The Characterization of Etaqualone and Differentiation from its 3- and 4-Ethyl Analogues

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ABSTRACT: The synthesis, analysis, and characterization of 3-(2-ethylphenyl)-2-methyl-quinazolin-4-one (commonly referred to as etaqualone) are briefly discussed. Analytical data (mass spectrometry, nuclear magnetic resonance spectroscopy, and infrared spectroscopy) are presented to differentiate it from its 3- and 4-ethylphenyl analogues.

KEYWORDS: etaqualone, 3-(2-ethylphenyl)-2-methyl-quinazolin-4-one, 3-(3-ethylphenyl)-2-methyl-quinazolin-4-one, 3-(4-ethyl-phenyl)-2-methyl-quinazolin-4-one, designer drug, synthesis, characterization, forensic chemistry.

Although etaqualone (Figure 1, structure **2**) was first synthesized and patented in 1963 [1], it has recently become a popular "research chemical" for sale over the Internet. Etaqualone is the ethyl analogue of methaqualone (Figure 1, structure **1**). Illicit etaqualone has been reported recently in Europe [2]. There are several literature citations for methaqualone analogues [3-7], however, analytical data for the forensic identification of etaqualone and its 3-ethylphenyl and 4-ethylphenyl analogues (Figure 1, structures **3** and **4**, respectively) are needed. Herein, we report the synthesis and analytical profiles of etaqualone, **3** and **4** (nuclear magnetic resonance, mass spectrometry, and infrared spectroscopy), to assist forensic chemists who may encounter these substances in casework.

Experimental

Chemicals, Reagents, and Materials

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

Synthesis of Etaqualone and its Positional Isomers

In accordance with *Journal* policy, exact experimental details are not provided, but are outlined in Figure 2. Briefly, N-acetylanthranilic acid was refluxed with 2-ethylaniline in the presence of PCl_3 to give etaqualone (**1**). 3-(3-Ethylphenyl)-2-methyl-quinazolin-4-one (**3**) and 3-(4-ethylphenyl)-2-methyl-quinazolin-4-one (**4**) were produced by utilizing 3-ethylaniline and 4-ethylaniline, respectively. All compounds were converted their respective HCl ion pair with diethyl ether containing HCl.

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. 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 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.

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.

Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were obtained on an Agilent VNMRS 600 MHz NMR using a 5 mm Protune broad band detection, variable

