Methiopropamine: An Analytical Profile

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ABSTRACT: Spectroscopic and chromatographic data are provided for methiopropamine, an internet-available compound, possessing CNS stimulant properties. Analytical data (infrared spectroscopy, mass spectrometry, and proton/carbon nuclear magnetic resonance spectroscopy) are presented for methiopropamine and its synthetic intermediates.

KEYWORDS: methiopropamine, 1-(thiophen-2-yl)-2-methylaminopropane, methamphetamine analog, designer drugs, chemical analysis, forensic chemistry.

Methiopropamine (Figure 1) is currently one of many internet-available compounds sold as "legal highs." The IUPAC name for methiopropamine is 1-(thiophen-2-yl)-2-methylaminopropane. Although it is claimed to be legal, it is a 2-thienyl analog of the Schedule II controlled substance, methamphetamine, and may be controlled within the United States [1]. Methiopropamine was first synthesized in 1942 to compare its pharmacological properties with phenyl-related derivatives [2]. An analytical profile of methiopropamine is presented to assist forensic chemists who may encounter this substance in casework. Mass spectra of two synthetic intermediates are also given.

Experimental

Chemical, Materials, and Reagents

All solvents were distilled-in-glass products of Burdick and Jackson Labs (Muskegon, MI, USA). All other chemicals were of reagent-grade quality and products of Aldrich Chemical (Milwaukee, WI).

Synthesis

In accordance with Journal policy, exact synthesis details are not provided. The procedure of Blicke and Burckhalter [2] was utilized (Figure 2).

Infrared Spectroscopy (FTIR)

Infrared spectra were obtained on a Thermo-Nicolet Nexus 670 FTIR equipped with a single bounce attenuated total reflectance (ATR) accessory. Instrument parameters were: resolution = 4 cm^{-1}; gain = 8; optical velocity = 0.4747; aperture = 150; and scans/sample = 16.

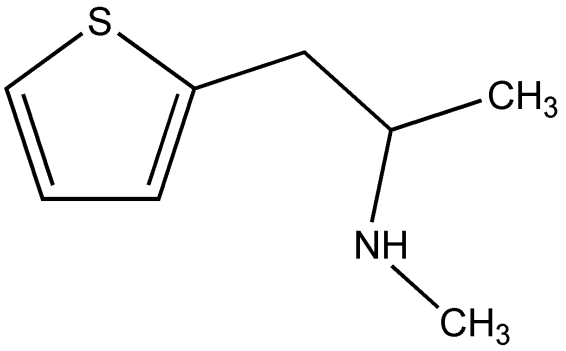


Figure 1 - Structural formula of methiopropamine.

Gas Chromatography/Mass Spectrometry (GC/MS)

