TECHNICAL NOTE

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The Identification of Nitromethaqualone and Its Differentiation from Some Positional Isomers

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ABSTRACT: Nitromethaqualone [2-methyl-3(2′-methoxy-4′-nitrophenyl)-4(3H)-quinazolinone] and its three positional isomers formed by moving the nitro group on the phenyl ring containing the 2′-methoxyl group have been synthesized and characterized. Mass spectra, infrared spectra, nuclear magnetic resonance spectra, and the gas-liquid chromatographic behavior of these compounds are presented. It is shown that infrared spectroscopy, nuclear magnetic resonance spectroscopy, and electron impact mass spectroscopy combined with gas-liquid chromatography are capable of differentiating nitromethaqualone from any of the studied isomers, methaqualone, and mecloqualone.

KEYWORDS: toxicology, nitromethaqualone, chemical analysis, methaqualone, mecloqualone

The abuse of the hypnotic methaqualone [2-methyl-3-o-tolyl-4(3H)-quinazolinone] and related quinazolinones is well known [*1*]. Methaqualone was first prepared in 1951 and introduced in 1965 for use as a nonaddictive sleeping aid. Its manufacture in this country ceased in 1983 and its illicit use has declined. Methaqualone is now a Schedule I Controlled Substance under the Controlled Substances Act [*2*]. A second member of this class of hypnotics which has been abused in this country is mecloqualone [2-methyl-3-o-chlorophenyl-4(3H)-quinazolinone].[2] Mecloqualone was first synthesized in 1960. Although it is available in Europe by prescription, it has never had an accepted medical use in the United States and was made a Schedule I Controlled Substance in 1975 [*3*]. A third member of this hypnotic class of compounds is nitromethaqualone [2-methyl-3(2′-methoxy-4′-nitrophenyl)-4(3H)-quinazolinone]. This much more potent hypnotic has been available by prescription in Europe since 1967. A single therapeutic dose is 15 mg, compared to 150 mg for methaqualone or mecloqualone. An overdose of this drug, when taken with alcohol, is said to provoke a toxic hallucinosis [*4*].

This drug is occasionally seen at ports of entry in this country but is not controlled under the Controlled Substances Act at this time. The synthesis routes reported for the syntheses of

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quinazolinones are uncomplicated and easily adapted for clandestine laboratory use. These same procedures, with only minor changes in the reactants, can be used to produce closely related compounds. It is not uncommon for a clandestine laboratory operator to produce analogs or homologs of prescription or controlled substances, either to evade the law or to gain an enhanced effect. Examples of these which have been seen in forensic science laboratories are various compounds based on the mescaline molecule, the thiophene and other analogs based on phencyclidine, and more recently, a meperidine homolog and various compounds based on fentanyl. The 2-ethyl homolog of methaqualone has also been encountered. A substance can be controlled only after it is chemically identified. Therefore, there is a need for methodology that will differentiate an abused substance from its positional isomers and related compounds. This has been done for both methaqualone and mecloqualone [5] but not nitromethaqualone. This paper presents the infrared (IR), nuclear magnetic resonance (NMR), and electron impact mass spectra (MS) of nitromethaqualone and its three positional isomers formed by moving the nitro group on the phenyl ring containing the 2′-methoxyl group. The gas-liquid chromatographic (GLC) behaviors of these compounds are also presented.

Experimental Procedure

Apparatus

Mass spectra were obtained on a Finnigan 4530 quadrupole mass spectrometer. Ionizing voltage was 70 eV. Source temperature was 200°C. Scan rate was 0.5 s/scan and the scan range was 40 to 400 mass units. Sample introductions were made via a 25-m by 0.31-mm inside diameter (ID) fused silica capillary column with a 0.52-μm film thickness of OV-1. Split ratio was approximately 50-1. Column temperature was 250°C and the injector temperature was 270°C. Infrared spectra were obtained on a Perkin-Elmer 783 infrared spectrometer and used the KBr dispersion technique. Nuclear magnetic resonance spectra were obtained on a Varian EM-390 NMR spectrometer. Gas-liquid chromatograms were obtained on a Hewlett-Packard 5880A gas chromatograph equipped with 6-ft (2-m) by 4-mm ID glass columns. Column packings utilized were 3% OV-1 and 3% OV-17 on 100-120 mesh Gas-Chrom Q. Injector and detector temperatures were 275°C.