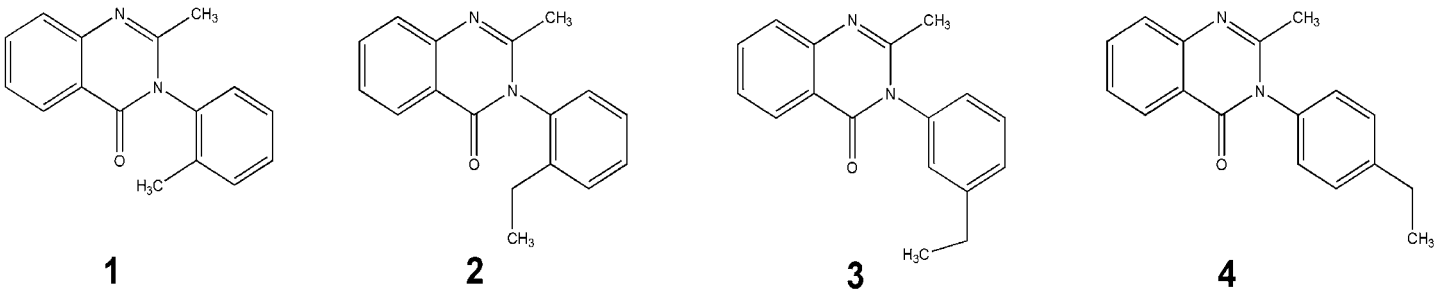
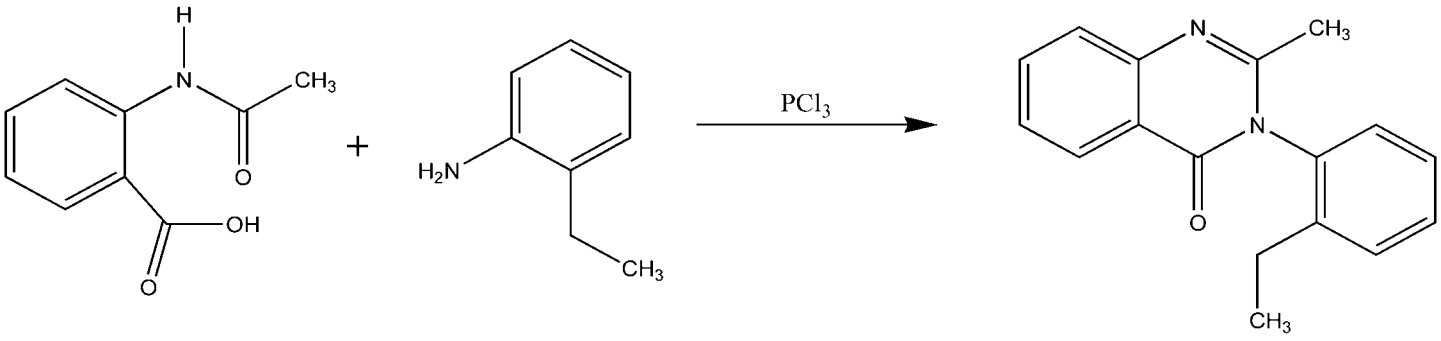


Figure 1 - Structural formulas. **1** = methaqualone, **2** = etaqualone, **3** = 3-ethyl analogue of etaqualone, and **4** = 4-ethyl analogue of etaqualone.

Table 1 - ^{1}H and ^{13}C NMR data for etaqualone positional isomers dissolved in $CDCl_3$.

Position	2-ethylphenyl			3-ethylphenyl			4-ethylphenyl		
	Carbon (ppm)	Proton (ppm)	^{1}H multiplicity and J_{HH} (Hz)	Carbon (ppm)	Proton (ppm)	^{1}H multiplicity and J_{HH} (Hz)	Carbon (ppm)	Proton (ppm)	^{1}H multiplicity and J_{HH} (Hz)
quinazoline									
2	154.6	-		154.4	-		154.6	-	
4	162.0	-		162.3	-		162.4	-	
4a	120.8	-		120.8	-		120.8	-	
5	127.5	8.29	dd 7.9, 1.6	127.1	8.28	dd 8.0, 1.2	127.1	8.28	dd 7.7, 1.5
6	126.6	7.48	m	126.6	7.47	dd 8.0, 7.5	126.6	7.46	t 7.7
7	134.6	7.78	ddd 7.9, 7.4, 1.6	134.5	7.75	ddd 8.0, 7.5, 1.5	134.5	7.77	td 7.7, 1.5
8	127.2	7.70	d 7.9	126.7	7.68	d 8.0	126.7	7.68	d 7.7
8a	147.7	-		147.5	-		147.5	-	
2-CH_3	24.1	2.19	s	24.3	2.25	s	24.4	2.26	s
phenyl									
1	136.3	-		137.7	-		135.2	-	
2	140.8	-		127.3	7.09	bs	127.7	7.17	d 8.4
3	129.5	7.15	d 7.7	146.4	-		129.4	7.38	d 8.4
4	128.1	7.38	m	128.8	7.34	d 7.7	145.5	-	
5	129.8	7.46	m	129.8	7.47	dd 8.0, 7.5	129.4	7.38	d 8.4
6	126.8	7.47	m	125.1	7.08	bd	127.7	7.17	d 8.4
CH_2-CH_3	23.6	2.43	m	28.6	2.74	q 7.5	28.6	2.75	q 7.7
CH_2-**CH_3**	13.6	1.18	t 7.6	15.1	1.28	t 7.5	15.3	1.31	t 7.7

b = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet



N-acetylanthranilic acid **2-ethylaniline** **etaqualone**

Figure 2 - Synthetic route for etaqualone.