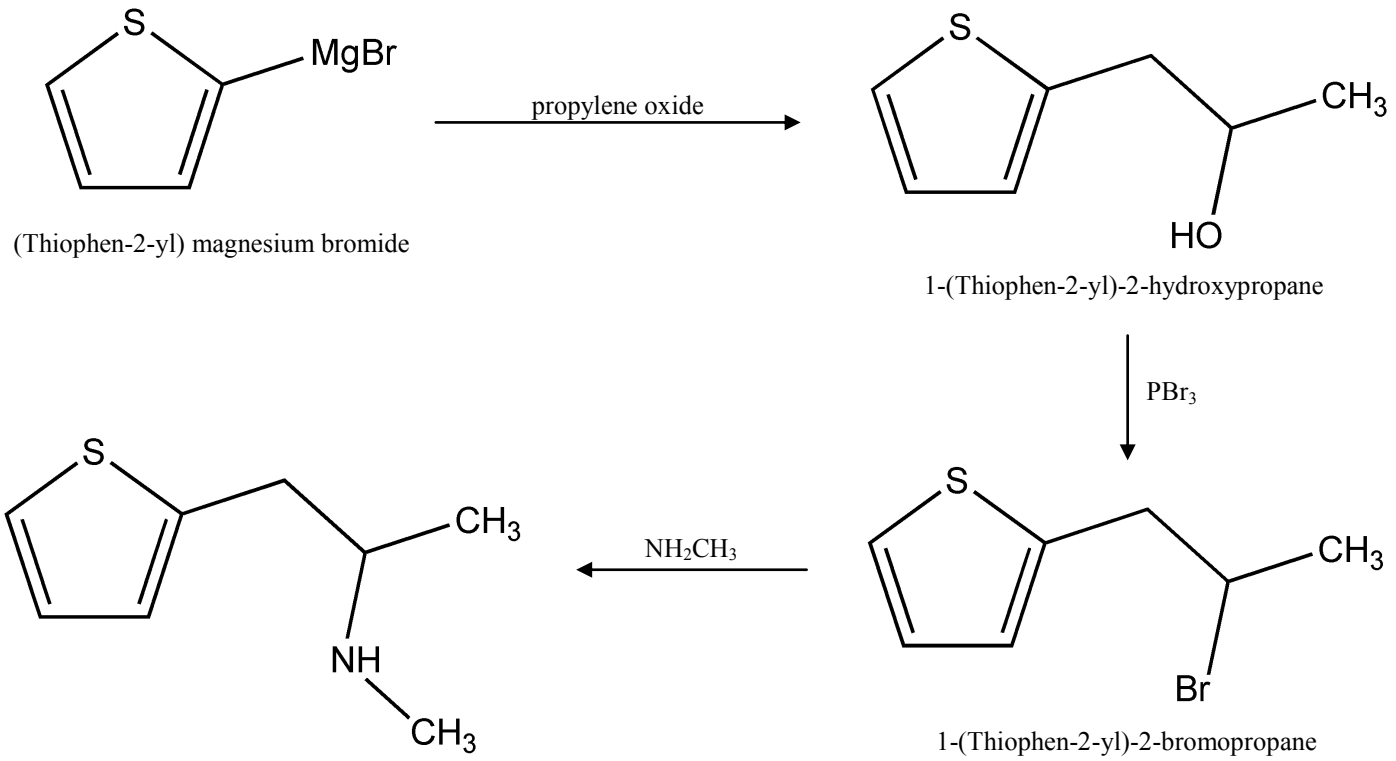
Mass spectra were obtained on an Agilent Model 5975C quadrupole mass-selective detector (MSD) that was interfaced with an Agilent Model 7890A gas chromatograph (GC). The MSD was operated in the electron ionization (EI) mode with an ionization potential of 70 eV, a scan range of 34-600 amu, and at a scan rate of 2.59 scans/s. The GC was fitted with a 30 m x 0.25 mm ID fused-silica capillary column coated with 0.25 μm 100% dimethylpolysiloxane, DB-1 (J & W Scientific, Rancho Cordova, CA). The oven temperature was programmed as follows: initial temperature, 100°C; initial hold, 0.0 min; program rate, 6°C/min; final temperature, 300°C; final hold, 5.67 min. The injector was operated in the split mode (21.5:1) at 280°C. The MSD source was operated at 230°C.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Proton (^{1}H), carbon (^{13}C), and 2-dimensional NMR spectra were obtained on an Agilent VNMRS 600 MHz NMR using a 5 mm Protune broad band detection, variable temperature, pulse field gradient probe (Agilent, Palo Alto, CA). Samples were dissolved in deuterochloroform ($CDCl_3$) containing 0.03% v/v tetramethylsilane (TMS) as the 0 ppm reference compound. The sample temperature was maintained at 26°C. Standard Agilent pulse sequences were used to acquire ^{1}H, proton-decoupled ^{13}C, and gradient versions of HSQC and HMBC spectra. Data processing was performed using software from Agilent and Applied Chemistry Development (ACD/Labs, Toronto, Canada). Structure elucidation and the prediction of ^{1}H and ^{13}C spectra was accomplished using ACD/Labs software.

Discussion

The FTIR spectrum of methiopropamine HCl (Figure 3) displays absorbances (2400-2800 cm^{-1}) which are consistent with a secondary amine HCl ion-pair and significant aliphatic CH absorbance in the region of 2800-3000 cm^{-1}. The 500-1500 cm^{-1} region is peak (band) enriched for discriminative purposes.