Syntheses

Compounds I to IV, shown in Fig. 1 and Table 1, were prepared by reacting *N*-acetylanthranilic acid with the appropriately substituted anilines. The 2-methoxy-3-nitroaniline needed for Compound I was obtained by methoxy substitution for the chlorine in 2,6-dinitrochlorobenzene with sodium methoxide. Reduction of one of the nitro groups with sodium sulfide by the method of Hartman and Silloway [6] gave the desired substituted aniline. The

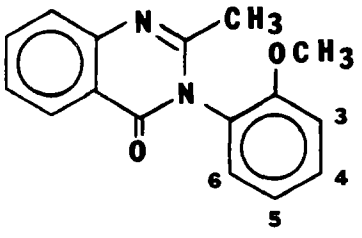

FIG. 1—*Structure of nitromethaqualone (Compound II).*

TABLE 1—*Positional isomers used in this study.*

Position	Compound			
	I	II	III	IV
3	NO_2	H	H	H
4	H	NO_2	H	H
5	H	H	NO_2	H
6	H	H	H	NO_2

2-methoxy-4-nitroaniline and 2-methoxy-5-nitroaniline needed for the syntheses of Compounds II and III, respectively, were purchased from commercial sources. The reaction sequence of Ingold [7] was used to prepare the 2-methoxy-6-nitroaniline, contaminated with positional isomers, needed for the synthesis of Compound IV. Compound IV was isolated from the resulting mixture of positional isomers obtained by the use of adsorption chromatography utilizing a silica gel column and chloroform:hexane (3+1) as the mobile phase. All four compounds were obtained as the bases by recrystallization from acetone-dilute ammonium hydroxide (NH_4OH) solution.

Results and Discussion

Gas-Liquid Chromatography

The results obtained using two liquid stationary phases are shown in Table 2. Using either phase, nitromethaqualone (Compound II) can be differentiated from all the studied isomers and methaqualone or mecloqualone.

Infrared

Figures 2, 3, 4, and 5 show the IR spectra of Compounds I, II, III, and IV, respectively. Although the spectra are similar, any of the studied isomers can be differentiated from methaqualone, mecloqualone, and any of the other studied isomers. As expected, the most notable differences are in the aromatic C-H out-of-plane bending region (1000 to 600 cm^{-1}).

Nuclear Magnetic Resonance

Figures 6, 7, 8, and 9 show the NMR spectra of Compounds I, II, III, and IV, respectively. Chemical shift values are expressed in parts per million. The chemical shift differ-

TABLE 2—*GLC data.*

Compound No.	A[a] $R_t(R_R)$	B[b] $R_t(R_R)$
I	6.56 min (2.20)	10.7 min (2.90)
II	9.51 min (3.19)	17.6 min (4.78)
III	11.5 min (3.85)	21.3 min (5.79)
IV	8.91 min (2.99)	16.6 min (4.50)
Methaqualone	2.98 min (1.00)	3.68 min (1.00)
Mecloqualone	3.72 min (1.25)	5.16 min (1.40)

[a]A = 3% OV-1 6-ft (2-m) by 4 mm ID 240°C.
[b]B = 3% OV-17 6-ft (2-m) by 4 mm ID 265°C.

