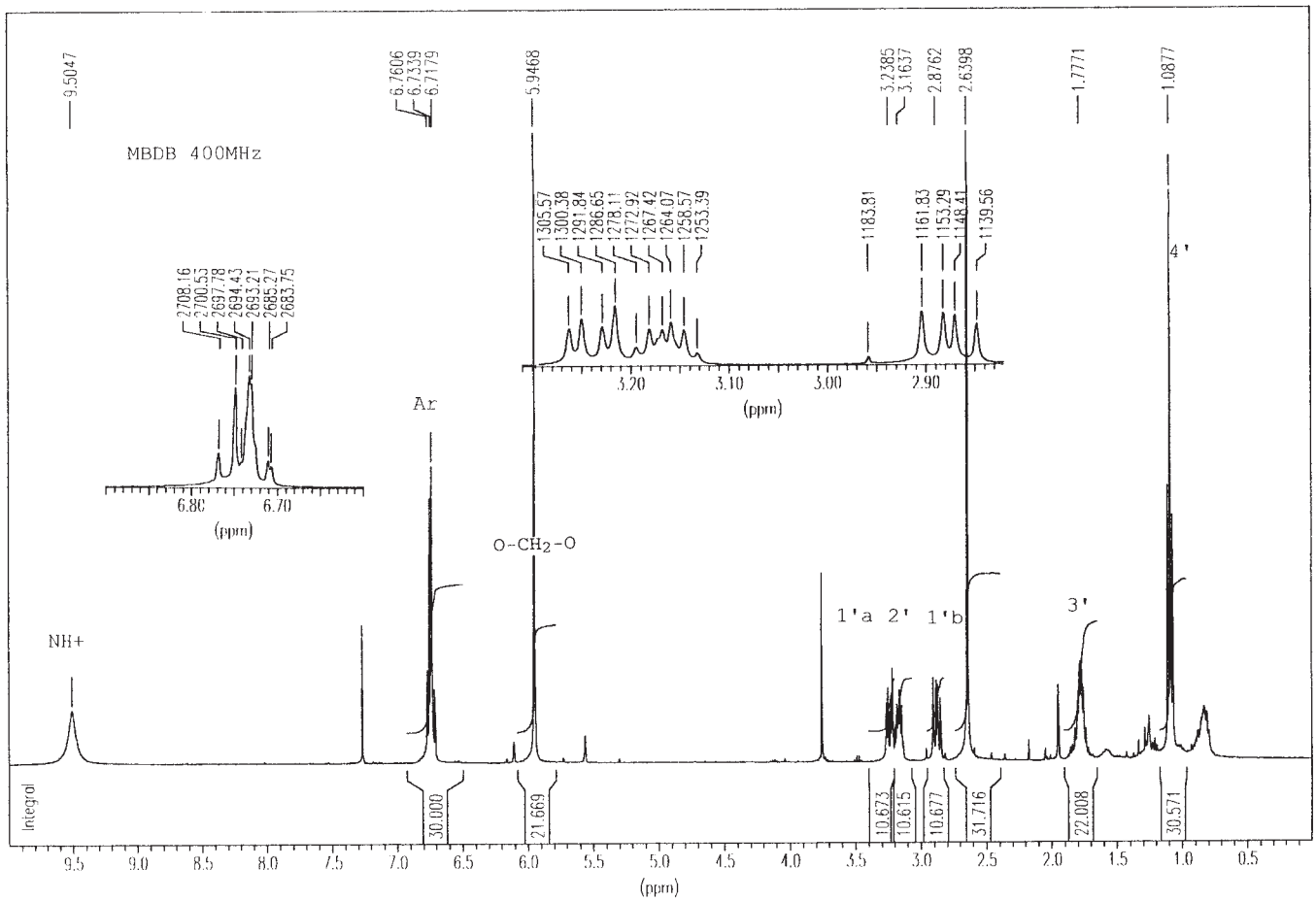


Fig 4. 400-MHz FT-^{1}H-NMR spectrum for MBDB hydrochloride in $CDCl_3$.

MBDB sample and this corroborates the previous results obtained in CGC-MS.

Conclusion

Separation of MDA derivatives (MDMA, MDEA, MBDB and EBDB) by HPLC is efficient with the column and solvents we used. For GC analysis, it is essential to use high performance capillary columns to separate MDA derivatives with very similar structures (such as the two isomers MDEA and MBDB) and detection/identification is then carried out by coupling to a mass spectrometer. Even if the mass spectrum of MBDB is somewhat similar to that of the isomeric propanamine MDEA, nevertheless differences in their mass spectra allow differentiation and their CGC retention times provide an additional distinguishing parameter.