(Thiophen-2-yl) magnesium bromide

1-(Thiophen-2-yl)-2-hydroxypropane

1-(Thiophen-2-yl)-2-bromopropane

1-(Thiophen-2-yl)-2-methylaminopropane

Figure 2 - Synthetic route for methiopropamine.

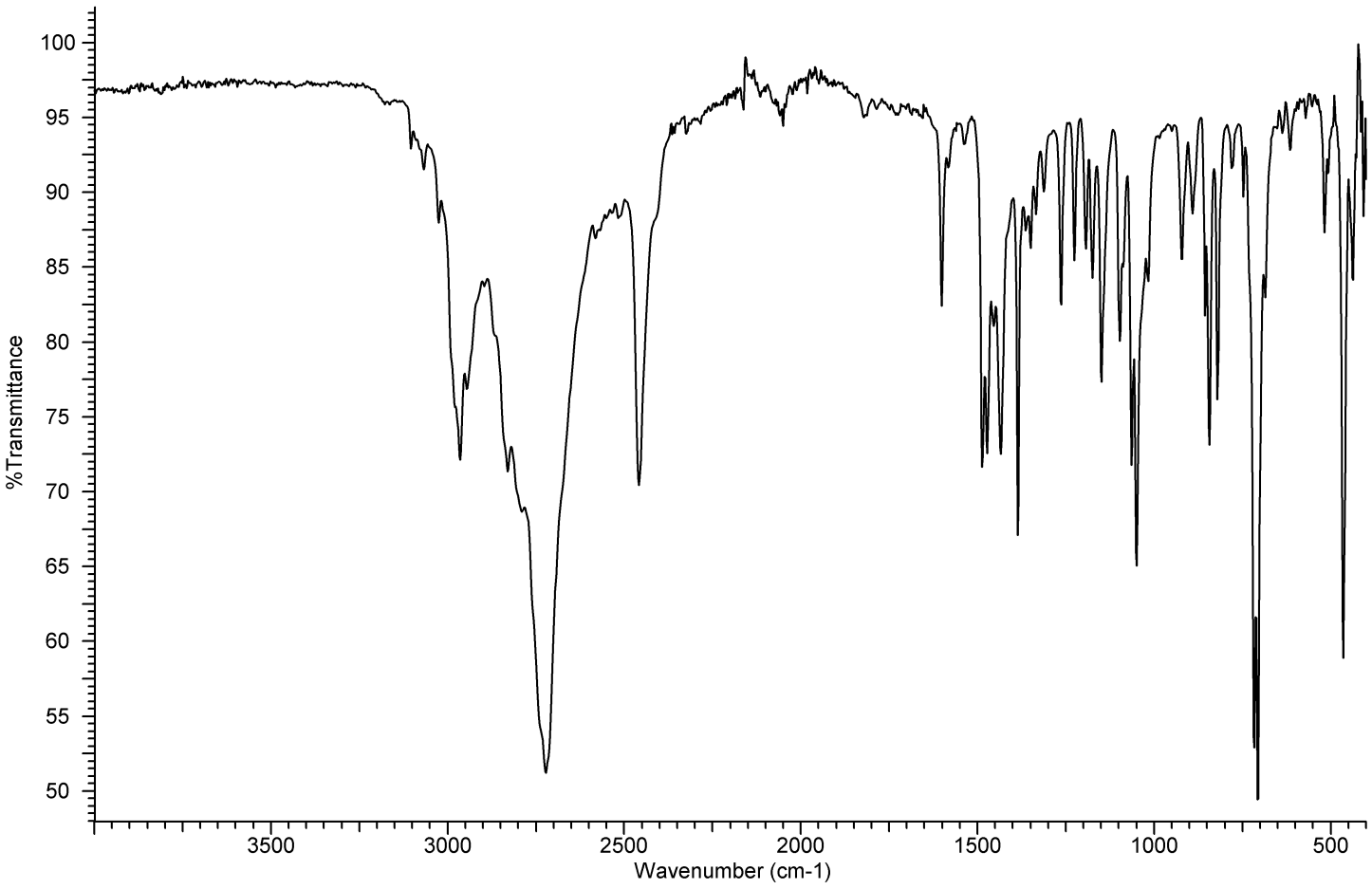


Figure 3 - Infrared spectrum of methiopropamine HCl.