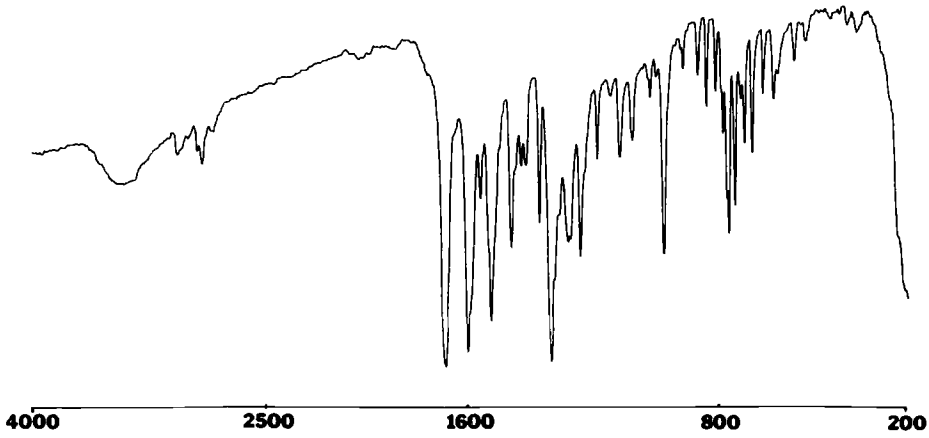

FIG. 2—*The infrared spectrum of Compound I in KBr.*

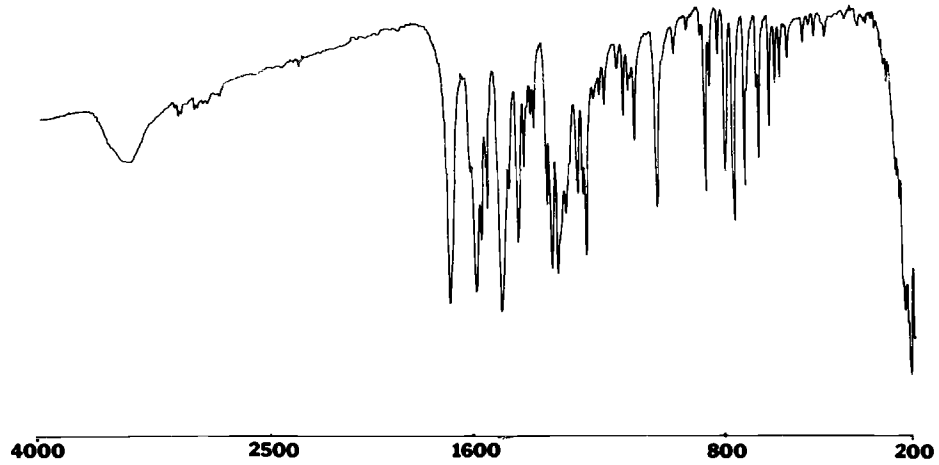

FIG. 3—*The infrared spectrum of Compound II in KBr.*

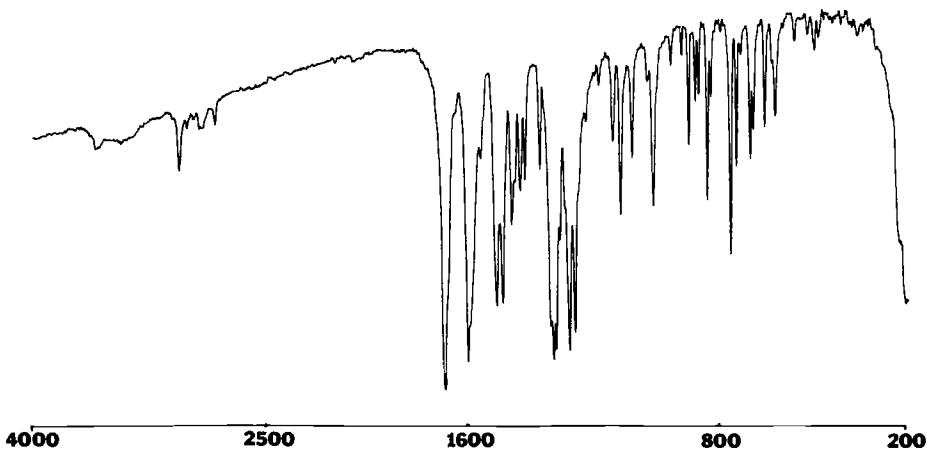

FIG. 4—*The infrared spectrum of Compound III in KBr.*

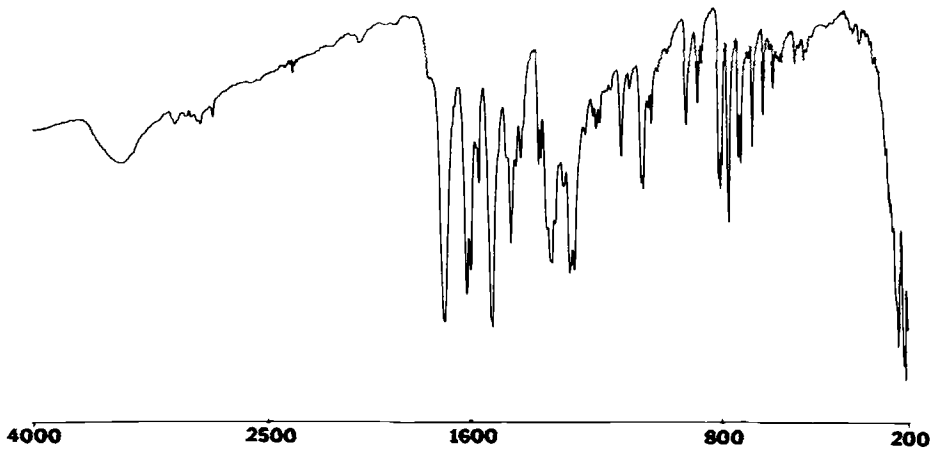

FIG. 5—*The infrared spectrum of Compound IV in KBr.*

ences of both the methoxyl group and the methyl group between positional isomers are small. The spectra are similar between 0 and 6 ppm. The resonance signals of the quinazolinone system protons overlap with those of the phenyl ring. Aromatic protons ortho to a nitro group show a marked downfield shift. Consequently, a change in the position of the nitro group produces marked changes in the resonance pattern of the aromatic area of the spectra. The NMR spectra of the isomers are sufficiently detailed to permit the differentiation of any of the studied isomers from each other or from methaqualone and mecloqualone.