temperature, pulse field gradient probe (Agilent, Palo Alto, CA) for **4** and an Agilent 400MR using a 5 mm Protune indirect detection, variable temperature, pulse field gradient probe for **2** and **3**. The samples were base extracted with sodium bicarbonate in deuterium oxide (D_2O) into 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 collect the following spectra: Proton, carbon (proton decoupled), and gradient versions of 2 dimensional experiments COSY, NOESY, HSQC, and HMBC. Data processing and structure elucidation were performed using Structure Elucidator software from Applied Chemistry Development (ACD/Labs, Toronto, Canada).

Results and Discussion

Table 1 contains the proton and carbon data for all three compounds as the free base. Assignments were carried out using proton chemical shifts and peak patterns, carbon chemical shifts, and COSY, NOESY, HSQC, and HMBC correlations.

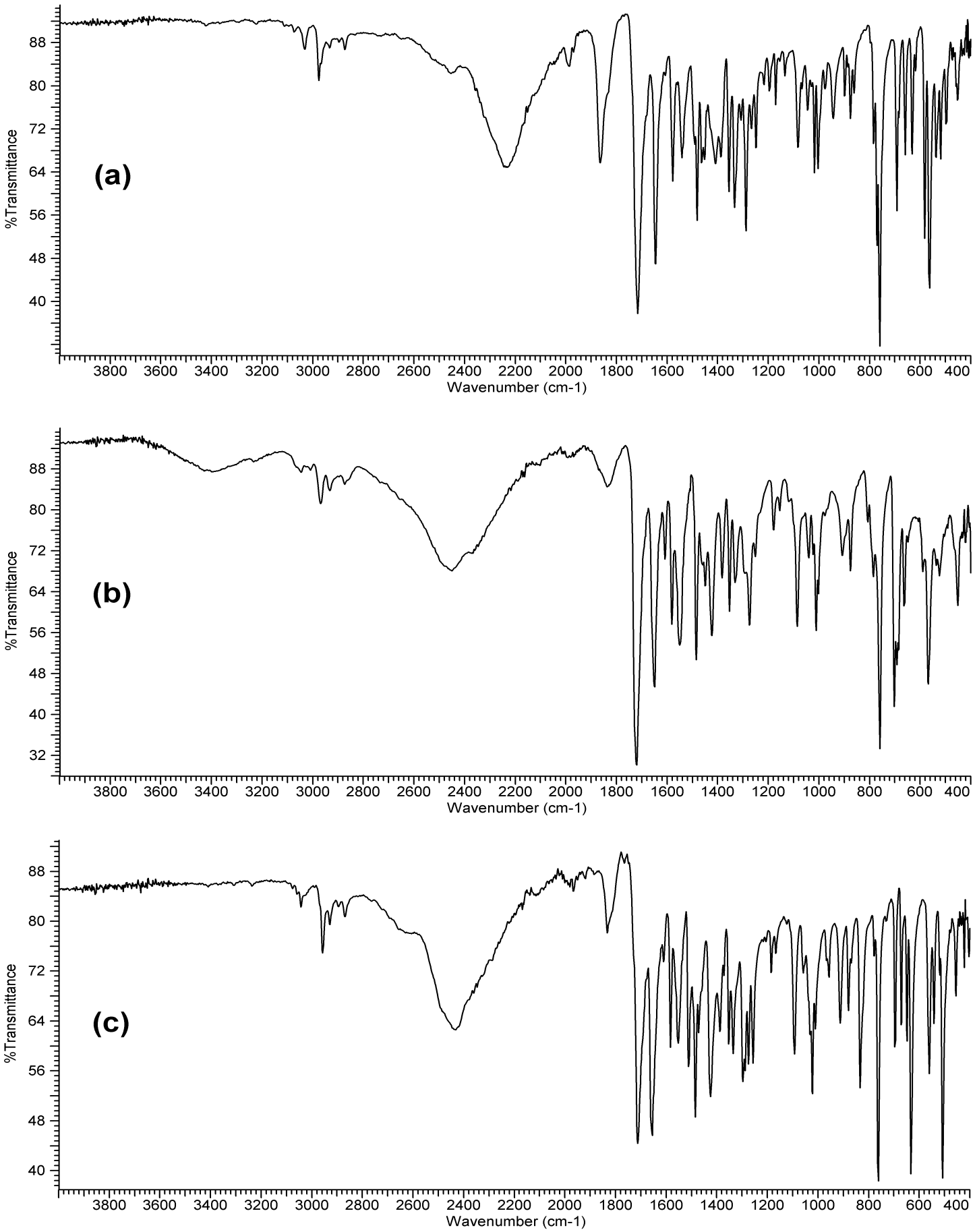


Figure 3 - FTIR of (a) = etaqualone HCl, (b) = 3-ethyl analogue of etaqualone HCl, and (c) = 4-ethyl analogue of etaqualone HCl.