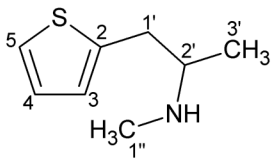
Position	Carbon (ppm)	Proton (ppm, J)	Structure
2	137.6	-	
3	127.0	6.93 (d, 3.5 Hz)	
4	127.3	6.96 (dd, 4.7, 3.5 Hz)	
5	125.0	7.20 (d, 4.7 Hz)	
1'	33.5	3.18 (dd, 14.5, 10.3 Hz), 3.62 (dd, 14.5, 4.1 Hz)	
2'	57.2	3.34 (dqd, 10.3, 7.0, 4.1 Hz)	
3'	15.8	1.43 (d, 7.0 Hz)	
1"	30.3	2.71 (t, 5.6 Hz)	
amine	-	9.75 (bs)	

Figure 4 - ^{1}H and ^{13}C NMR spectra and associated data for methiopropamine HCl in $CDCl_3$. Proton abbreviations: bs = broad singlet, d = doublet, q = quartet, t = triplet.

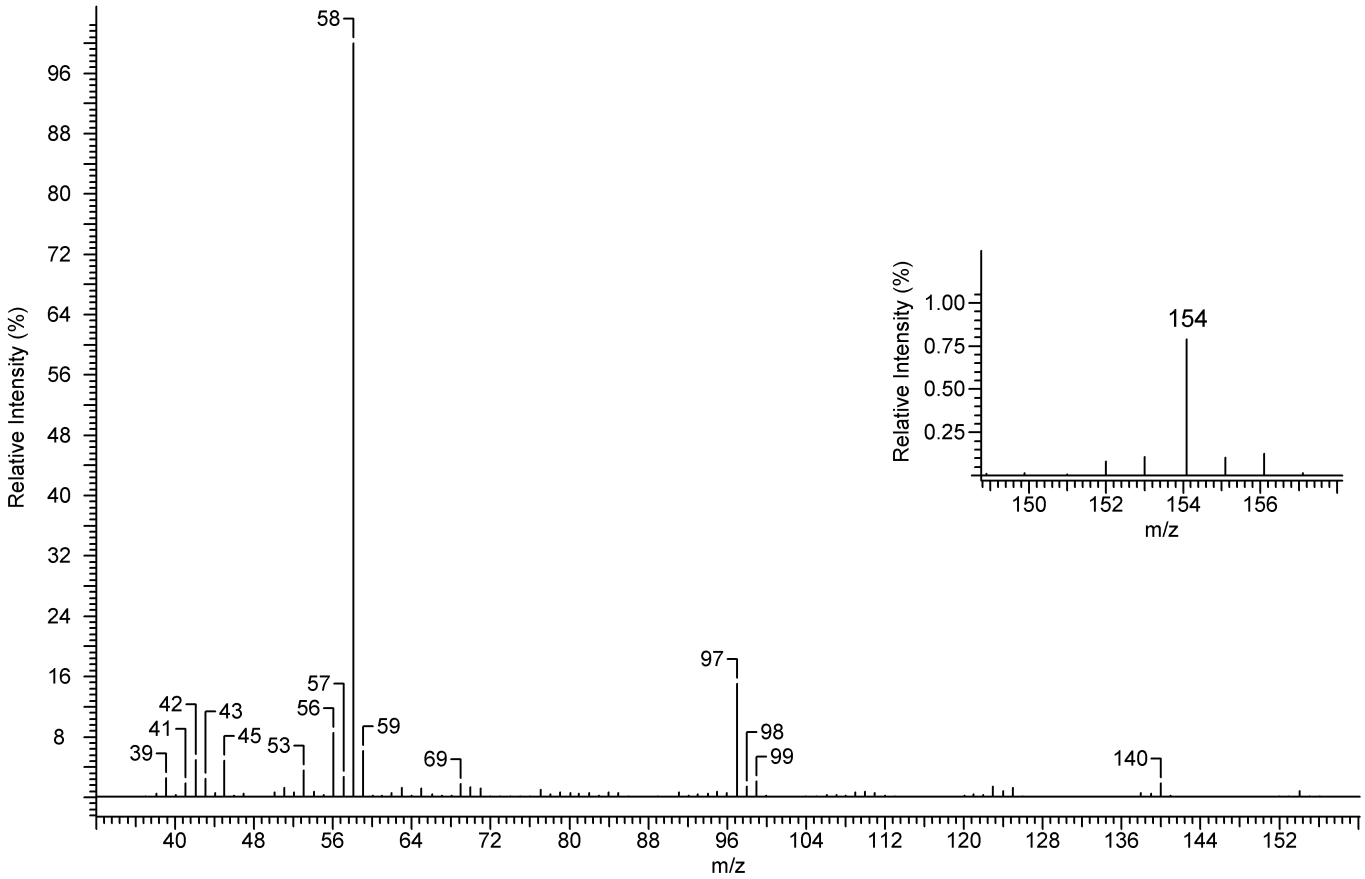


Figure 5 - Electron ionization mass spectrum of methiopropamine.

Table 1 - Gas chromatographic retention times (R_t) for the methiopropamine and related compounds[a].

Compound	R_t (min)
1-(Thiophen-2-yl)-2-hydroxypropane	4.21
1-(Thiophen-2-yl)-2-methylaminopropane	5.00
Methamphetamine	5.01
1-(Thiophen-3-yl)-2-methylaminopropane[b]	5.15
1-(Thiophen-2-yl)-2-bromopropane	5.62

[a]Conditions given in the experimental section.
[b]Tentatively characterized.

The ^{1}H and ^{13}C spectra and the assignment table are found in Figure 4. A substituted propyl chain (CH_3-CH-CH_2-) is clearly indicated by the methyl proton doublet at 1.43 ppm, methine multiplet at 3.34 ppm, and methylene non-equivalent protons at 3.18 and 3.62 ppm (both doublet of doublets). The methine proton chemical shift of 3.34 ppm and carbon of 57.2 ppm indicates it is bonded to nitrogen and not the aromatic ring. The aromatic proton splitting patterns and coupling constants represent a continuous CH=CH-CH= chain, requiring substitution at C-2. The N-methyl protons are a triplet due to coupling with the two amine hydrogens (this is the HCl salt).