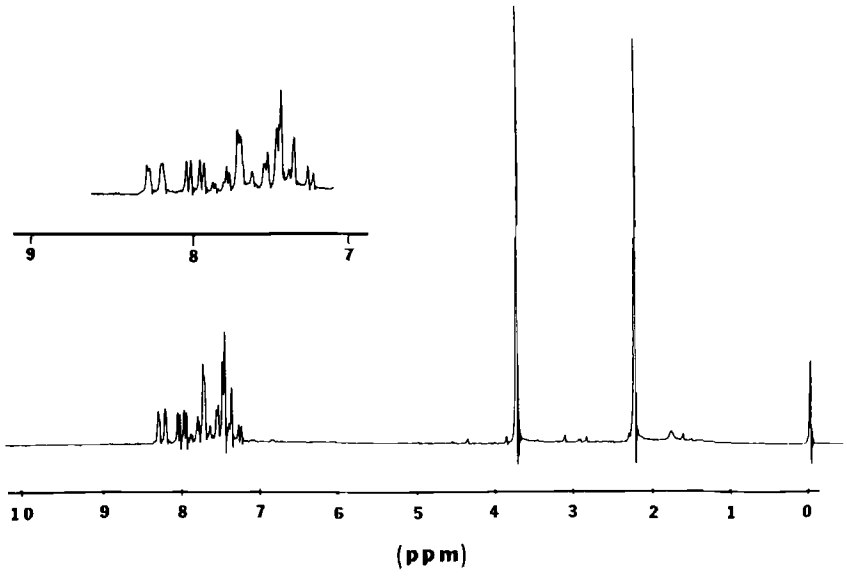

FIG. 6—*The NMR spectrum of Compound I base in deuterochloroform ($CDCl_3$).*

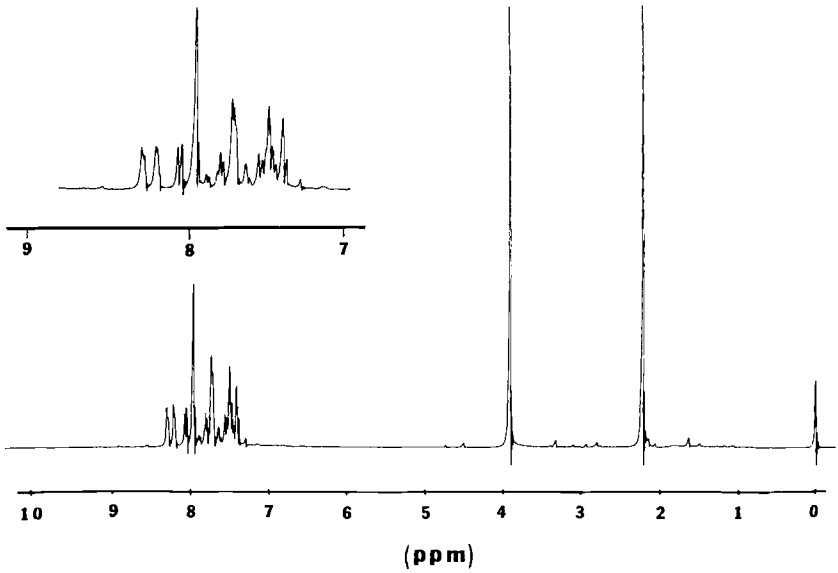

FIG. 7—*The NMR spectrum of Compound II base in $CDCl_3$.*

Electron Impact Mass Spectra

Figures 10, 11, 12, and 13 show the EI induced mass spectra of Compounds I, II, III, and IV, respectively. The molecular ion at m/z 311 clearly differentiates nitromethaqualone from methaqualone and mecloqualone, with molecular weights of 250 and 270 mass units, respectively. The three studied positional isomers of nitromethaqualone also show promi-