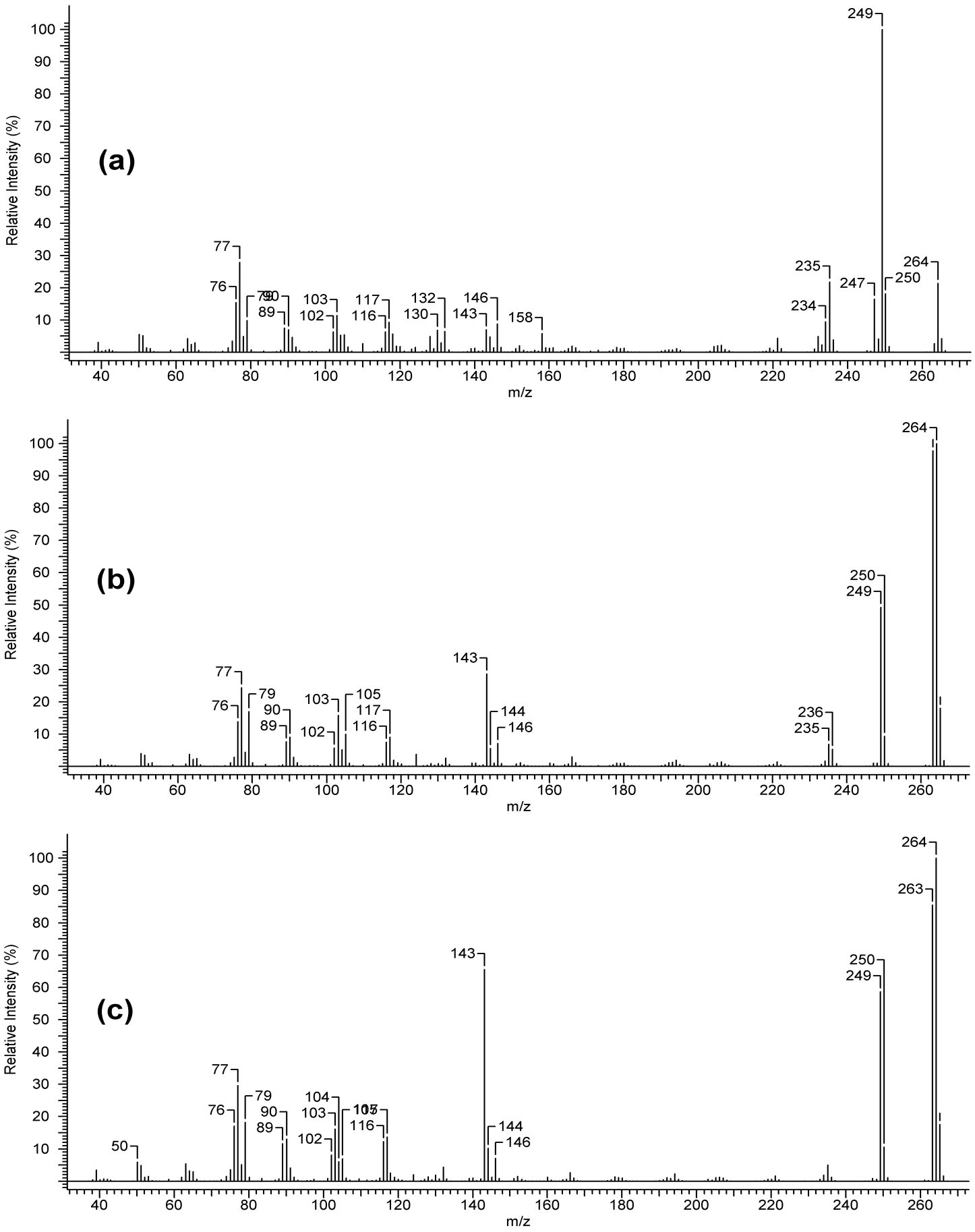


Figure 4 - Mass spectrum of (a) = etaqualone, (b) = 3-ethyl analogue of etaqualone, and (c) = 4-ethyl analogue of etaqualone.

The ethyl group position (i.e., *ortho*-, *meta*-, or *para*-) on one of the benzene rings was obvious from the proton peak patterns and COSY correlations. Each compound was easily differentiated by its NMR spectrum.

The infrared spectra of **2**, **3**, and **4** are illustrated in Figure 3. The FTIR (Figures 3a-c) for each compound exhibited a strong carbonyl stretch between 1712-1721 cm^{-1}, but have dissimilar absorbances between 400-1700 cm^{-1}. Most notably, the amine HCl bands for etaqualone (Figure 3a) are further downfield at *ca*. 2000-2350 cm^{-1} compared to the 3- and 4-ethyl isomers having absorbances at *ca*. 2200-2600 cm^{-1} (Figures 3b and 3c).

The mass spectra of **2**, **3**, and **4** are illustrated in Figure 4. Etaqualone produces a moderate molecular ion at *m/z* 264 and a base peak at *m/z* 249 (Figure 4a). The 3- and 4-ethyl isomers (Figures 4b and 4c) are easily differentiated from etaqualone since each produces a molecular ion as the base peak at *m/z* 264 and a pronounced ion at *m/z* 143 (etaqualone has only a minor ion at *m/z* 143). The 3- and 4-ethyl isomers are differentiated from each other by the relative intensity of the ion at *m/z* 143.