The mass spectrum of methiopropamine (Figure 5) is fragment ion rich, however most ions are at low abundance. Two prominent mass fragments are produced at *m/z* 58 (base peak) and *m/z* 97, respectively. The ion at *m/z* 97 is from rearrangement of the 2-alkylthiophen moiety to give the thiopyrilium ion $C_5H_5S^+$ [3]. Although a molecular ion is not observed, an M-1 ion at *m/z* 154 is produced (analogous to the M-1 ion for methamphetamine). The mass spectra for the intermediates 1-(thiophen-2-yl)-2-hydroxypropane and 1-(thiophen-2-yl)-2-bromopropane are illustrated in Figure 6.

Prior to recrystallization of the final methiopropamine HCl product, a minor compound with slightly different chemical shifts was detected by proton NMR. One of the aromatic protons was a broad singlet, indicating that substitution was at C-3. The mass spectrum of this compound was virtually identical to that of methiopropamine, with a slightly later retention time (Table 1). It was tentatively characterized as the positional isomer 1-(thiophen-3-yl)-2-aminopropane; i.e., with the 2-methylaminopropane group at the 3 position of the thiophene ring. It should be noted that the 3-yl positional isomer is not available for sale.

Conclusions

Analytical data is presented to assist forensic laboratories that encounter methiopropamine in case exhibits. The three presented spectral techniques each provide unequivocal characterization.

References

1. Code of Federal Regulations. 21 U.S.C. § 802(32)(A).
2. Blicke FF, Burckhalter JH. α-Thienylaminoalkanes. J. Am. Chem. Soc. 1942;64(3):477-80.
3. Porter QN. Mass spectrometry of heterocyclic compounds, 2nd ed., John Wiley and Sons, New York, NY 1985:376-8.

