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Identification of Some Chemical Analogues and Positional Isomers of Methaqualone

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ABSTRACT: The drug 2-methyl-3-ortho-tolyl-4-quinazolinone (methaqualone) and 15 chemical analogues and positional isomers were synthesized and identified by spectroscopic techniques. The series of analogues studied includes the compounds formed through substitution of hydrogen or halogen atoms in place of the methyl group of the 3-tolyl substituent in methaqualone. Additionally, the substituent's positional orientation of ortho, meta, or para is considered. Infrared, nuclear magnetic resonance, and mass spectra of the compounds are distinctive, and reference spectra are provided. Gas-liquid and thin-layer chromatographic systems for analysis of the compounds as well as melting point and ultraviolet data are discussed.

KEYWORDS: toxicology, methaqualone, chemical analysis

The abuse of the hypnotic drug methaqualone [*1*] and to a lesser extent its chlorinated analogue, mecloqualone [*2*], has been recognized and is increasing within the United States. At present, mecloqualone is not commercially available in the United States, but it has been produced clandestinely. Mecloqualone (2-methyl-3-ortho-chlorophenyl-4-quinazolinone) was first synthesized in 1960 [*3*], and human metabolism studies were reported in 1974 [*4*]. Since it currently has no medical use in the United States, mecloqualone is controlled as a Schedule I drug by the Federal Comprehensive Drug Abuse Prevention and Control Act of 1970 (P.L. 91-513). In Europe, mecloqualone is available as a legitimately dispensed hypnotic drug.

The two sources of illegally distributed methaqualone are diversion from legitimate pharmaceutical firms and illegitimate manufacture in clandestine laboratories. Methaqualone (2-methyl-3-ortho-tolyl-4-quinazolinone) was first prepared in 1951 [*5*], and studies of its metabolism in man were reported in 1960 [*6, 7*] and in animals in 1963 [*8*]. Methaqualone was introduced pharmaceutically in 1965 for use as a nonaddictive, nonbarbiturate sleeping pill [*9, 10*]. In 1976 metabolite detection for forensic science purposes was reported [*11*]. Currently methaqualone is controlled by federal law as a Schedule II drug.

The reported synthetic routes for quinazolinones are uncomplicated, one- or two-step procedures that can be adapted to clandestine laboratory processes without difficulty. It is

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not uncommon for clandestine chemists to attempt to produce analogues or homologues of controlled substances either to obtain a greater physiologic effect or to evade the law. Since many of these analogues or homologues are not controlled under state or federal law, there is a need to provide differentiation and unequivocal identification.

Experimental Procedure

Compounds I to XVI (Fig. 1, Table 1) were prepared by reacting a toluene solution of aniline, or the appropriate substituted aniline, with *N*-acetylanthranilic acid in the presence of phosphorus trichloride [*12, 13*]. *N*-acetylanthranilic acid and each of the aniline compounds were reacted in a 1:1 molar ratio by refluxing with phosphorus trichloride (3 mL in 15-mL toluene), added by drops over a 10-min period. Refluxing was continued for 60 min after the addition of all the phosphorus trichloride. The reaction mixtures were cooled to room temperature and purified by dissolving them in hot methanol and filtering. Distilled water was added to the filtrate until a constant turbidity resulted; the solutions were then permitted to sit until crystals formed. Repetition of this procedure was necessary until the crystals were white. When a high concentration of colored contaminants persisted and white crystals were not easily obtained, chloroform extractions from hydrochloric acid or sodium hydroxide solutions [*14*] were employed. This extraction procedure, when used in conjunction with recrystallization, yielded high-purity crystals.

The hydrochloride salts of Compounds I to XVI were prepared by dissolving the free bases in methanol and bubbling hydrogen chloride gas into the solution. After the precipitation of the compounds, the solutions were filtered to obtain the hydrochloride salts.

The melting point ranges were determined by using Thomas-Hoover Unimelt apparatus and are uncorrected. The standard techniques of ascending thin-layer chromatography (TLC) were employed. Solvent migrations of 15 cm were made on channeled 20-cm glass LQD plates from Quantum Industries.

A Hewlett-Packard Model 5840A gas-liquid chromatograph (GLC) equipped with an automatic sampler was used. Infrared (IR) spectroscopy utilized the standard KBr disk method and was performed on a Perkin-Elmer 283 spectrophotometer whereas ultraviolet (UV) spectra were recorded on a Perkin-Elmer/Hitachi 200 spectrophotometer. Mass spectrometry was conducted with a Finnigan Model 3300 gas chromatograph/mass spectrometer. The optimum operating parameters for our unit required an analyzer temperature of 90°C and ionization voltage of 70 eV with the extractor and collector at 13.3 and 39.4 V, respectively. The lens was held at 16.7 V and the ion energy at 10.1 V. Samples were introduced via the probe. Nuclear magnetic resonance (NMR) spectra were recorded on a 90-MHz Varian EM 390 spectrometer.

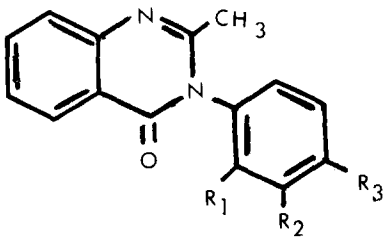


FIG. 1—*Schematic diagram of methaqualone and its analogues and positional isomers.*

TABLE 1—*List of compounds synthesized (see also Fig. 1).*

Compound	R_1	R_2	R_3	Chemical Name
I	H	H	H	2-methyl-3-phenyl-4-quinazolinone
II	CH_3	H	H	2-methyl-3-*o*-tolyl-4(3H)-quinazolinone
III	H	CH_3	H	2-methyl-3-*m*-tolyl-4(3H)-quinazolinone
IV	H	H	CH_3	2-methyl-3-*p*-tolyl-4(3H)-quinazolinone
V	F	H	H	2-methyl-3-*o*-fluorophenyl-4-quinazolinone
VI	H	F	H	2-methyl-3-*m*-fluorophenyl-4-quinazolinone
VII	H	H	F	2-methyl-3-*p*-fluorophenyl-4-quinazolinone
VIII	Cl	H	H	2-methyl-3-*o*-chlorophenyl-4-quinazolinone
IX	H	Cl	H	2-methyl-3-*m*-chlorophenyl-4-quinazolinone
X	H	H	Cl	2-methyl-3-*p*-chlorophenyl-4-quinazolinone
XI	Br	H	H	2-methyl-3-*o*-bromophenyl-4-quinazolinone
XII	H	Br	H	2-methyl-3-*m*-bromophenyl-4-quinazolinone
XIII	H	H	Br	2-methyl-3-*p*-bromophenyl-4-quinazolinone
XIV	I	H	H	2-methyl-3-*o*-iodophenyl-4-quinazolinone
XV	H	I	H	2-methyl-3-*m*-iodophenyl-4-quinazolinone
XVI	H	H	I	2-methyl-3-*p*-iodophenyl-4-quinazolinone

Results and Discussions

Melting Point

Melting point determinations were recorded for both the free bases and their hydrochloride salts (Table 2). With the exception of Compounds III and IX, a comparison of base/hydrochloride melting point pairs may be used to differentiate the compounds synthesized.

Ultraviolet Spectra

The absorption wavelength maxima for Compounds I to XVI were nearly identical and show only slight variation from wavelength maxima for unsubstituted quinazolinone.

Thin-Layer Chromatography

A number of TLC solvent systems were investigated, but none of these systems proved useful as a tool for differentiating the 16 compounds.

Gas-Liquid Chromatography

Methanol solutions of the hydrochloride salts were used at a concentration of 1 mg/mL. The results obtained with several liquid phases are presented in Table 3. Of the packings compared, 3% OV-25 provides the best separation of compounds. In each of these GLC systems, the halogen-containing compounds eluted in order of increasing atomic weight. For a given molecular weight compound, the ortho isomer eluted first and the para isomer last.

Mass Spectroscopy

Characterization of the analogues by mass spectroscopy is a simple process because of the differences in molecular weights. The mass spectra are presented in Fig. 2.

TABLE 2—*Melting point for methaqualone and some analogues (°C).*

Compound	Base	Hydrochloride
I	143-146[a]	240-243
II	115-117[b]	243-246
III	127-129[c]	246-249
IV	149-151[c]	250-253
V	117-119	228-231
VI	131-133	255-258
VII	132-134	261-264
VIII	125-128[d]	229-232
IX	127-129[c]	247-249
X	156-158[c]	256-258
XI	143-145	226-229
XII	116-119	250-253
XIII	172-173	253-256
XIV	132-134	225-228
XV	144-146	268-271
XVI	177-179	271-274

[a] P. Grammaticakis, in *Comptes Rendus de se Seances de l'Academie de Sciences*, Vol. 252, No. 25, June 1961, p. 4011, reported 147 to 149°C.

[b] Netherlands patent 295501, 1963, reported 113 to 114°C.

[c] G. Serventic and R. Marchesi, in *Bollettino Scientifico della Facolta di Chimica Industriale di Bologna*, Vol. 15, Oct. 1957, p. 119, reported 130°C for Compound III, 157°C for Compound IV, 129°C for Compound IX, and 149 to 150°C for Compound X.

[d] *The Merck Index*, 9th ed., Merck & Co. Inc., Rahway, N.J., 1976, reports 126 to 128°C.

TABLE 3—*Retention times (min) of some methaqualone analogues for column packings and oven temperatures indicated.*[a]

Compound	3% OV-25, 240°C	10% SP2100, 270°C	3% OV-1, 200°C
I	5.4	3.3	5.8
II	5.0	3.3	5.8
III	6.4	4.0	7.8
IV	6.9	4.2	8.3
V	4.0	3.0	4.9
VI	4.2	3.1	5.1
VII	4.5	3.2	5.7
VIII	7.3	4.2	7.8
IX	7.9	4.8	9.8
X	9.1	4.9	10.3
XI	10.2	5.0	10.1
XII	11.5	6.0	13.4
XIII	13.6	6.4	14.6
XIV	15.2	6.3	13.5
XV	18.6	7.9	19.8
XVI	22.1	8.5	21.2

[a] Columns were glass, 1.8 m (6 ft) long; injector, 275°C; flame ionization detector, 300°C; nitrogen flow, 55 mL/min. Support material for the 3% OV-25 and 3% OV-1 was 100-120 mesh Gas Chrom Q, and 100-120 mesh Supelcoport was used for the 10% SP2100.

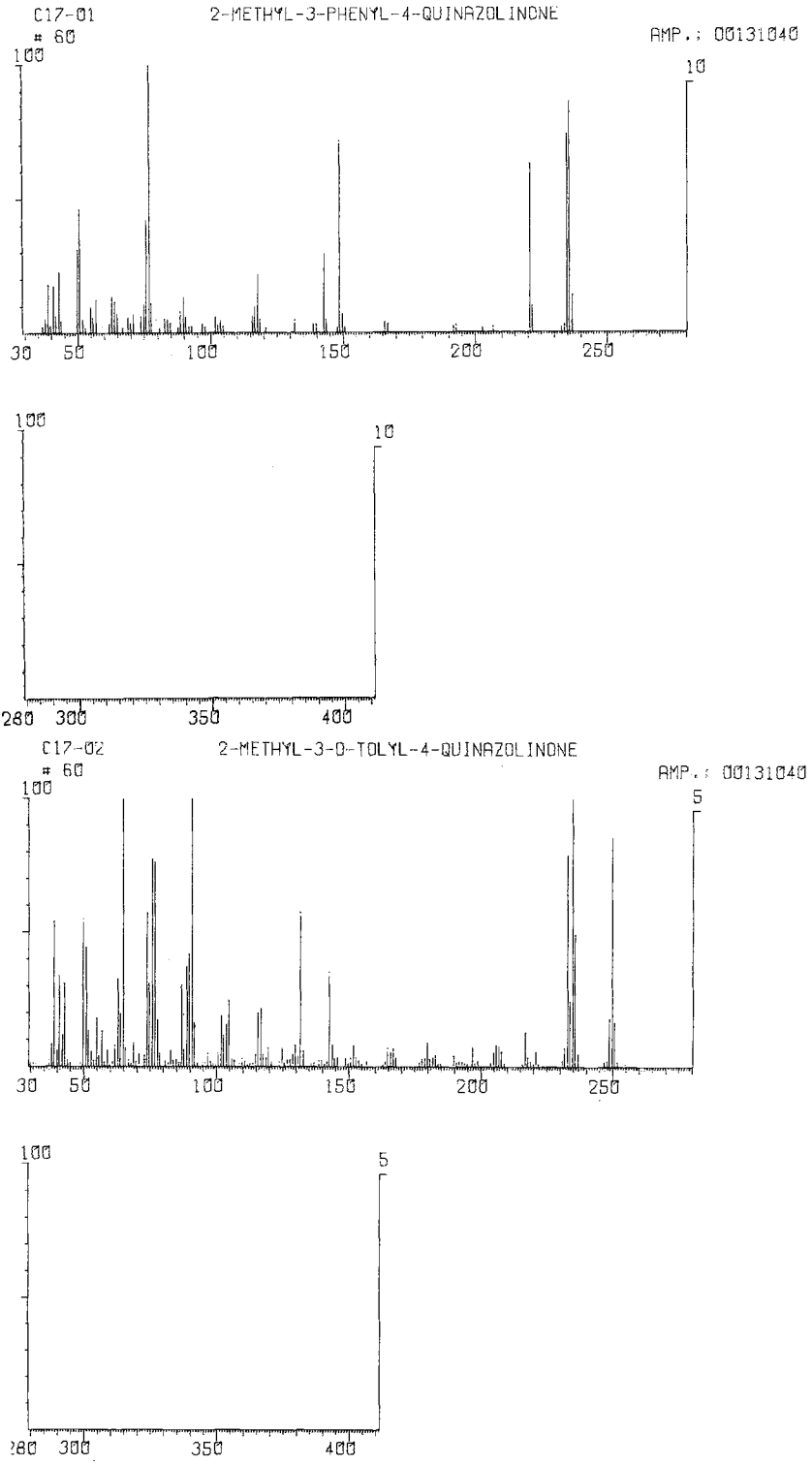
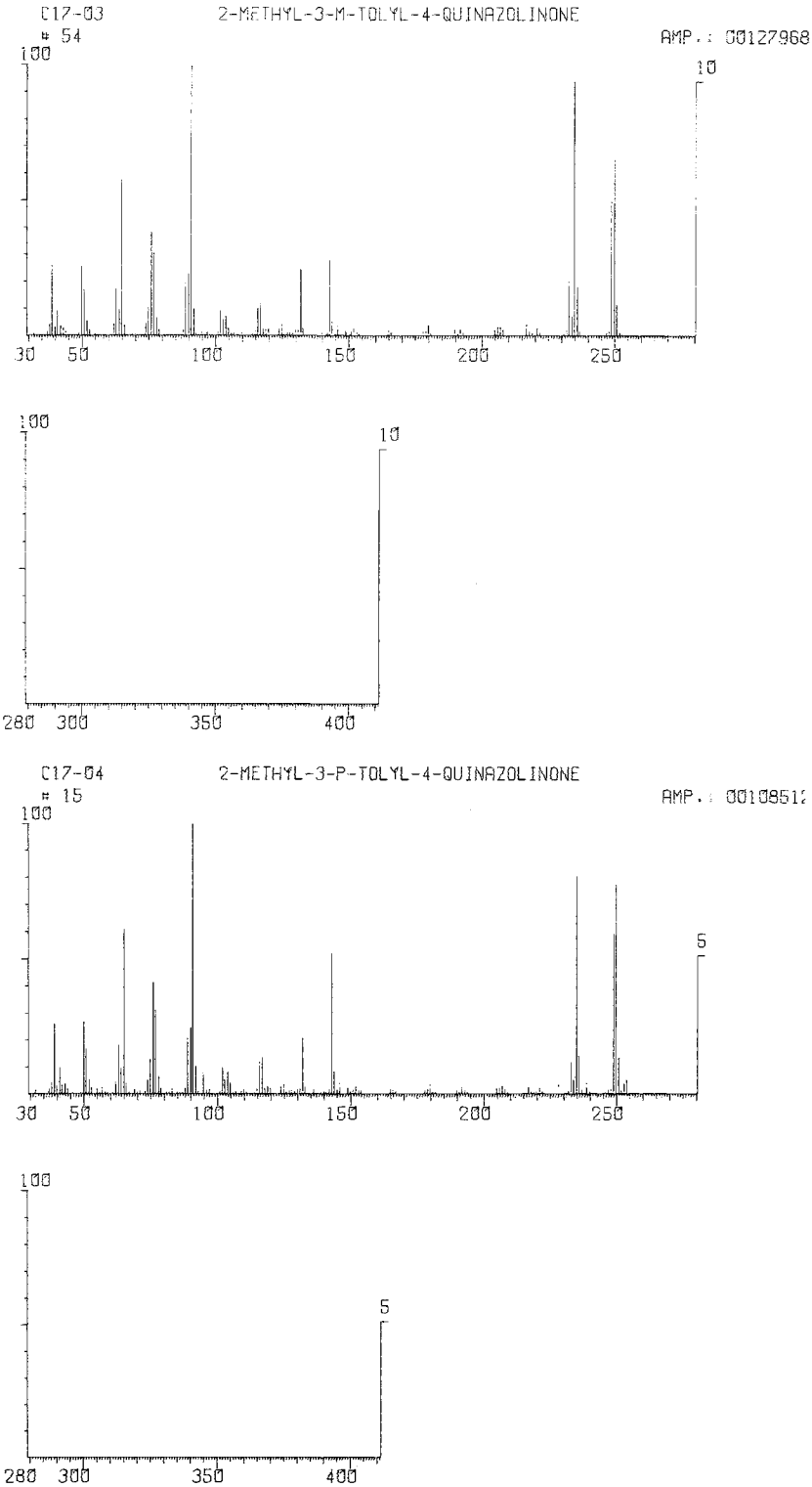