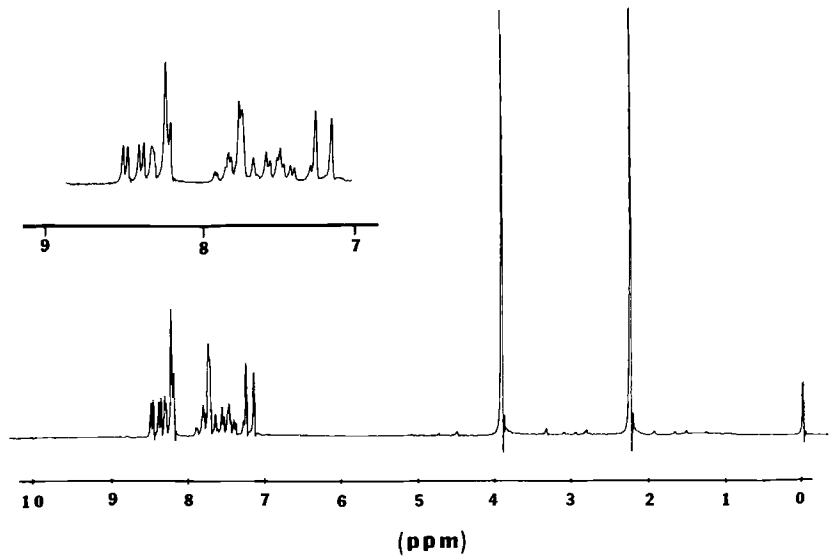

FIG. 8—*The NMR spectrum of Compound III base in $CDCl_3$.*

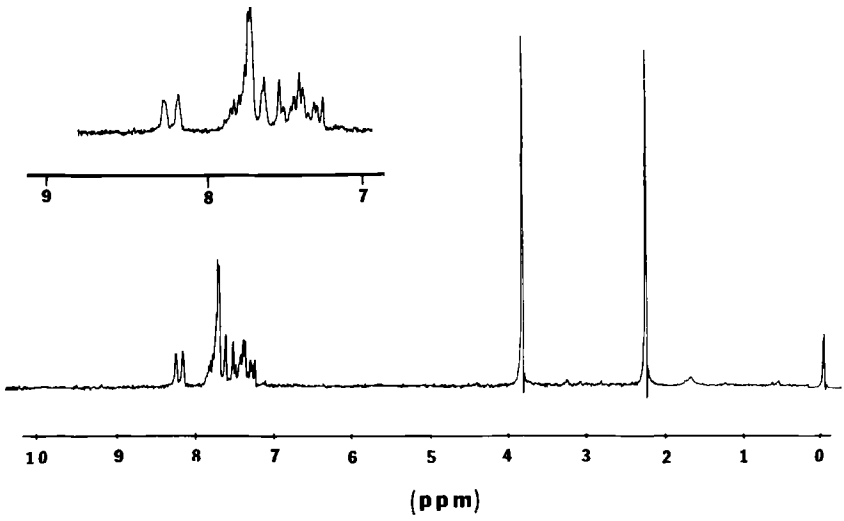

FIG. 9—*The NMR spectrum of Compound IV base in $CDCl_3$.*

nent *m/z* 311 molecular ions. In addition, all but one of the isomers, Compound IV with a base peak of *m/z* 265, share the *m/z* 280 base peak of nitromethaqualone.

Compound I shows a *m/z* 209 fragment, probably as a result of loss of a substituted ethylene group containing both the methoxyl and the nitro groups. This fragment, and several others in the mass spectrum of Compound I, allow its differentiation from nitrometh-