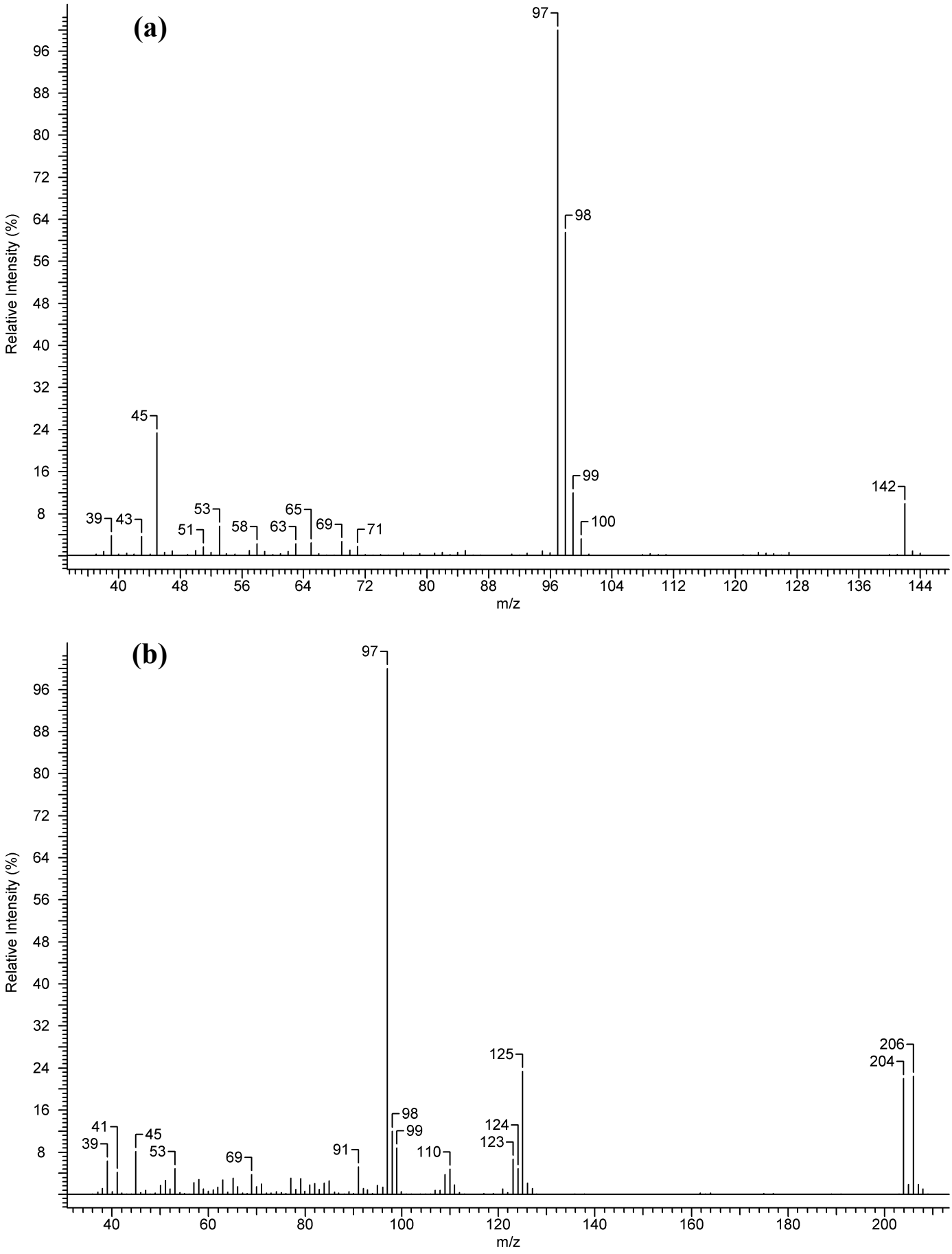


Figure 6 - Electron ionization mass spectrum of (a) 1-(thiophen-2-yl)-2-hydroxypropane and (b) 1-(thiophen-2-yl)-2-bromopropane.