FIG. 2—*Normalized mass spectra of Compounds I through XVI.*



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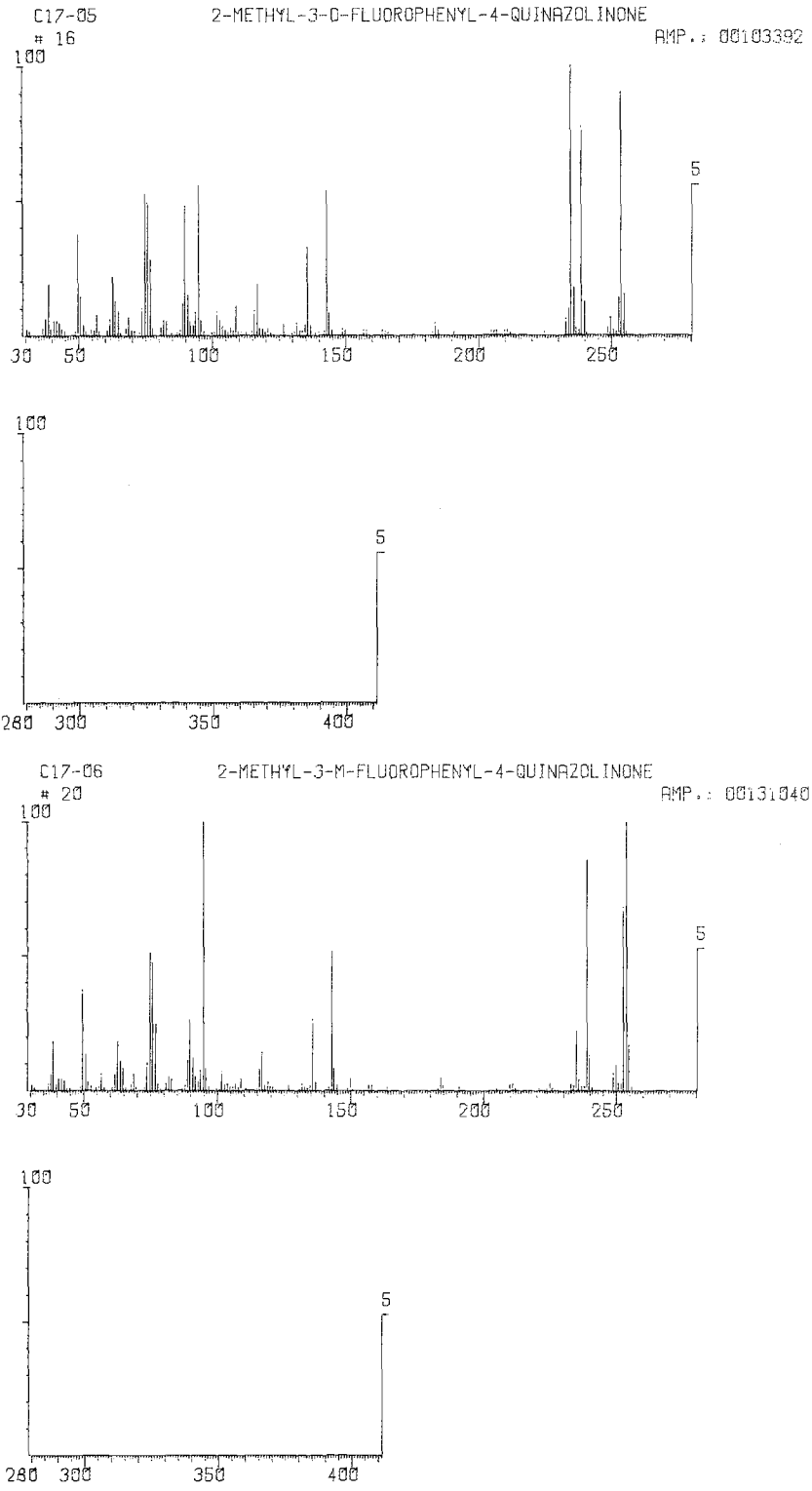

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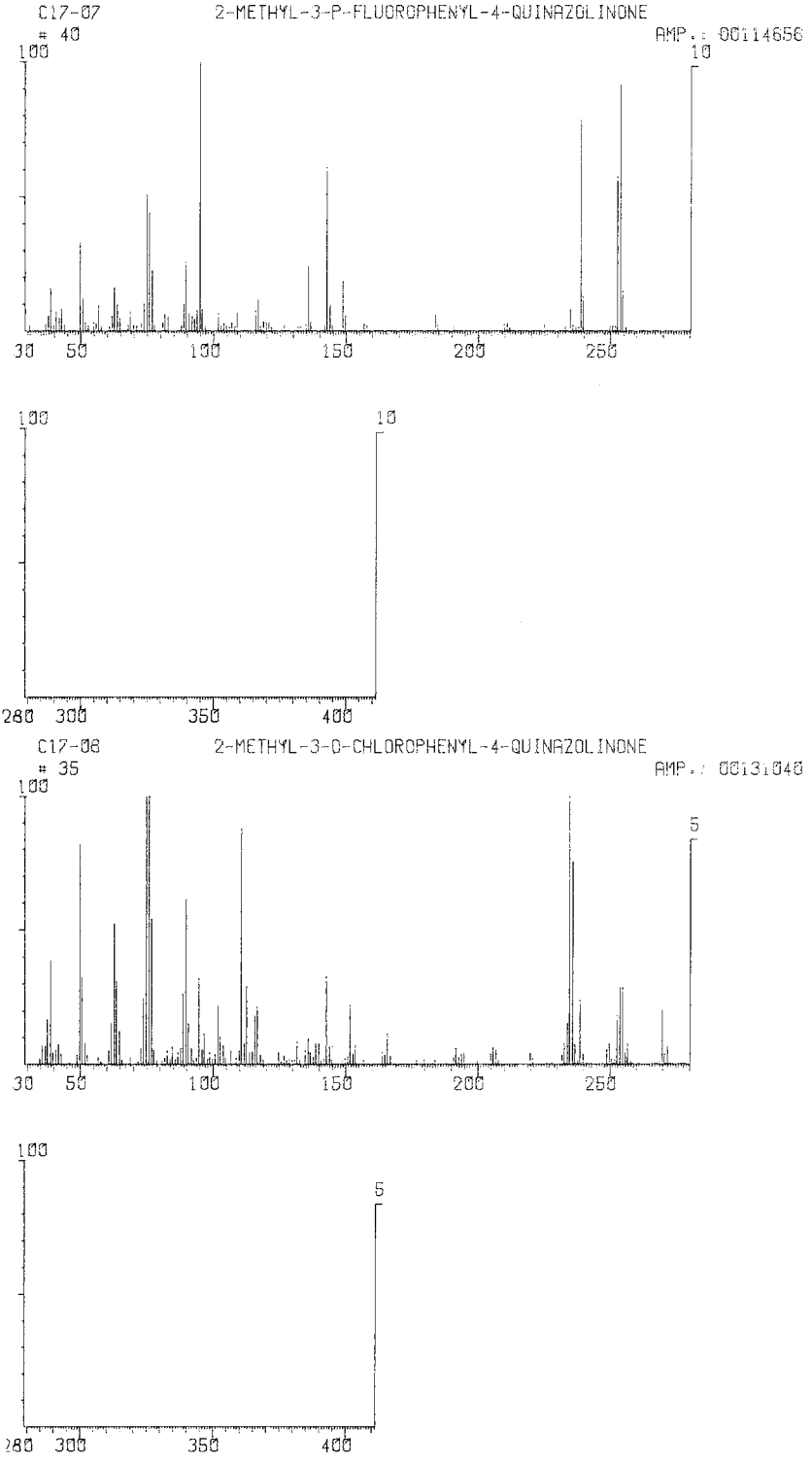

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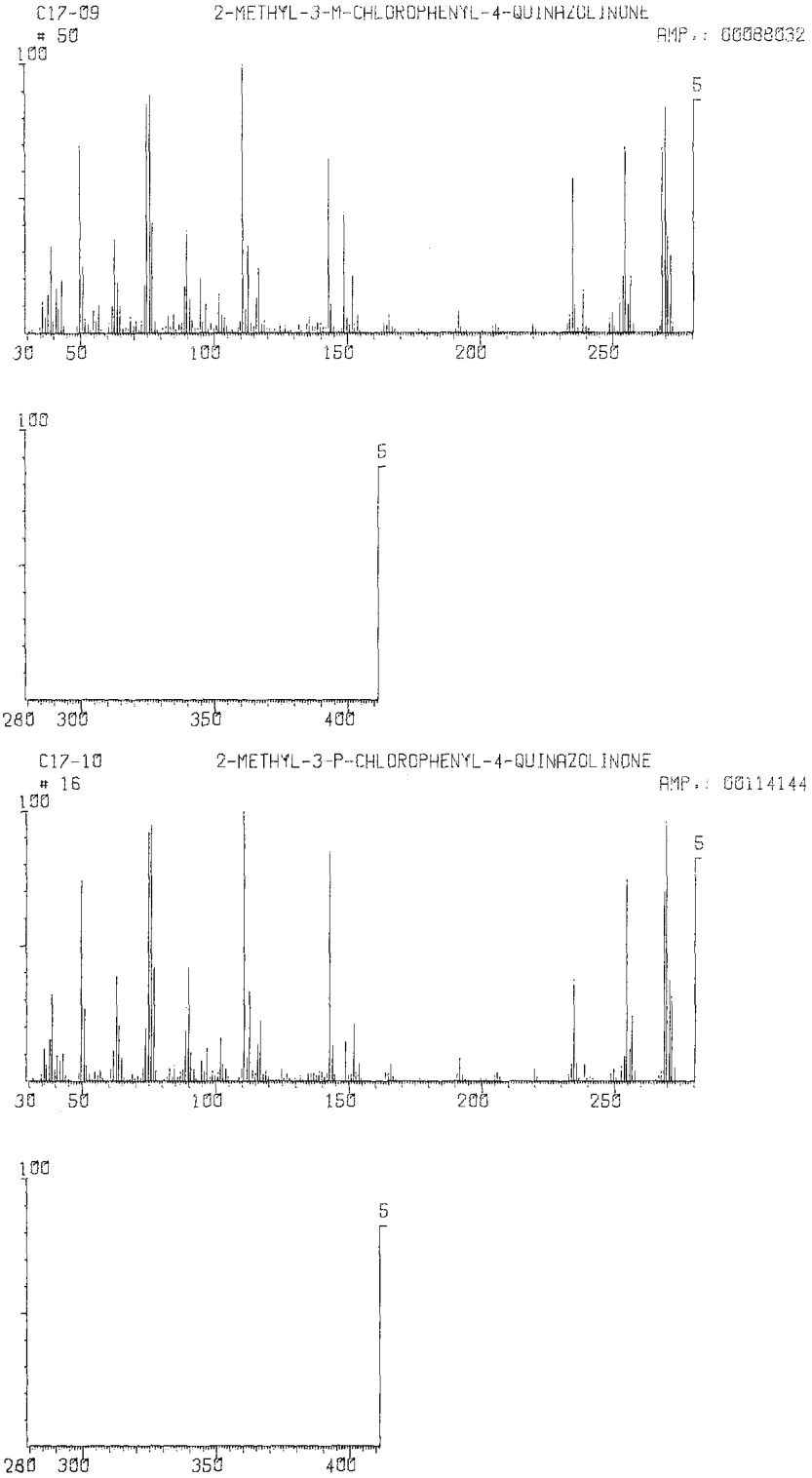

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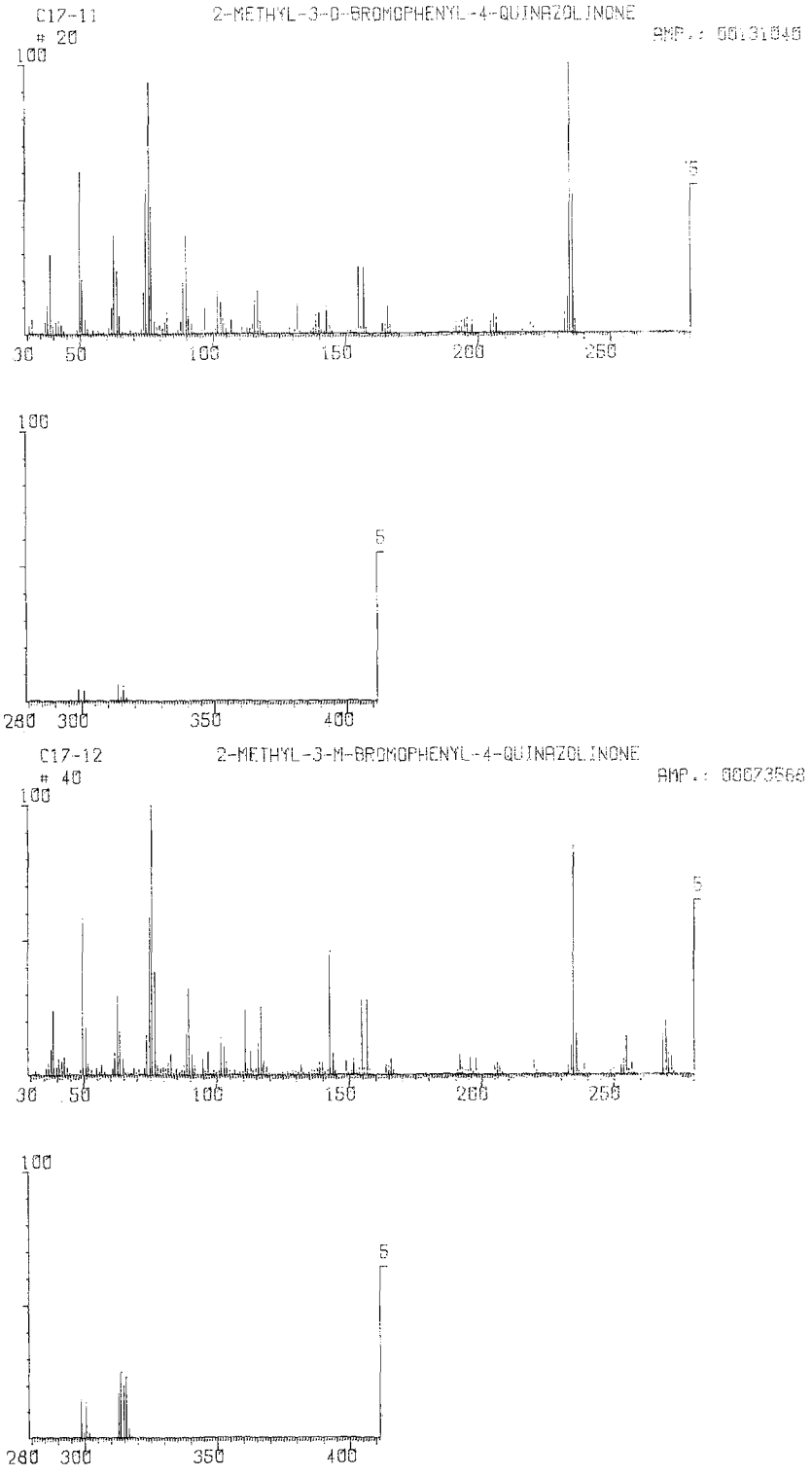