Conclusions

Analytical data are presented to assist forensic laboratories that encounter etaqualone or its 3- and 4-ethyl analogues in casework.

References

1. United Kingdom Patent GB936902, Quinazolinone Derivatives. September 1963.
2. Sedefov R, Gallegos A. European early warning system: Responding to novel recreational drugs. Symposium on novel recreational drugs of abuse, EAPCCT Annual Congress, Dubrovnik, Croatia. May 24-27, 2011.
3. Clark CC. The identification of nitromethaqualone and its differentiation from some positional isomers. J Forensic Sci. 1988;33(4):1035-1044.
4. Daenens P, Van Boven M. The identification of quinazolinones on the illicit market. J Forensic Sci. 1976;21 (3):552-563.
5. Angelos SA, Lankin DC, Meyers JA, Raney JK. The structural identification of a methyl analog of methaqualone via 2-dimensional NMR techniques. J Forensic Sci. 1993;38 (2):455-456.
6. Boyd PM, Moses PJ, Bowman L. Gas chromatographic-mass spectrometric analysis of methaqualone, phendimetrazine and phenmetrazine. Spectrosc. Lett. 1974;7(4&5):223-227.
7. Van Zyl EF. A survey of reported synthesis of methaqualone and some positional and structural isomers. Forensic Sci. Int. 2001;122(2-3):142-149.