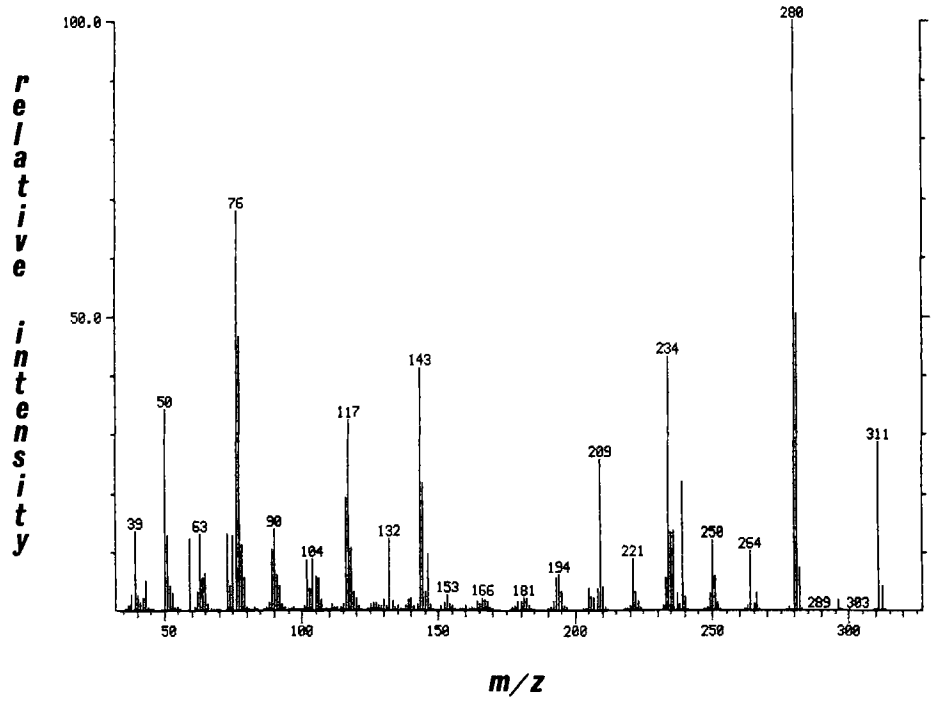

FIG. 10—*The EI mass spectrum of Compound I.*

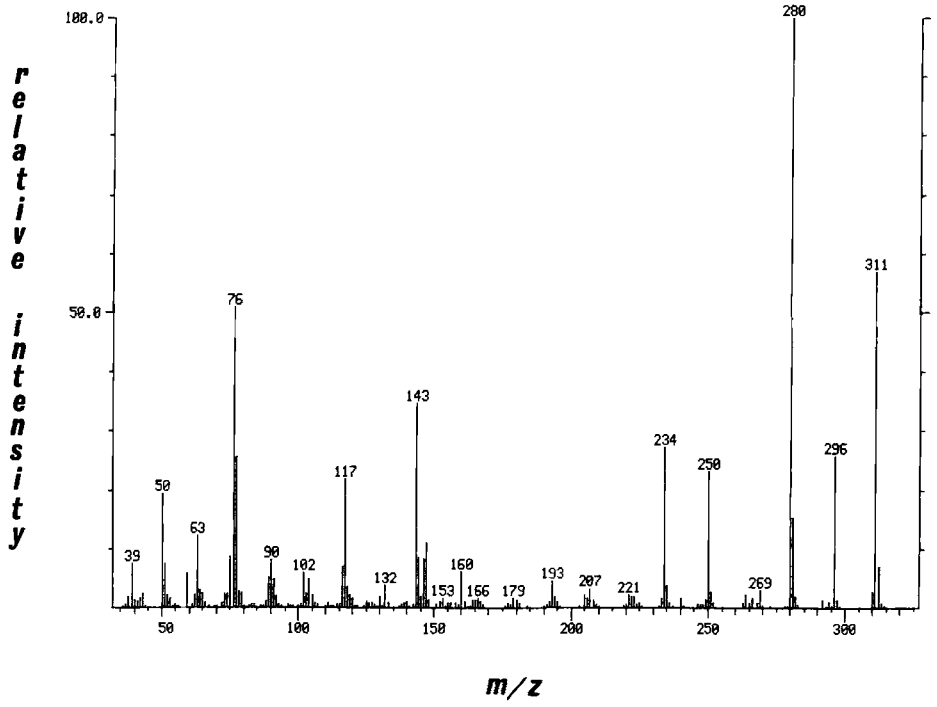

FIG. 11—*The EI mass spectrum of Compound II.*

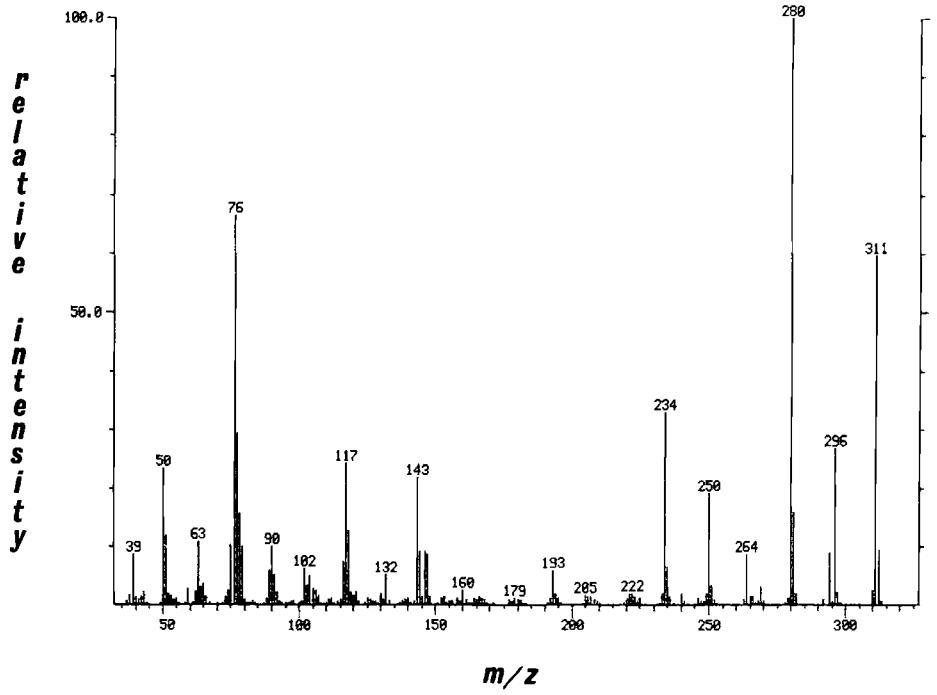

FIG. 12—*The EI mass spectrum of Compound III.*

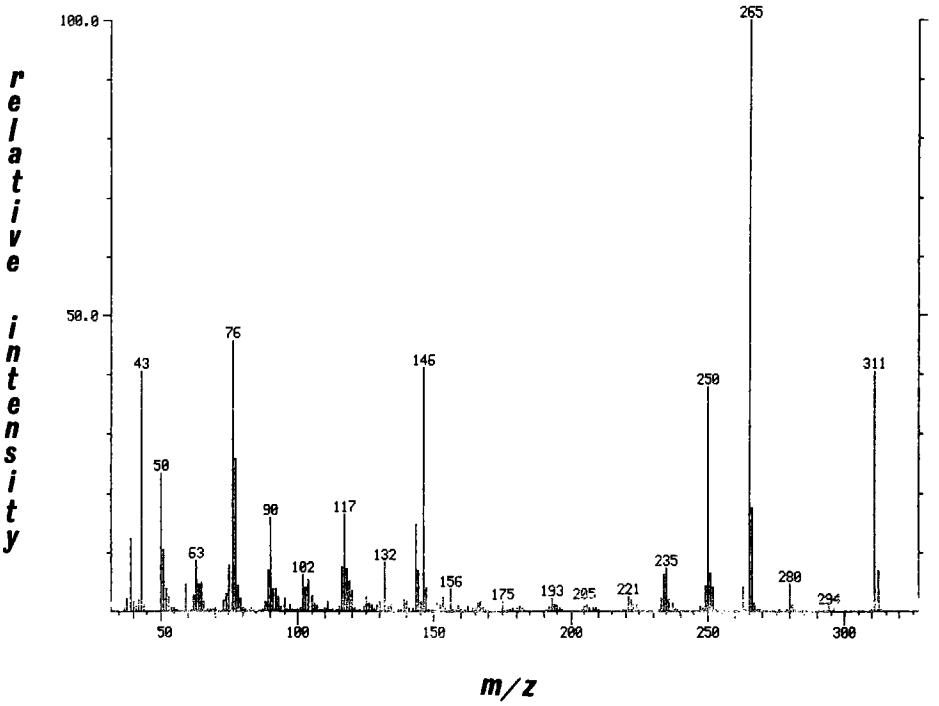

FIG. 13—*The EI mass spectrum of Compound IV.*

aqualone. The mass spectrum of Compound III, however, bears a striking resemblance to that of nitromethaqualone. Its enhanced *m/z* 264 and 294 allows its mass spectral differentiation from nitromethaqualone, but the intensities of both fragments are small (<10%). Care should be exercised in the identification of nitromethaqualone by mass spectroscopy alone unless standard material of both it and Compound III are available for direct comparison.

Conclusion

Following its extraction by organic solvents from an alkaline solution, nitromethaqualone can be identified by a variety of analytical techniques. Infrared spectroscopy and NMR spectroscopy permit differentiation of any of the studied isomers and the unequivocal identification of nitromethaqualone. Electron impact mass spectroscopy can establish the positive identification of nitromethaqualone when suitable reference material is available for direct comparisons or when the technique is combined with gas-liquid chromatography.

Acknowledgment

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