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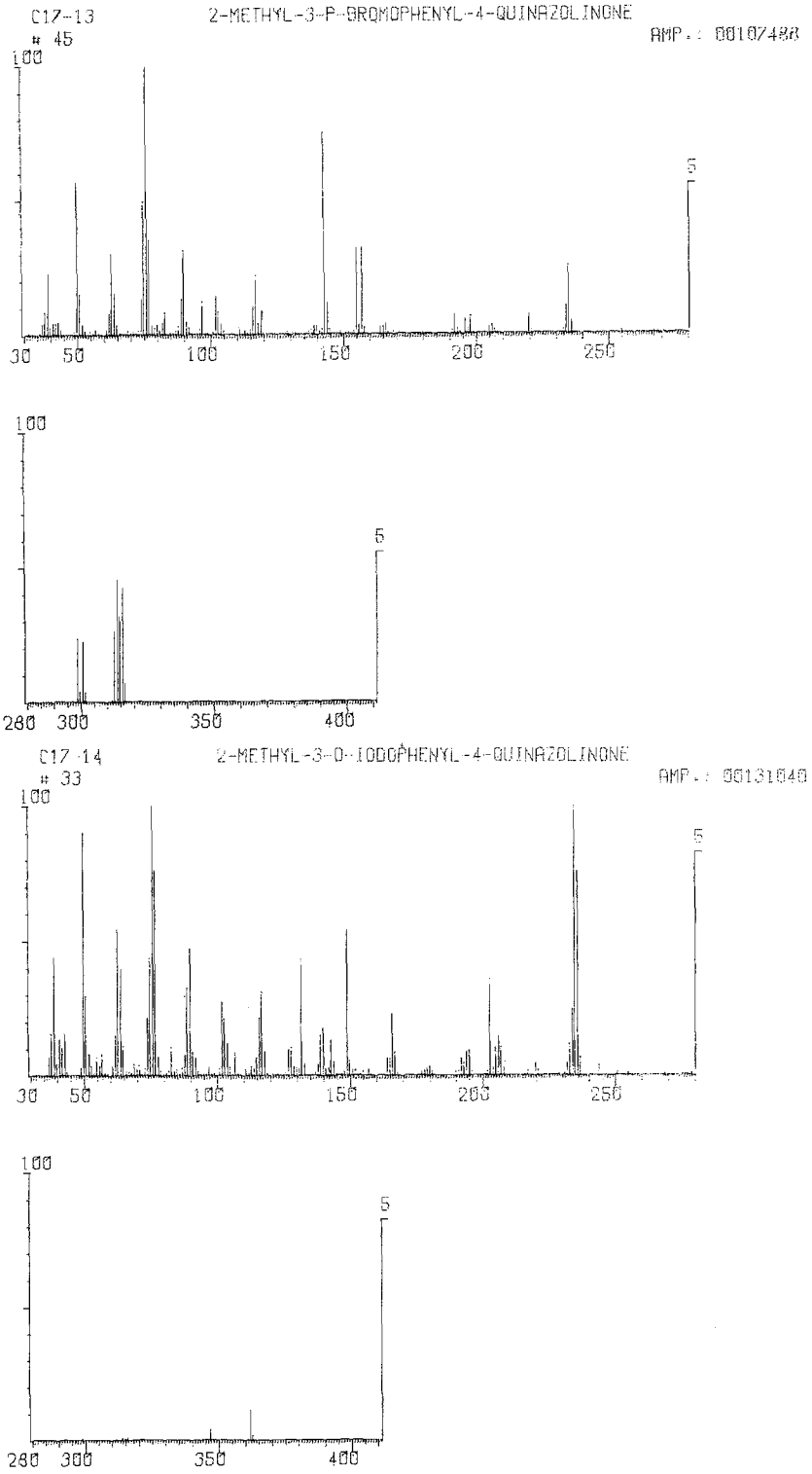

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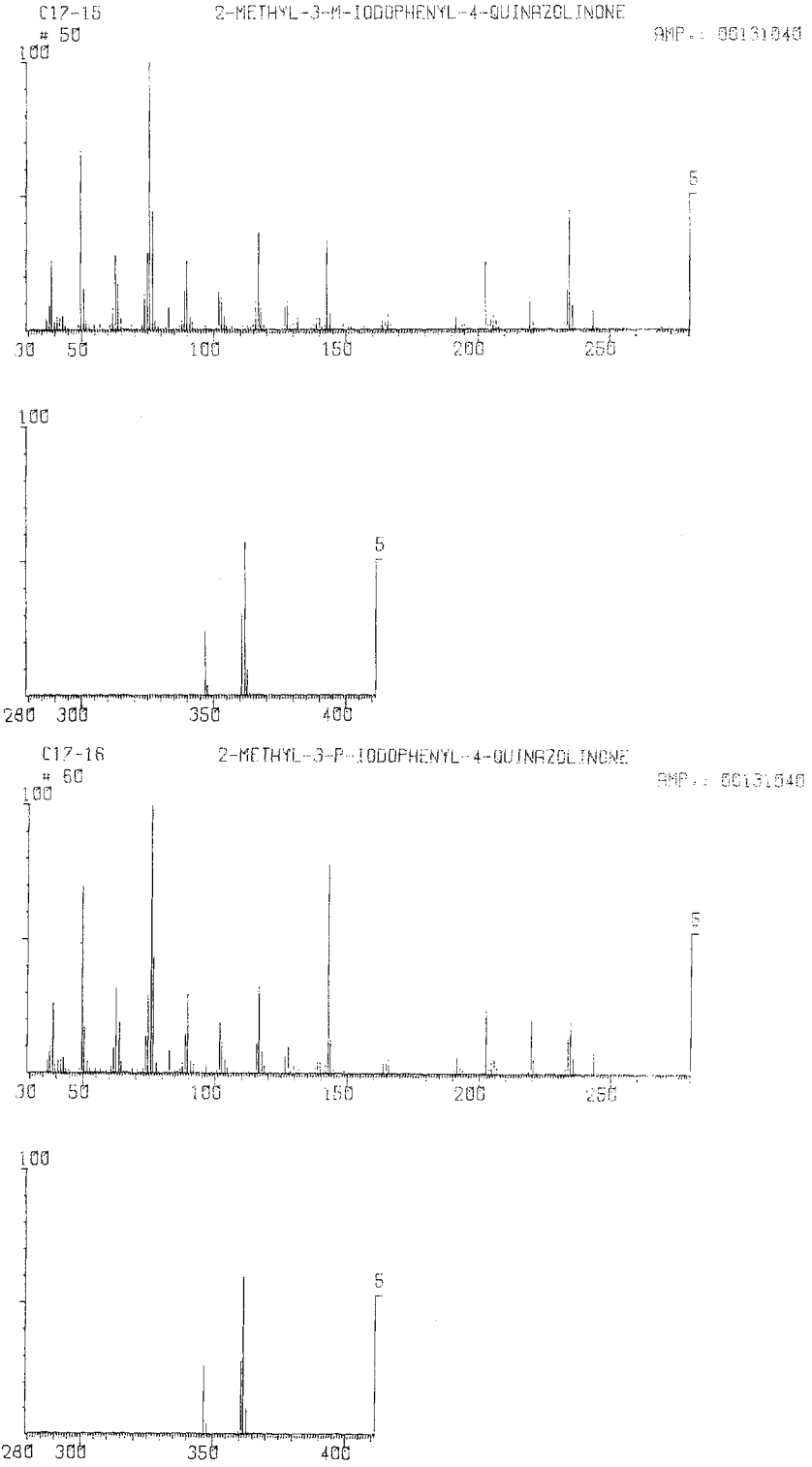


FIG. 2—*Continued.*

Close examination is required to determine the isomeric form of any one particular analogue. If the mass spectra are normalized, the unique identity of each of the 16 compounds can be established. The isomers within each type of analogue exhibit similar fragmentation patterns with the primary difference lying in their relative ion abundances or intensities (Table 4). All of the compounds considered, except for the brominated isomers, have even-numbered molecular ions. The presence of two nitrogen atoms coupled with an odd number of hydrogen atoms and the even atomic weight of bromine results in isomers yielding odd-number molecular ions.

Infrared Spectroscopy

Figure 3 provides the IR spectra of the free bases and Fig. 4 shows those of the hydrochloride salts of Compounds I to XVI. As expected, the IR spectra of these compounds were quite similar. The region from 1300 to 625 cm^{-1} is particularly useful in distinguishing the various halogen-containing compounds and their positional orientation. However, caution must be exercised in making identification of these compounds by their IR spectra. The hydrochlorides of Compounds XII and XV provide IR spectra that are nearly identical and must be carefully examined for differentiation. Further complications may arise because of polymorphism; the hydrochloride of Compound VIII (mecloqualone hydrochloride) exhibits three unique IR spectra [*14*].

Proton Magnetic Resonance Spectra

The proton magnetic resonance spectra (Fig. 5) were obtained on free base compounds dissolved in deuterochloroform. The chemical shifts are expressed in δ values (ppm). Compound II (methaqualone) has two resonance singlets resulting from the ortho-tolyl methyl group at 2.15 ppm and the quinazolinone ring methyl group at 2.25 ppm. A change in the position of the tolyl methyl group in Compounds II, III, and IV produces a resonance pattern change in the phenyl absorption peak and a corresponding shift upfield of the methyl peak. Both the meta- and para-tolyl isomers (Compounds III and IV) of methaqualone (Compound II) exhibit tolyl methyl peak shifts at 2.45 ppm. A slight shift of the

TABLE 4—*Relative intensities of selected mass fragments.*

Compound	Formula	Molecular Ion	*m/e* 132:143	143:149	142:143:144	234:235:236
I	$C_{15}H_{12}N_2O$	236	...	...	6:1:0	1:28:33
II	$C_{16}H_{14}N_2O$	250	3:2	...	0:4:1	1:4:2
III	$C_{16}H_{14}N_2O$	250	2:3	...	1:40:8	1:14:3
IV	$C_{16}H_{14}N_2O$	250	1:3	...	1:38:6	1:15:3
V	$C_{15}H_{11}FN_2O$	254	...	8:3	1:41:6	1:10:2
VI	$C_{15}H_{11}FN_2O$	254	...	80:1	1:41:6	1:11:2
VII	$C_{15}H_{11}FN_2O$	254	...	3:1	1:46:7	0:6:1
VIII	$C_{15}H_{11}ClN_2O$	270	...	...	2:3:4	1:6:5
IX	$C_{15}H_{11}ClN_2O$	270	...	...	1:34:4	1:8:2
X	$C_{15}H_{11}ClN_2O$	270	...	...	0:7:1	1:5:1
XI	$C_{15}H_{11}BrN_2O$	315	...	...	0:1:0	1:8:4
XII	$C_{15}H_{11}BrN_2O$	315	...	...	0:8:1	2:15:3
XIII	$C_{15}H_{11}BrN_2O$	315	...	...	0:0:0	2:5:1
XIV	$C_{15}H_{11}IN_2O$	362	...	...	1:5:2	1:4:3
XV	$C_{15}H_{11}IN_2O$	362	...	...	2:50:9	2:5:1
XVI	$C_{15}H_{11}IN_2O$	362	...	...	1:30:5	5:7:2

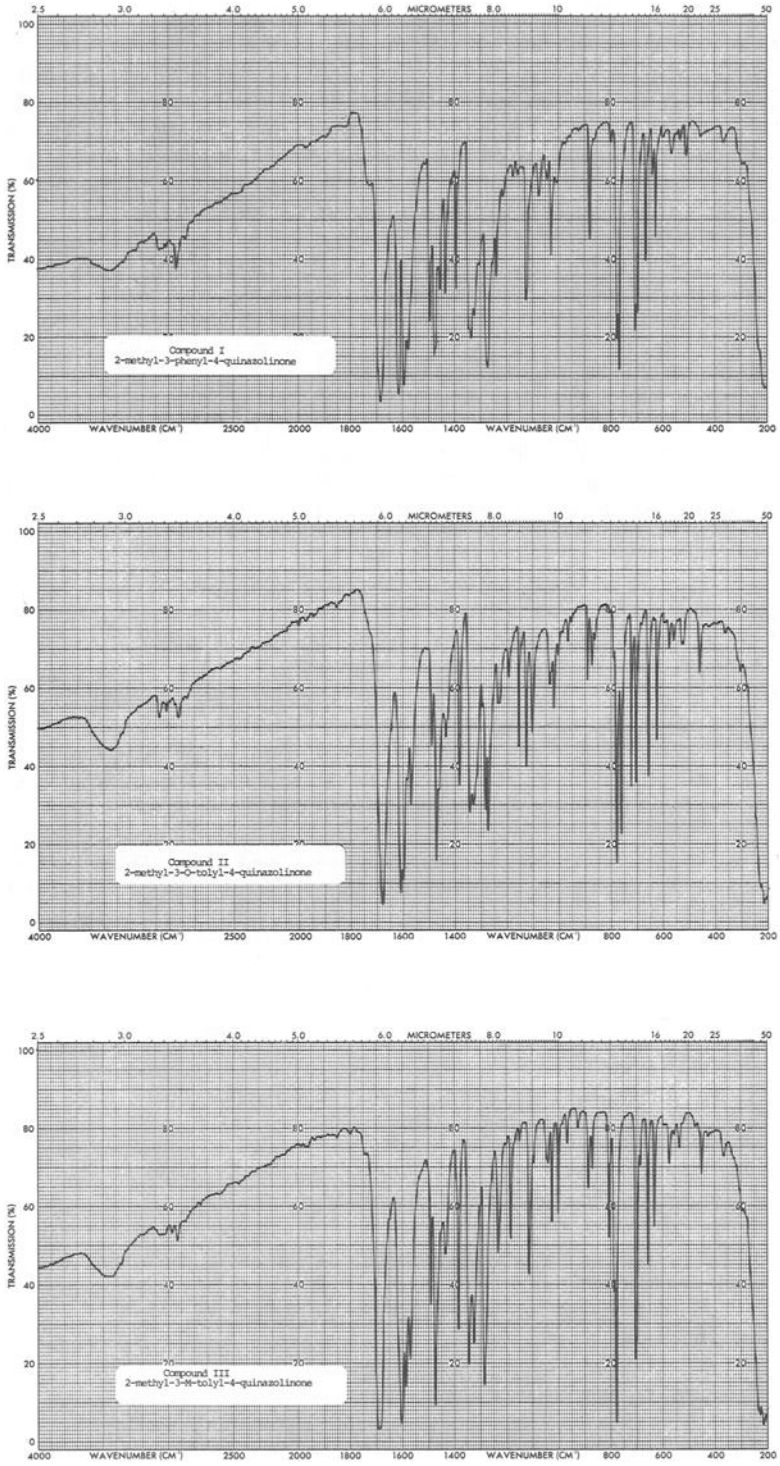
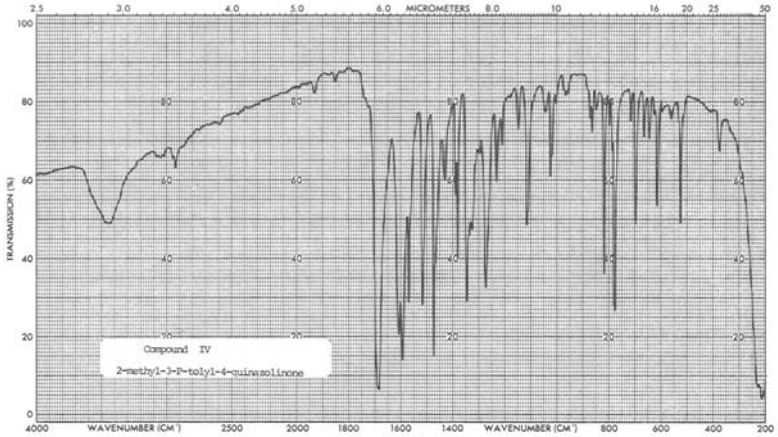
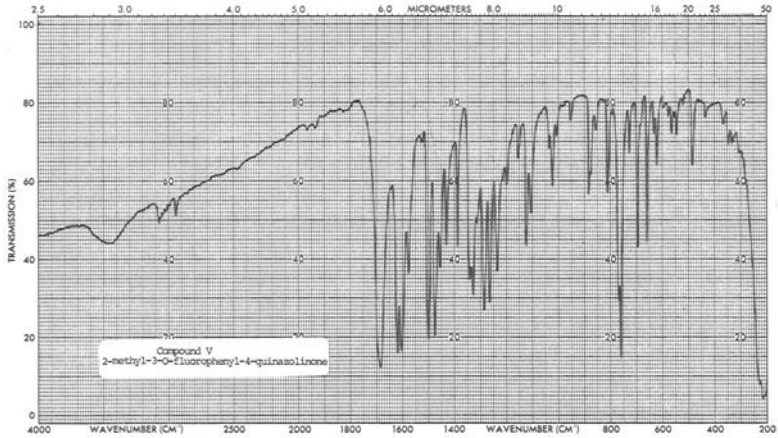
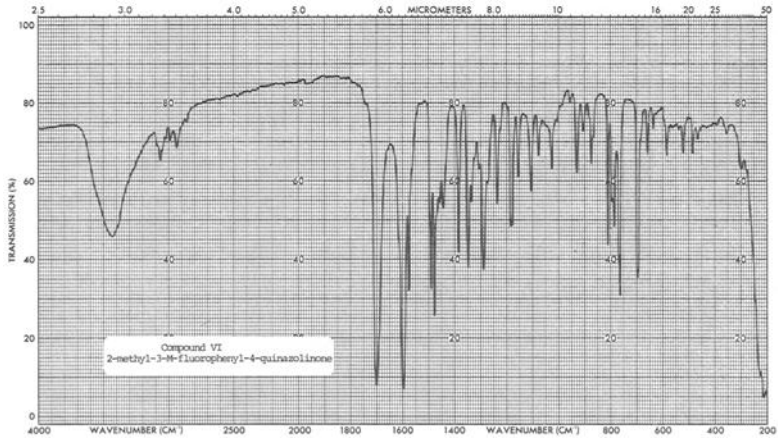