The legal context in which such analyses are likely to be used demands that their results be checked using a totally different method such as NMR. MDA and its N-substituted analogues and homologues can be easily and unequivocally differentiated by NMR. This has now become a routine technique which allows determination of the exact structure of the isomer present. Analysis of a batch of seized tablets using all the above-described techniques (HPLC, CGC-MS, NMR) showed that they were practically pure MBDB.

Acknowledgments

We would like to thank Delphine Debove for her contribution in syntheses and Patrick Berroy and Christophe Lombard for assistance in HPLC and CGC analyses respectively.

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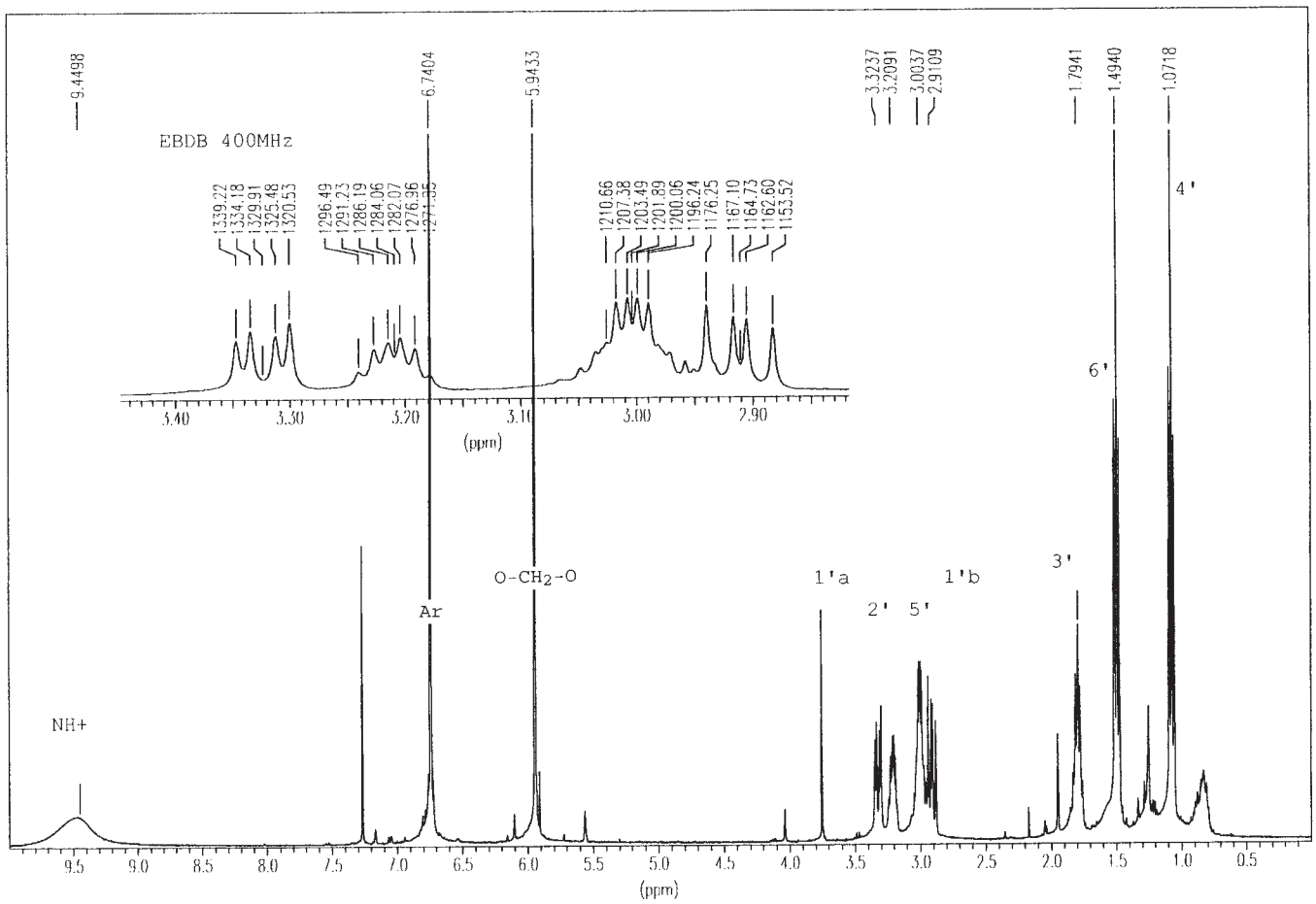

Fig 5. 400-MHz FT-^{1}H-NMR spectrum for EBDB hydrochloride in $CDCl_3$.

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