FIG. 3—*Infrared spectra of some analogues of methaqualone as their free bases; KBr pellet.*







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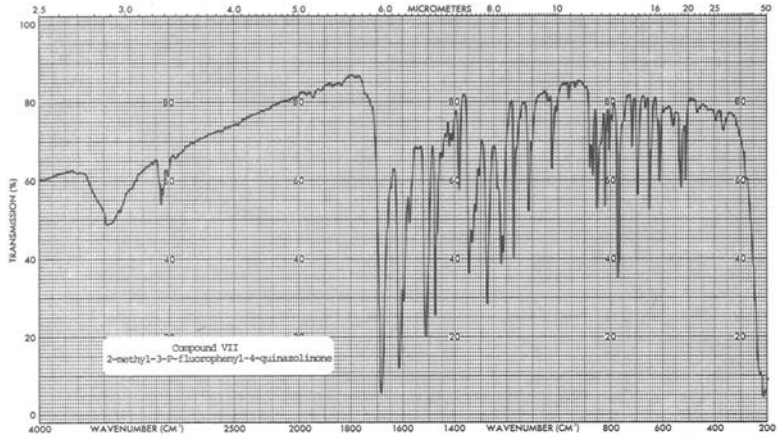

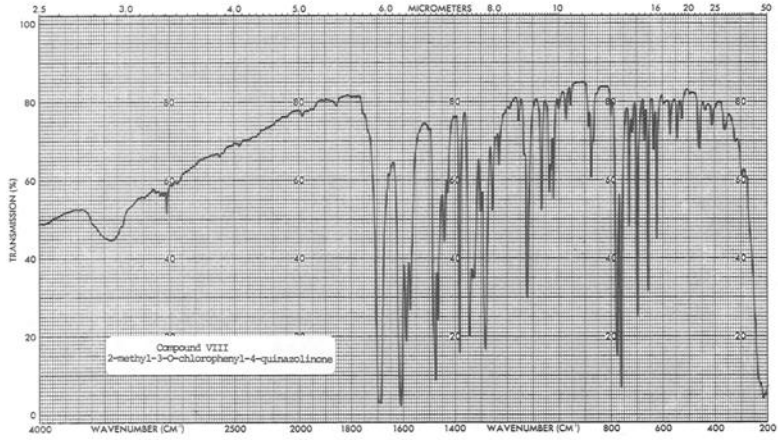

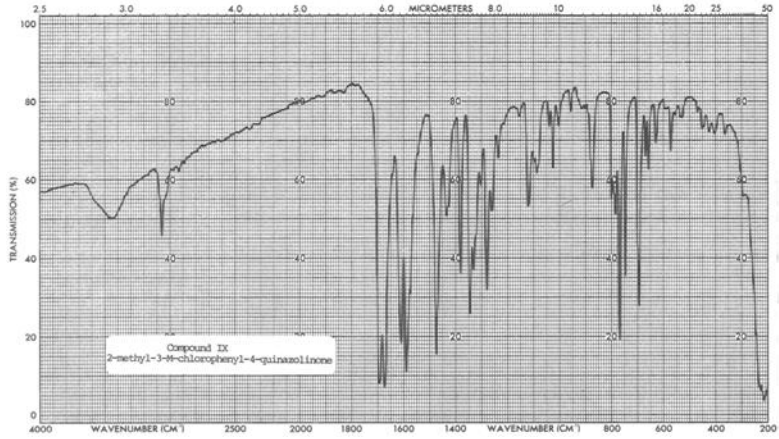

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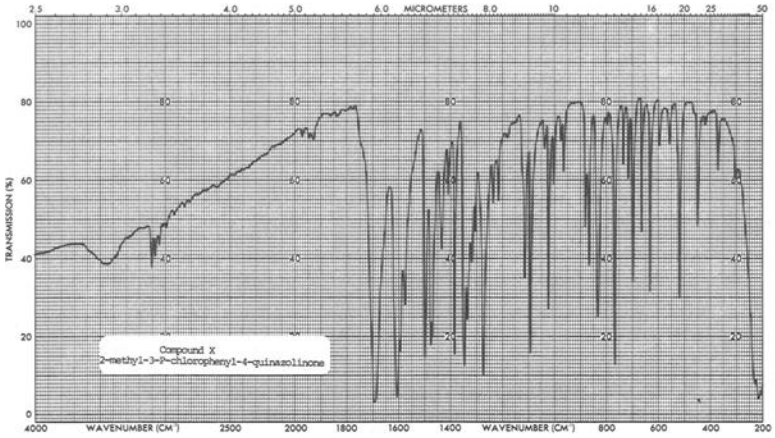

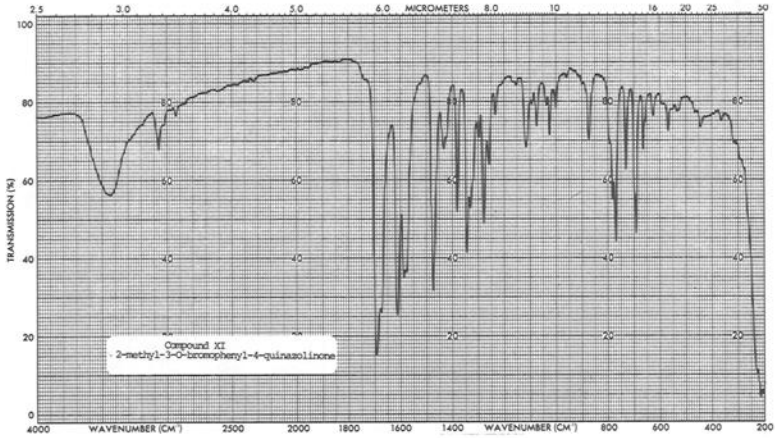

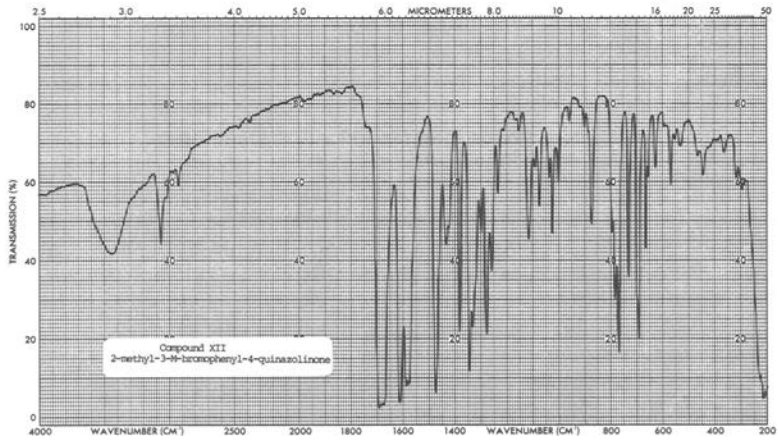

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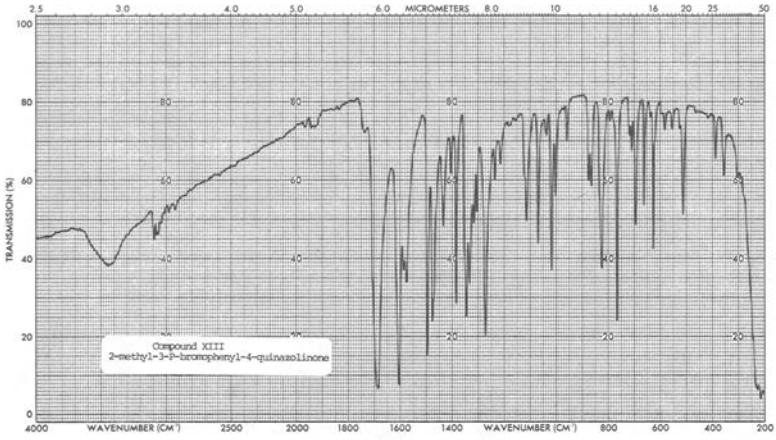

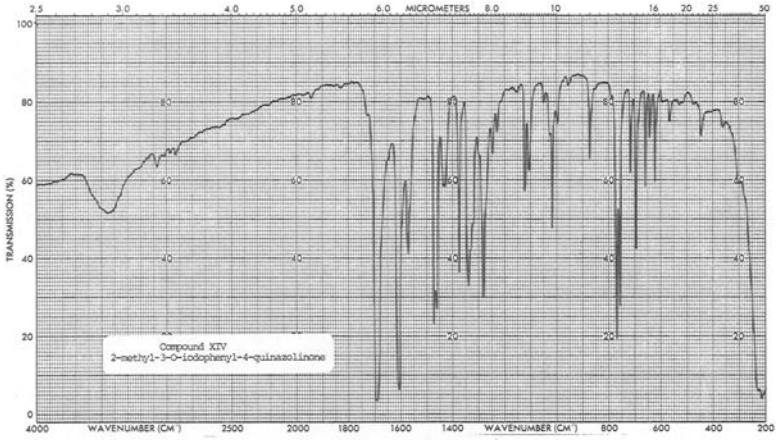

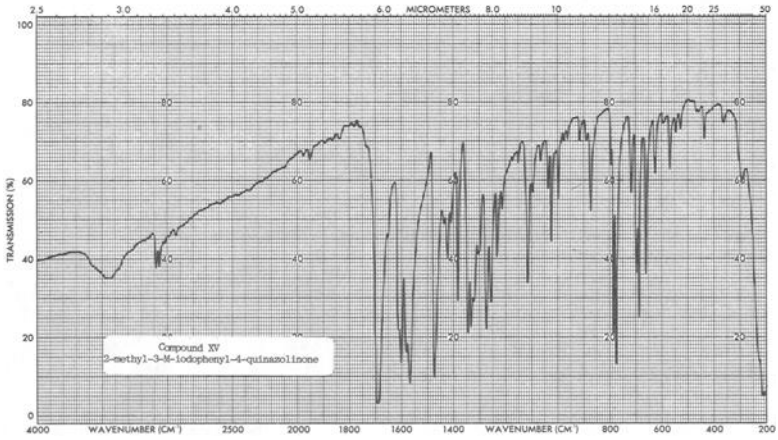

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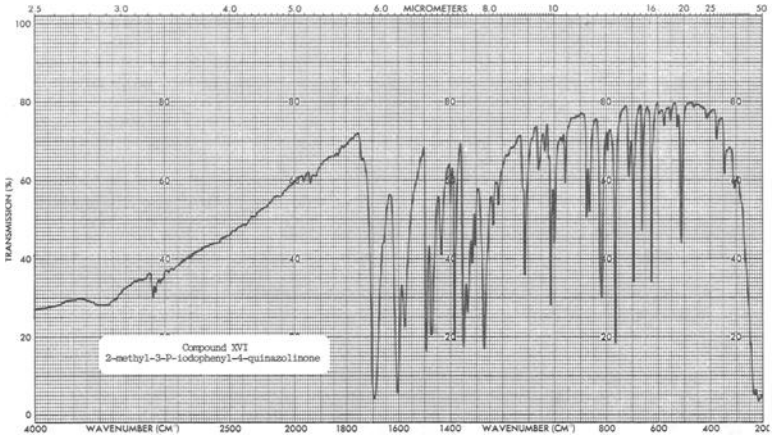

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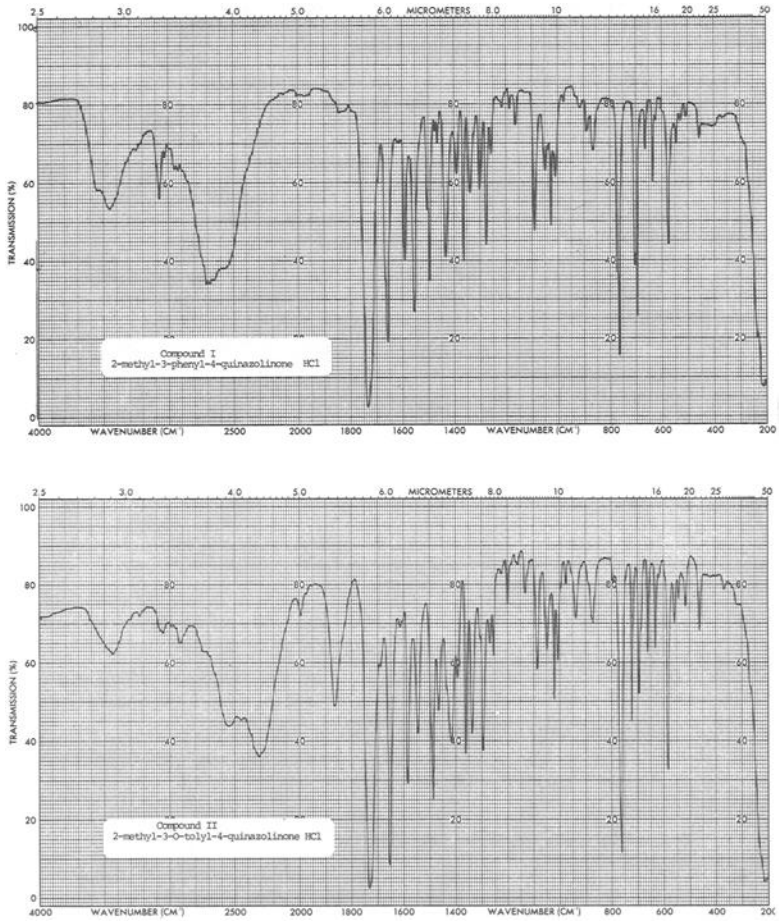
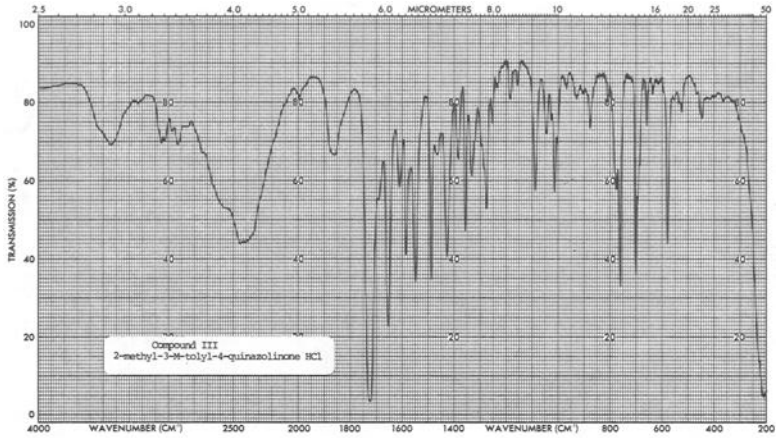
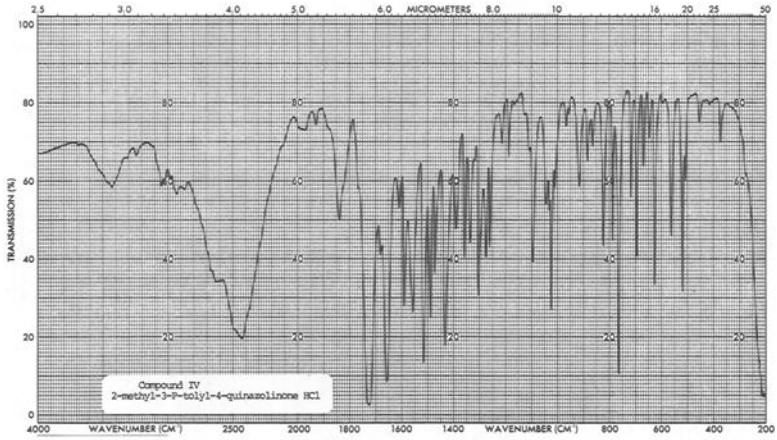
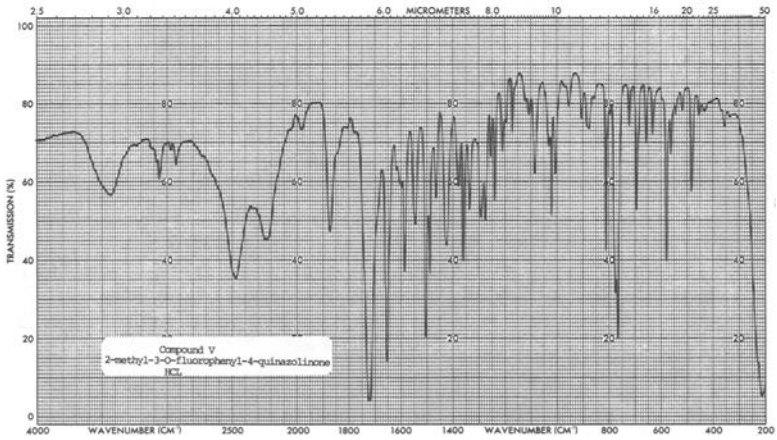


FIG. 4—*Infrared spectra of some analogues of methaqualone as their hydrochloride salts; KBr pellet.*







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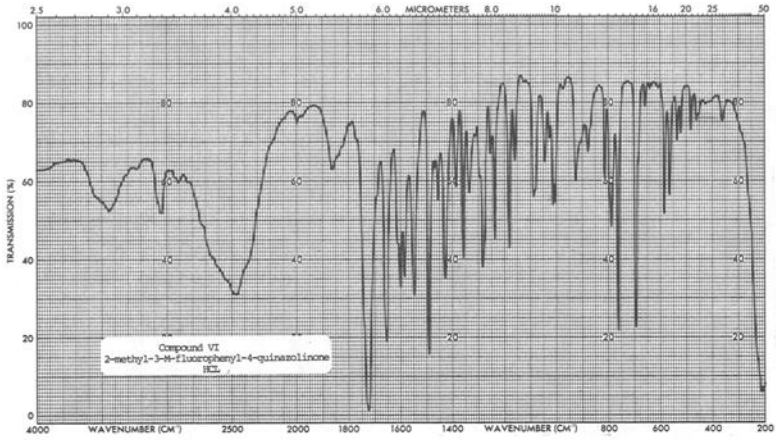
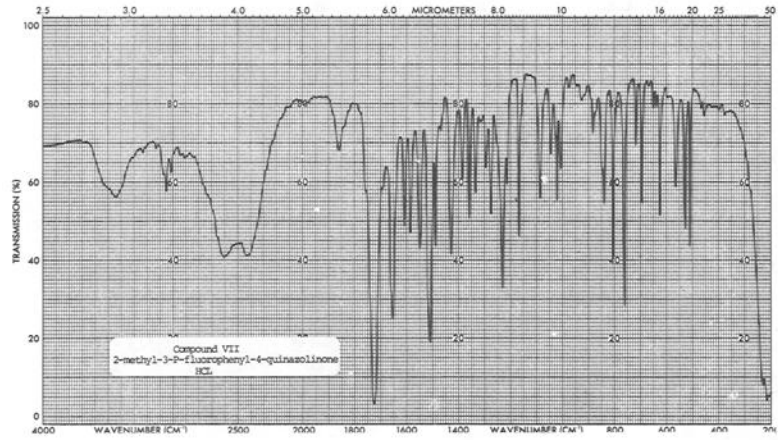




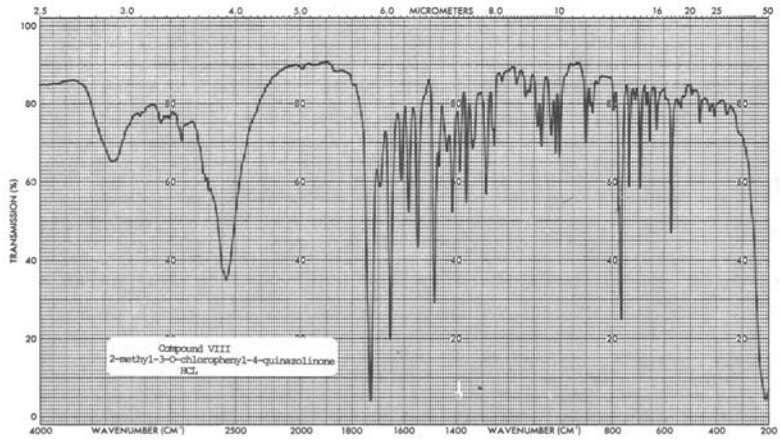
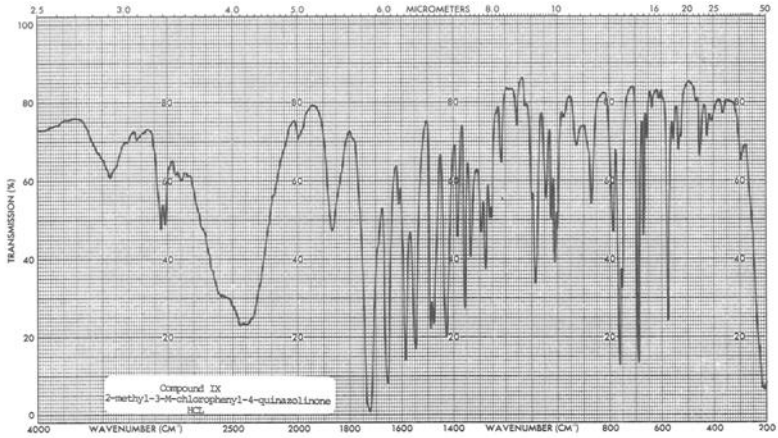
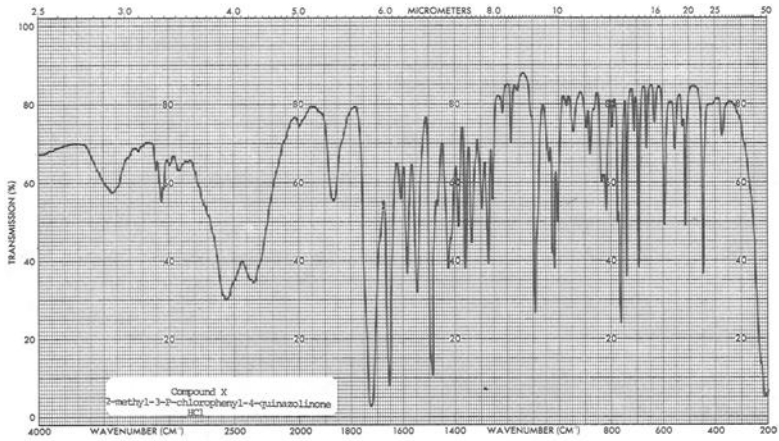


FIG. 4—*Continued.*





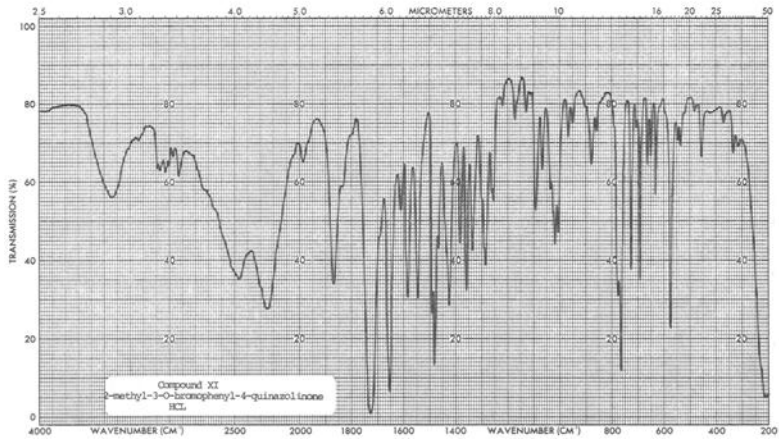
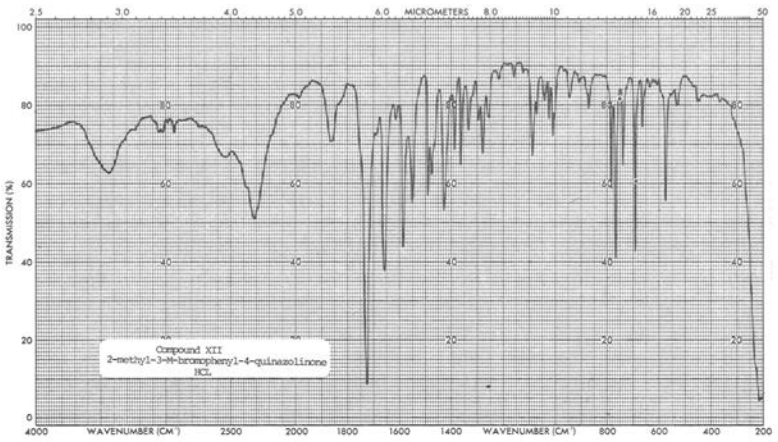
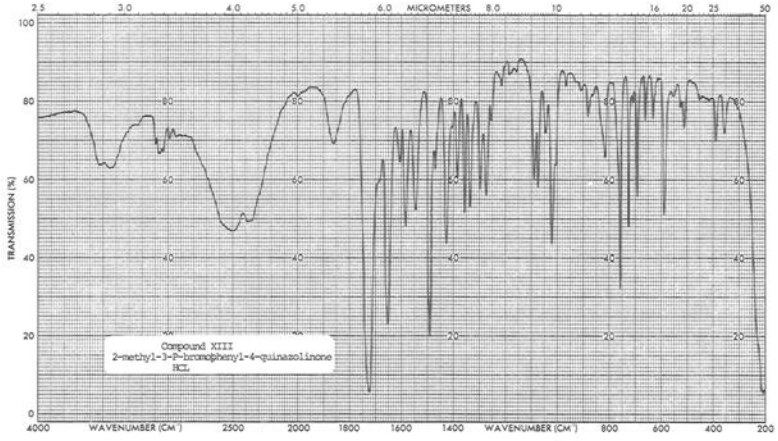


FIG. 4—*Continued.*





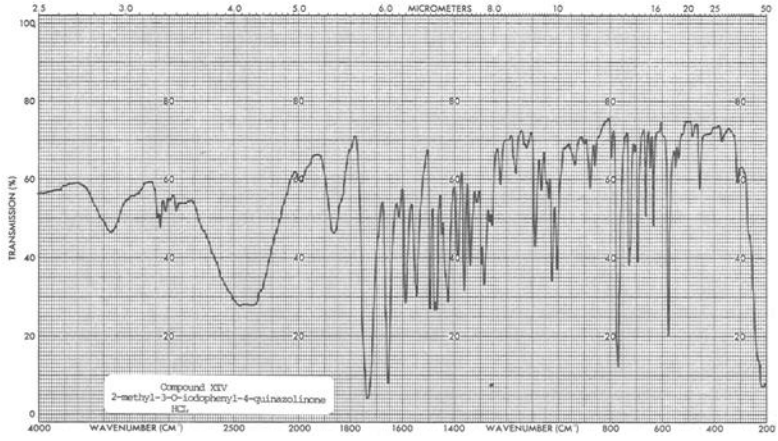


FIG. 4—*Continued.*

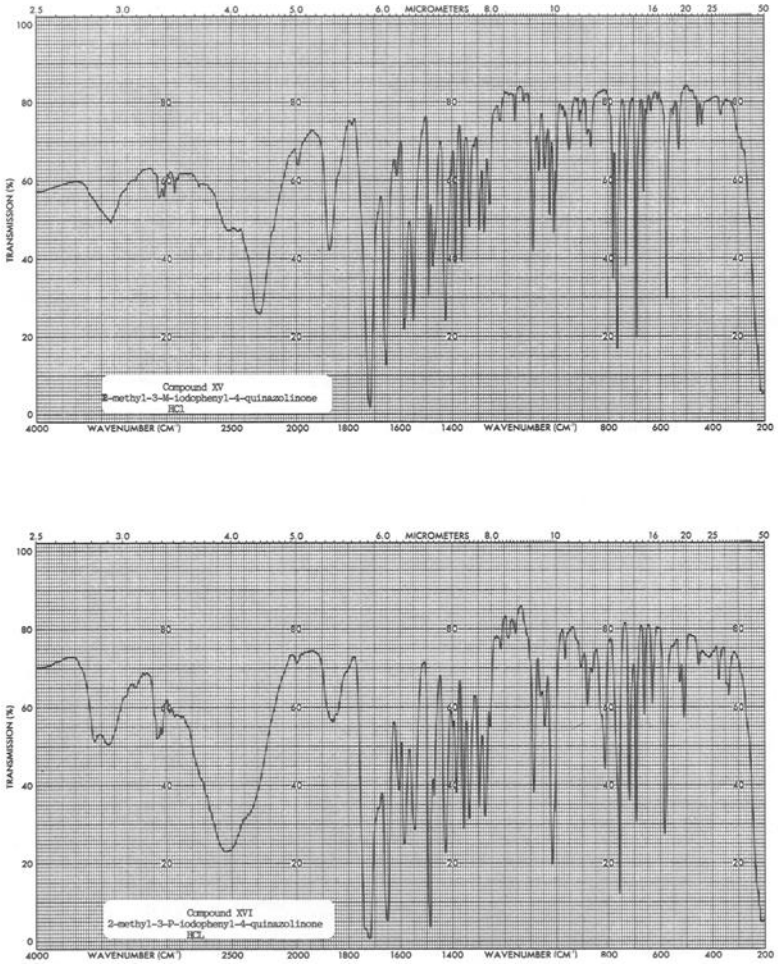


FIG. 4—*Continued.*

quinazolinone ring methyl peak at 2.3 ppm is also observed. The overlapping of the resonance signal of quinazolinone ring protons with that of the phenyl ring protons is exhibited by the complex pattern in the 7.2- to 8.8-ppm range. Consequently, any halogen substitution of the phenyl ring protons would show a distinct change in the splitting pattern in this area. With the different magnetic moments and isotopic ratios of the substituted halogens it is evident that characteristic spectra will be obtained for each analogue analyzed. These changes are detectable and greatly aid in compound identification.

Conclusions

This paper describes the synthesis of the 16 substituted quinazolinones and presents the analytical data for their identification. The accumulated data indicate that identification of these compounds can be accomplished most efficiently through use of an interfaced GLC/MS system. Although the IR spectra are similar, and in some cases virtually identical, careful examination will reveal a sufficient number of unique features to permit differenti-

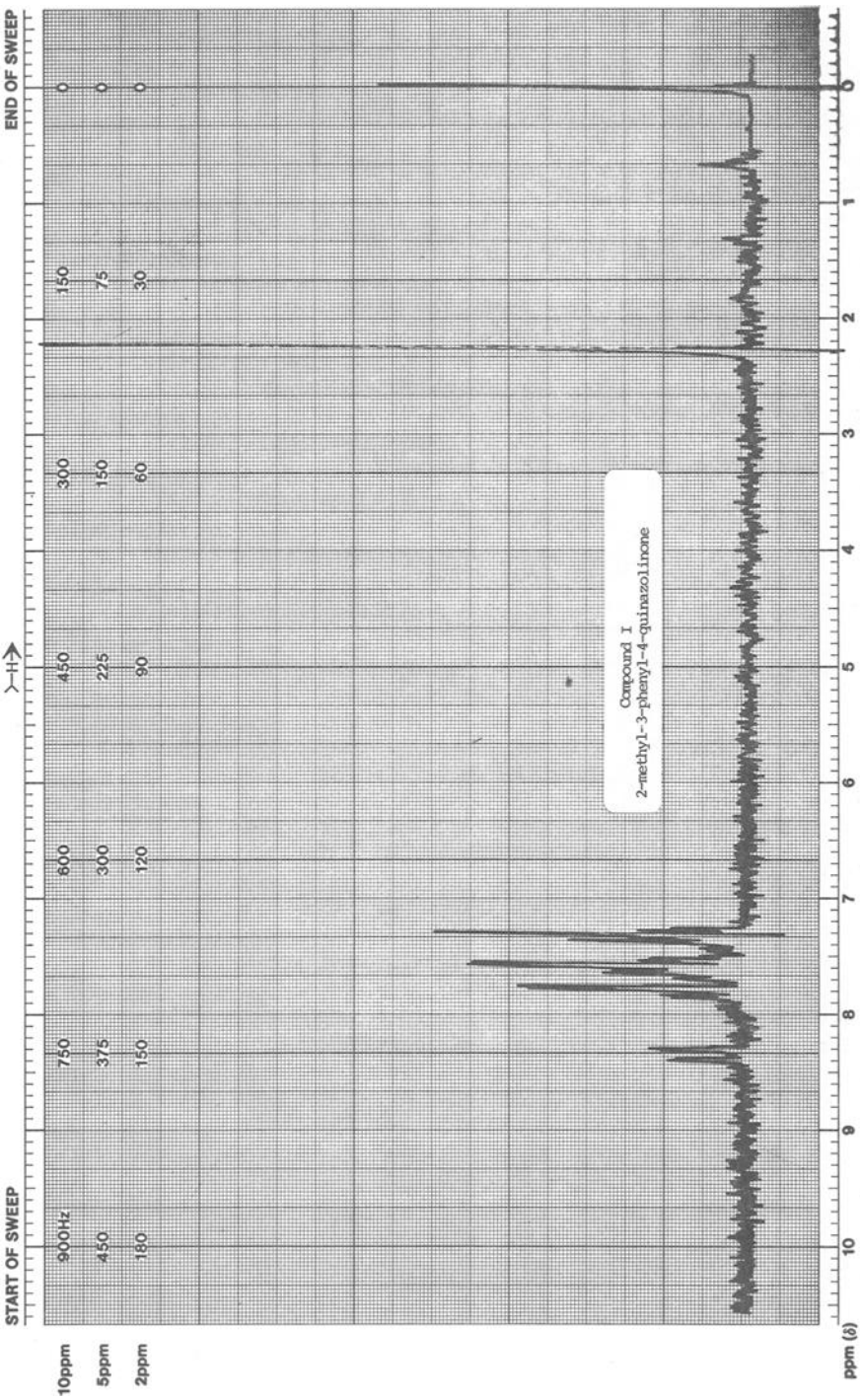


FIG. 5—*Nuclear magnetic resonance spectra of some analogues of methaqualone as their bases in deuterochloroform.*

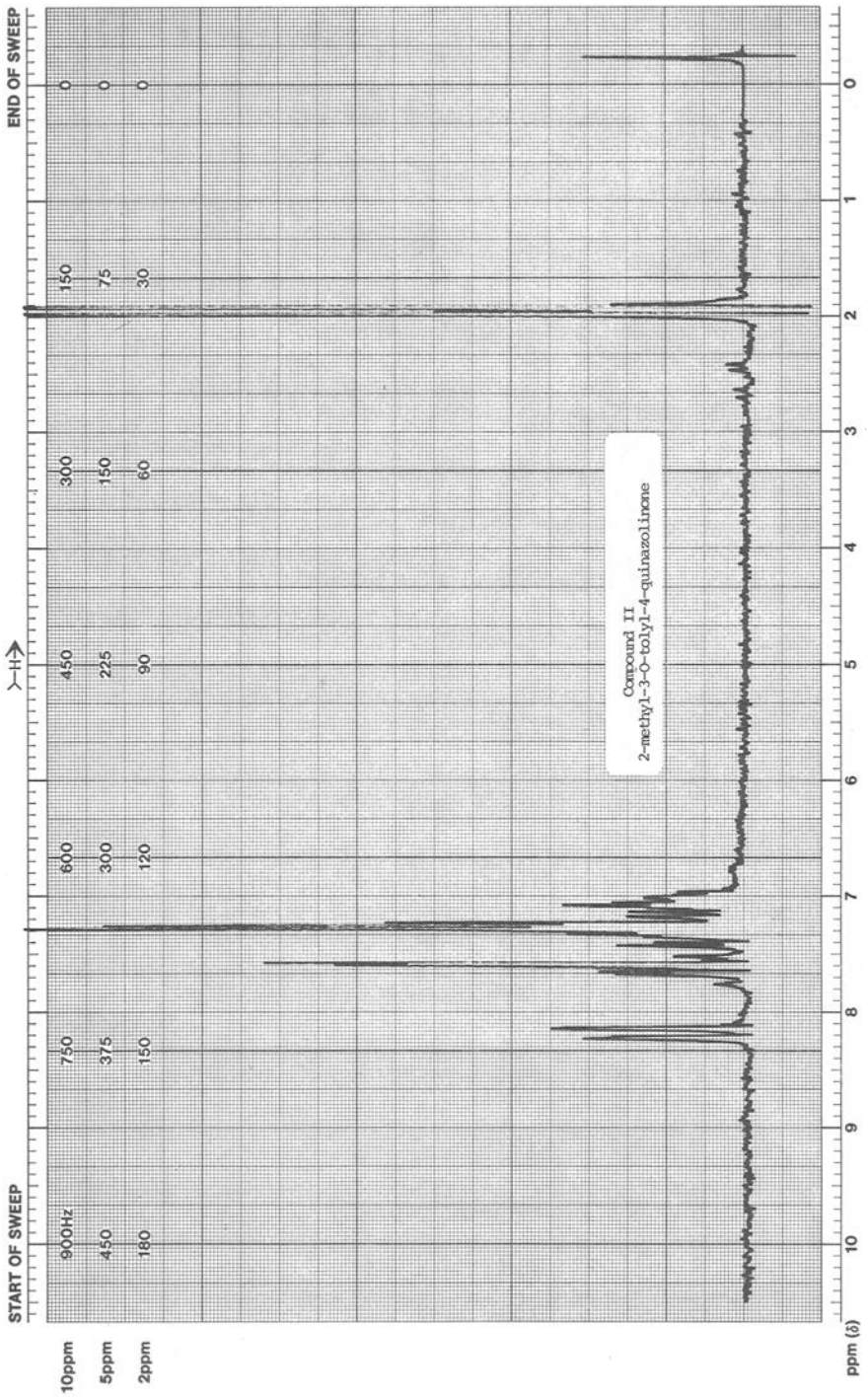


FIG. 5—*Continued.*

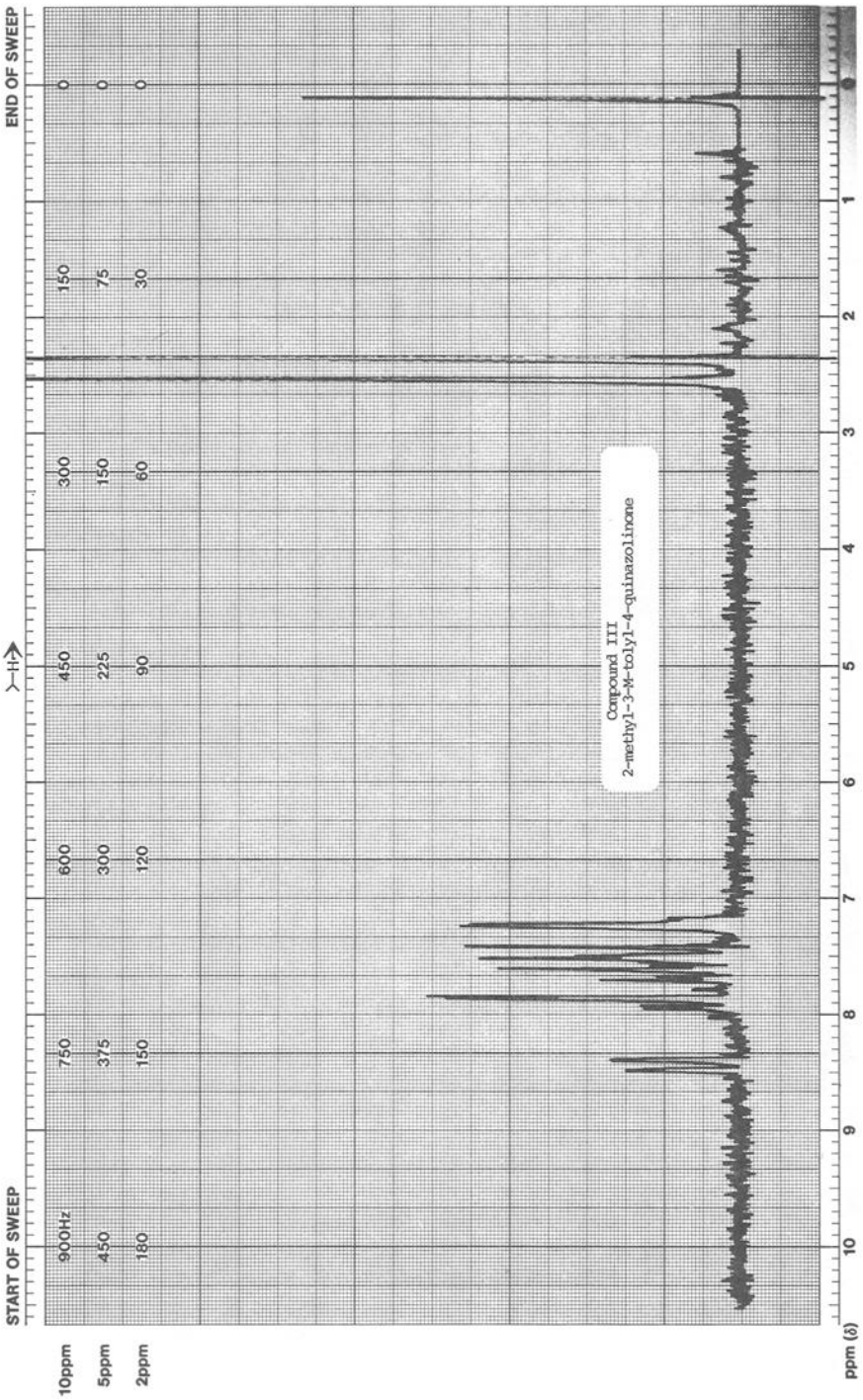


FIG. 5—*Continued.*

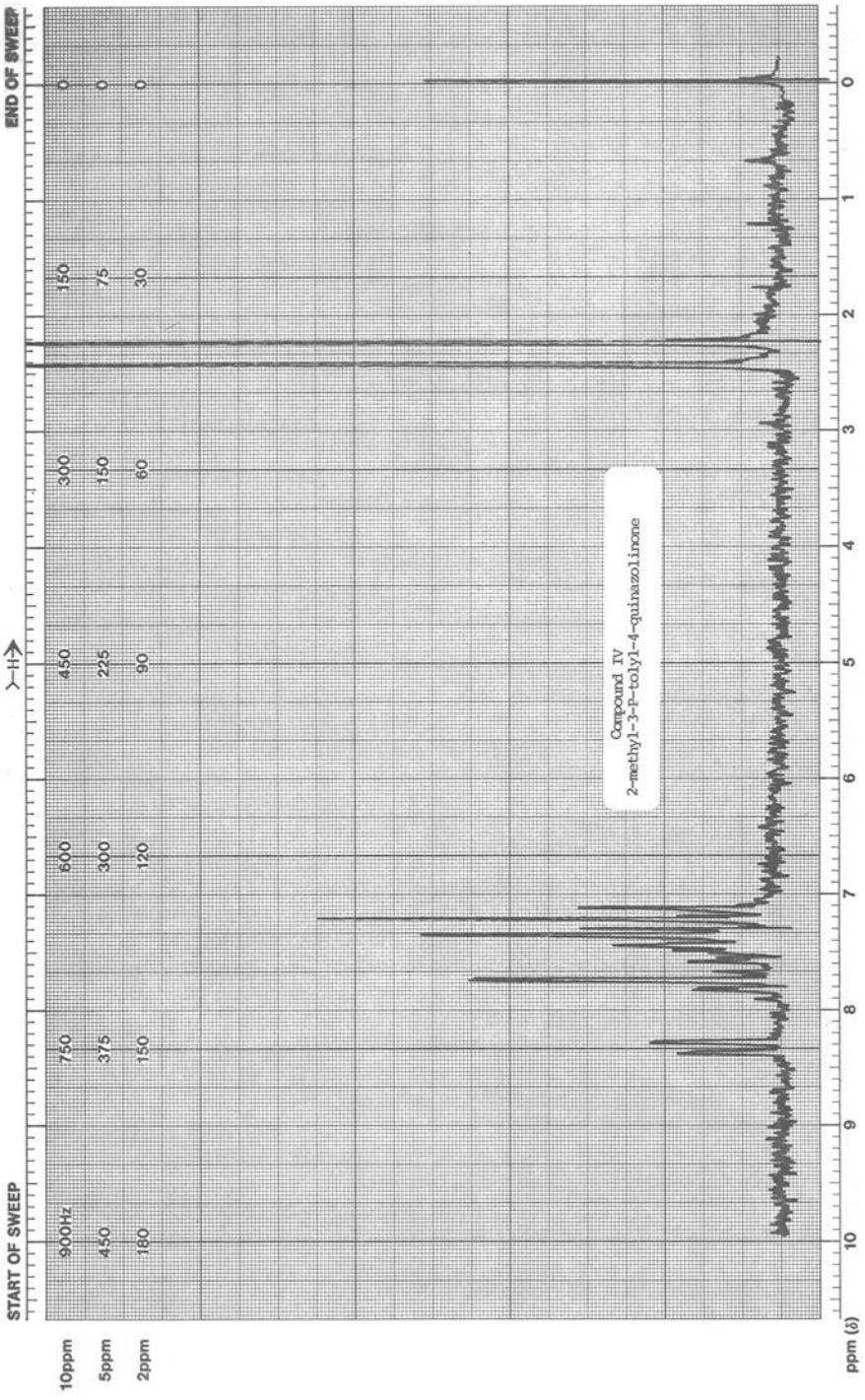


FIG. 5—*Continued.*

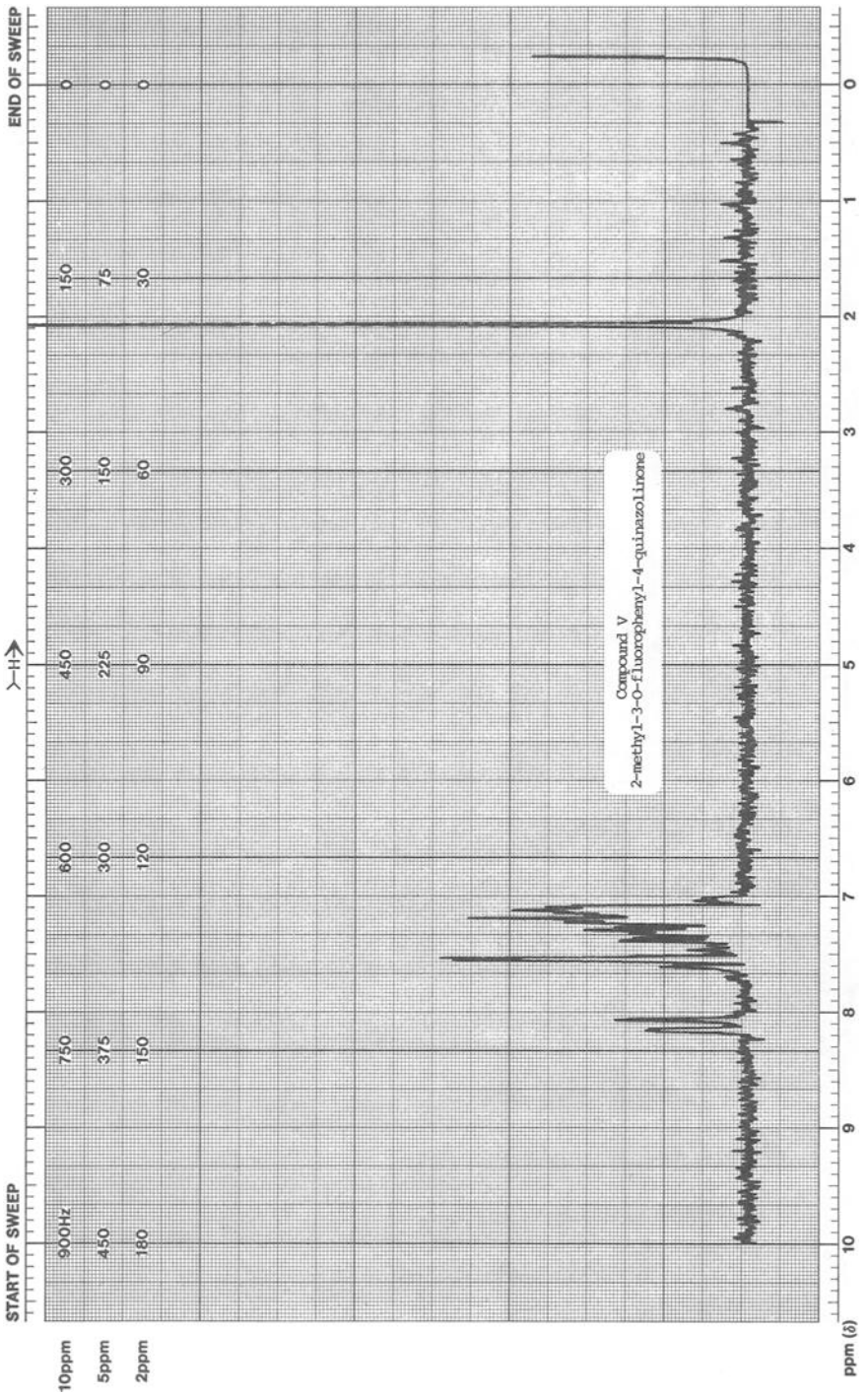


FIG. 5—*Continued.*

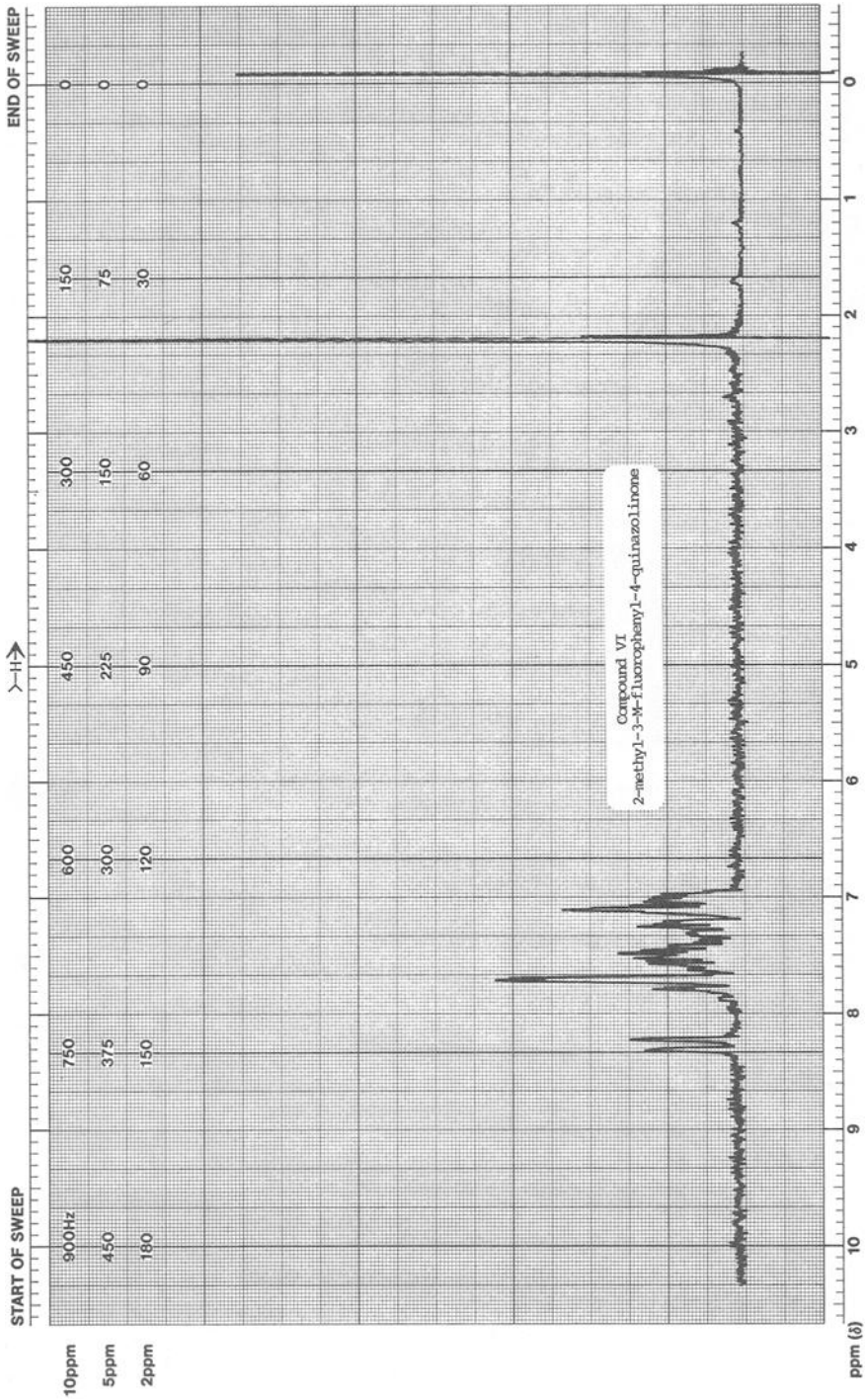


FIG. 5—*Continued.*

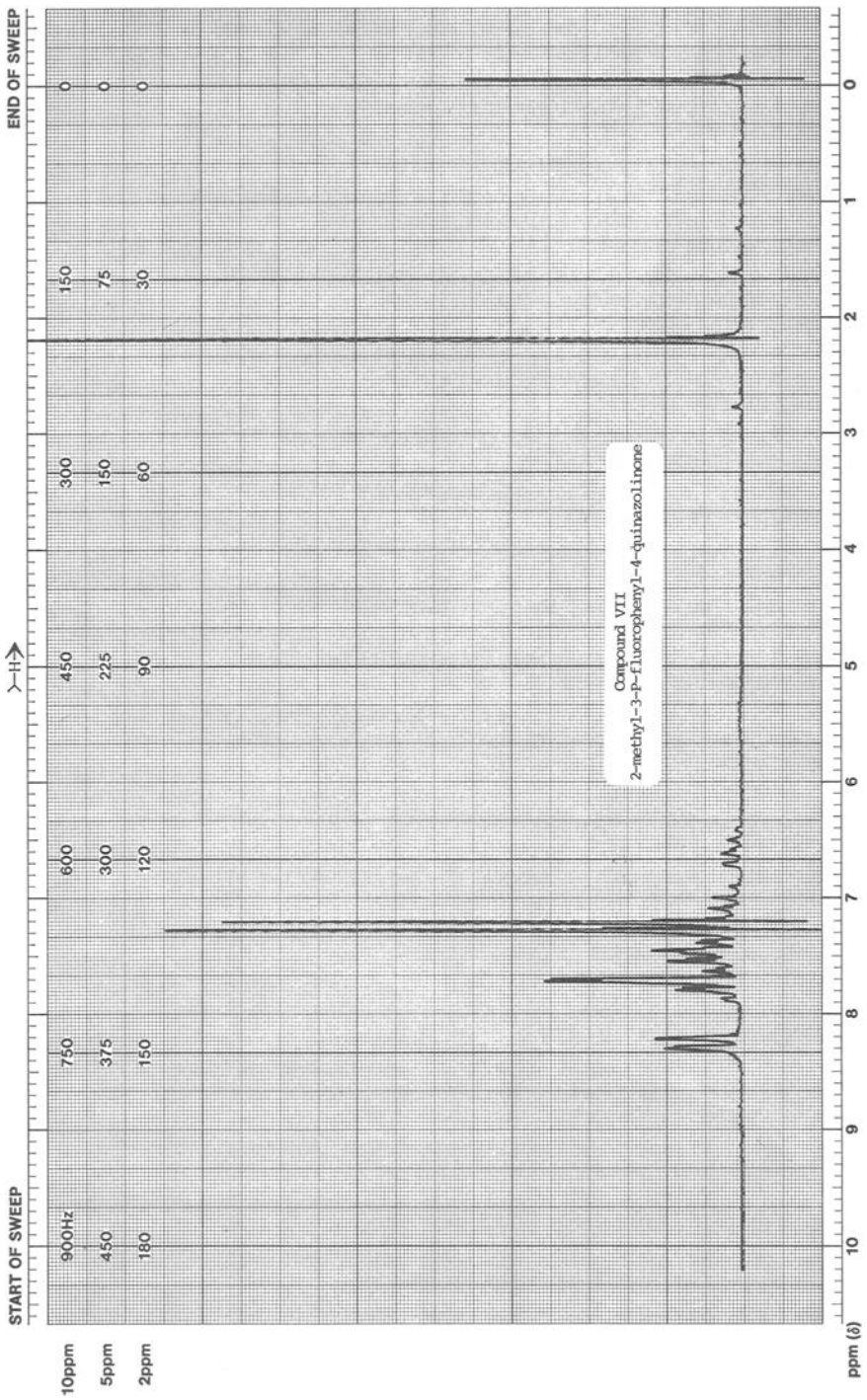


FIG. 5—*Continued.*

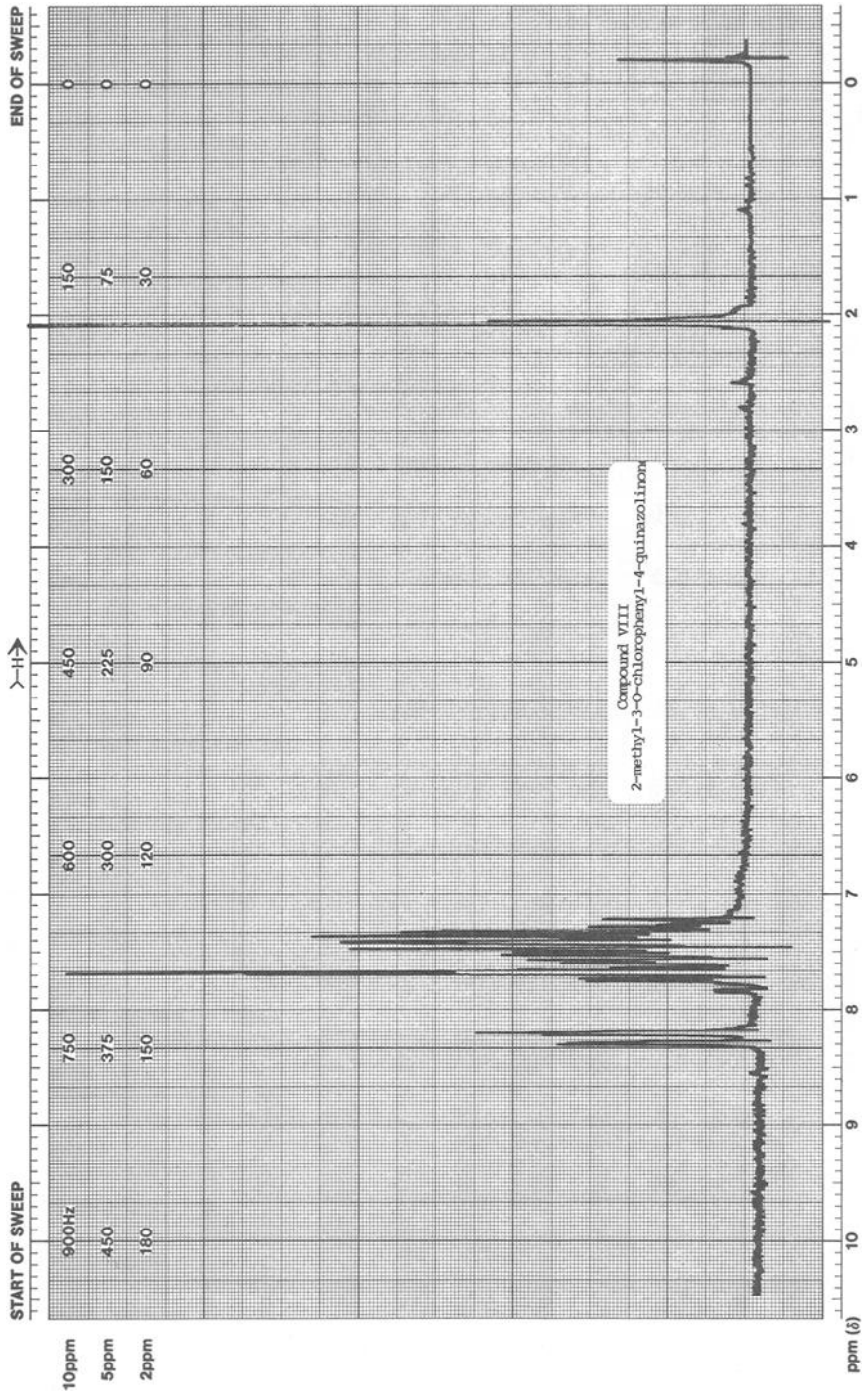


FIG. 5—*Continued.*

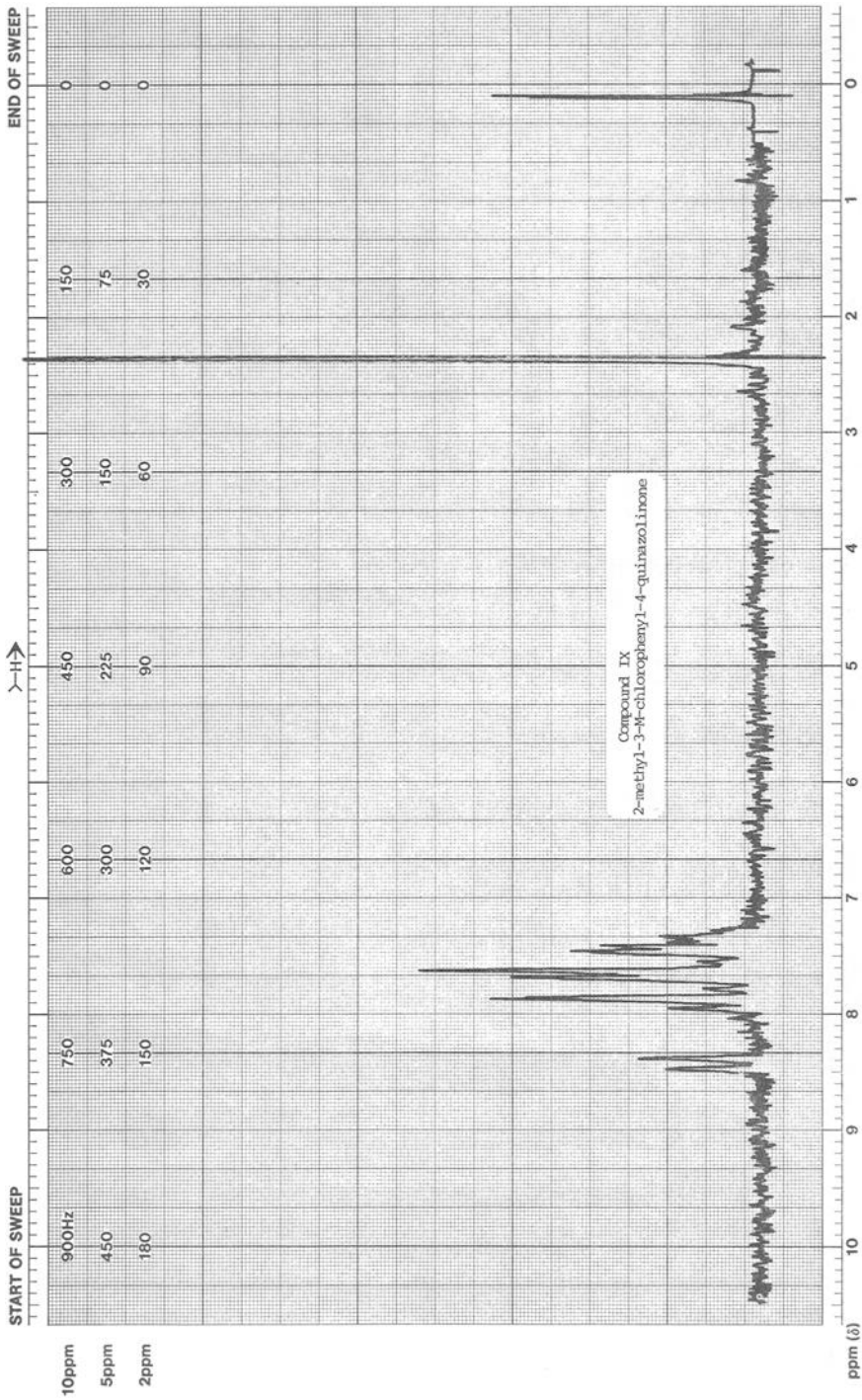


FIG. 5—*Continued.*

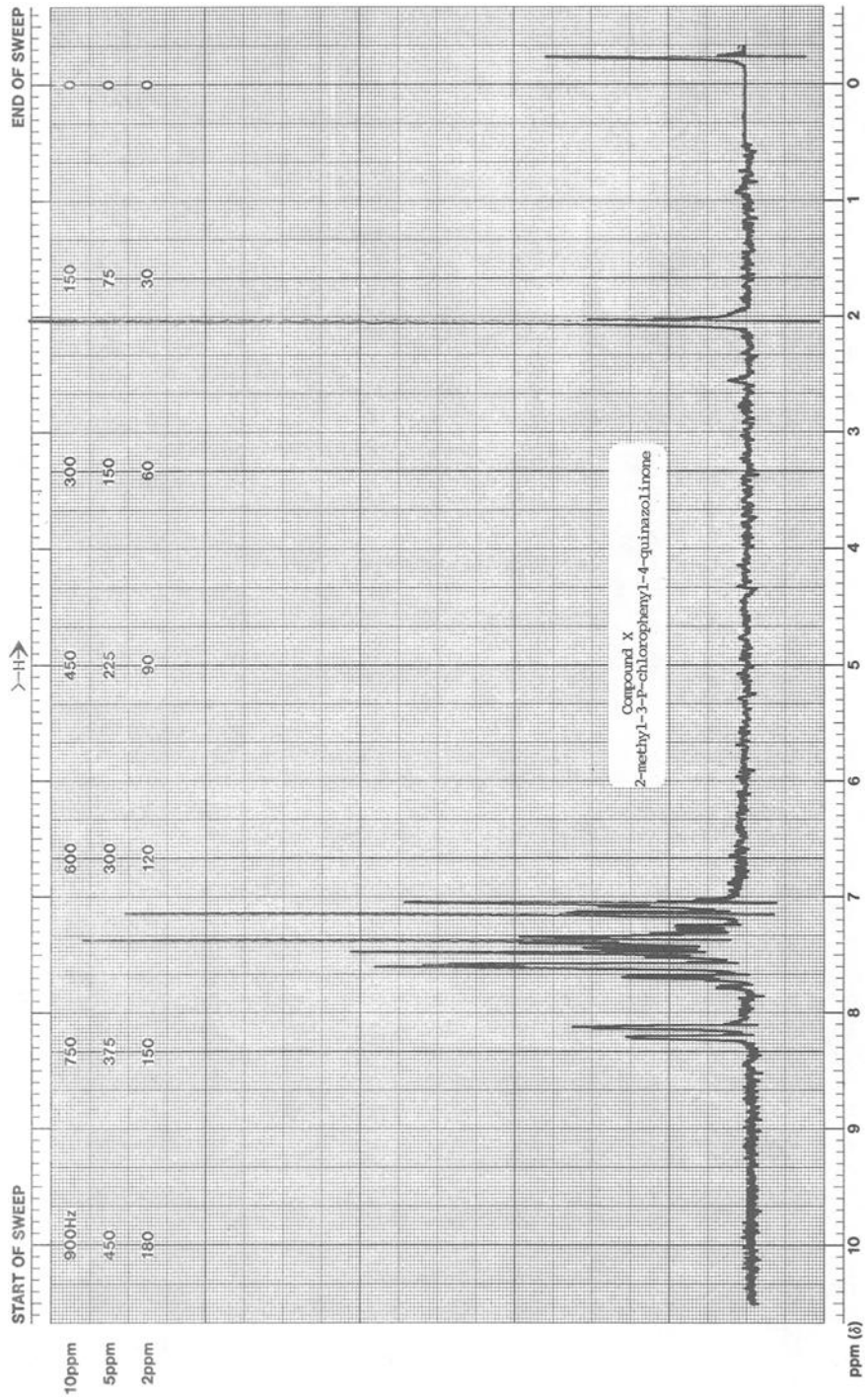


FIG. 5—*Continued.*

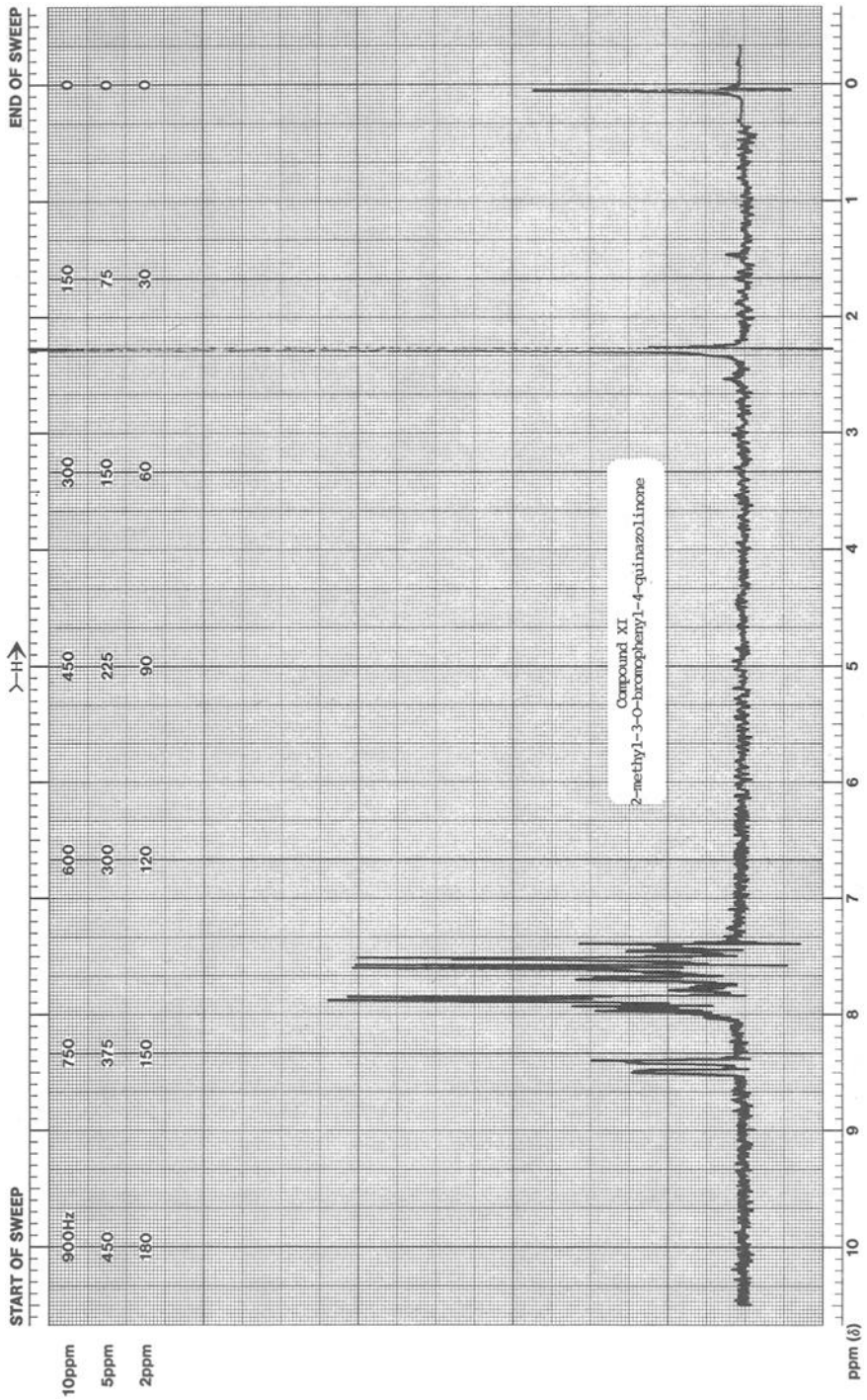


FIG. 5—*Continued.*

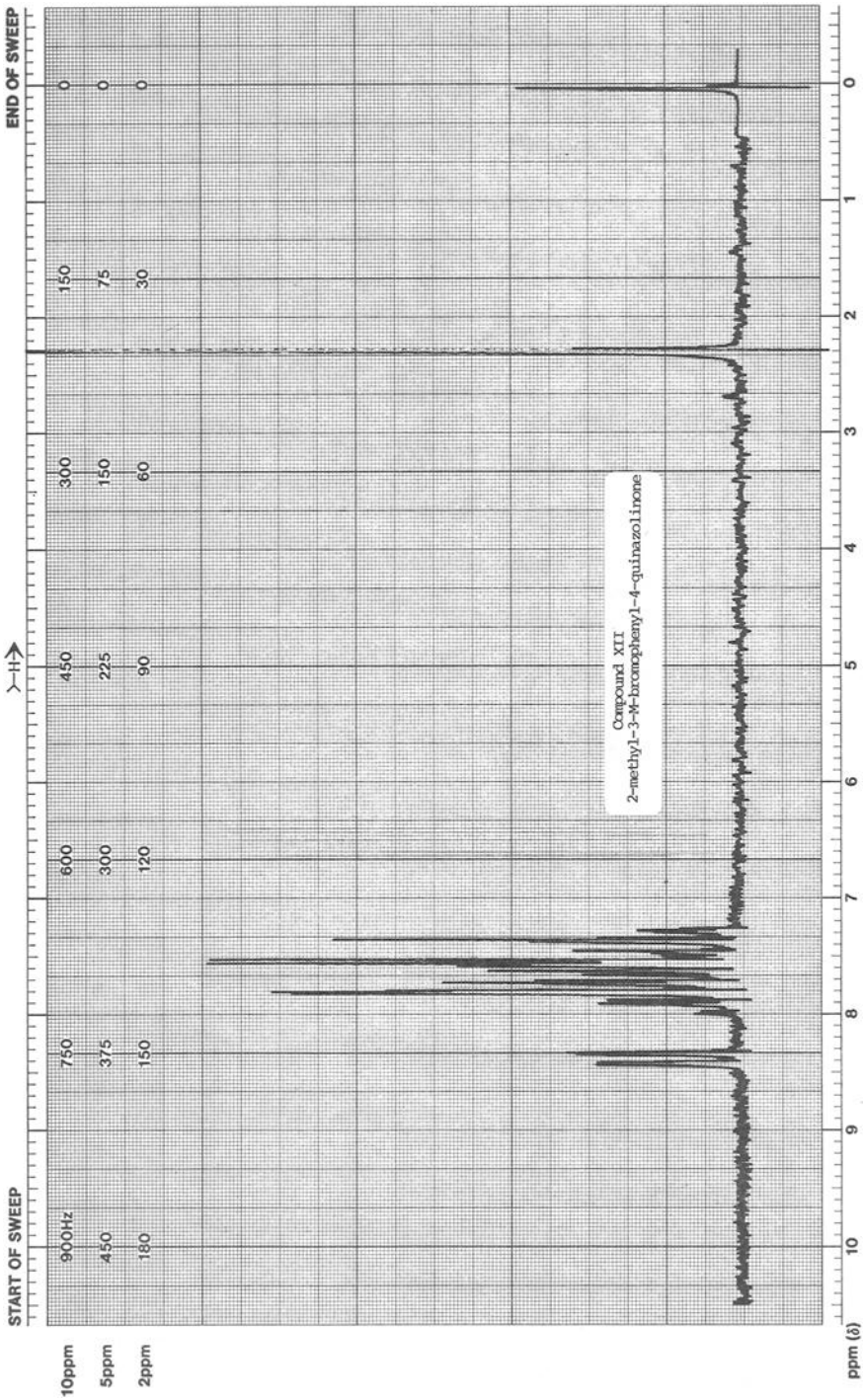


FIG. 5—*Continued.*

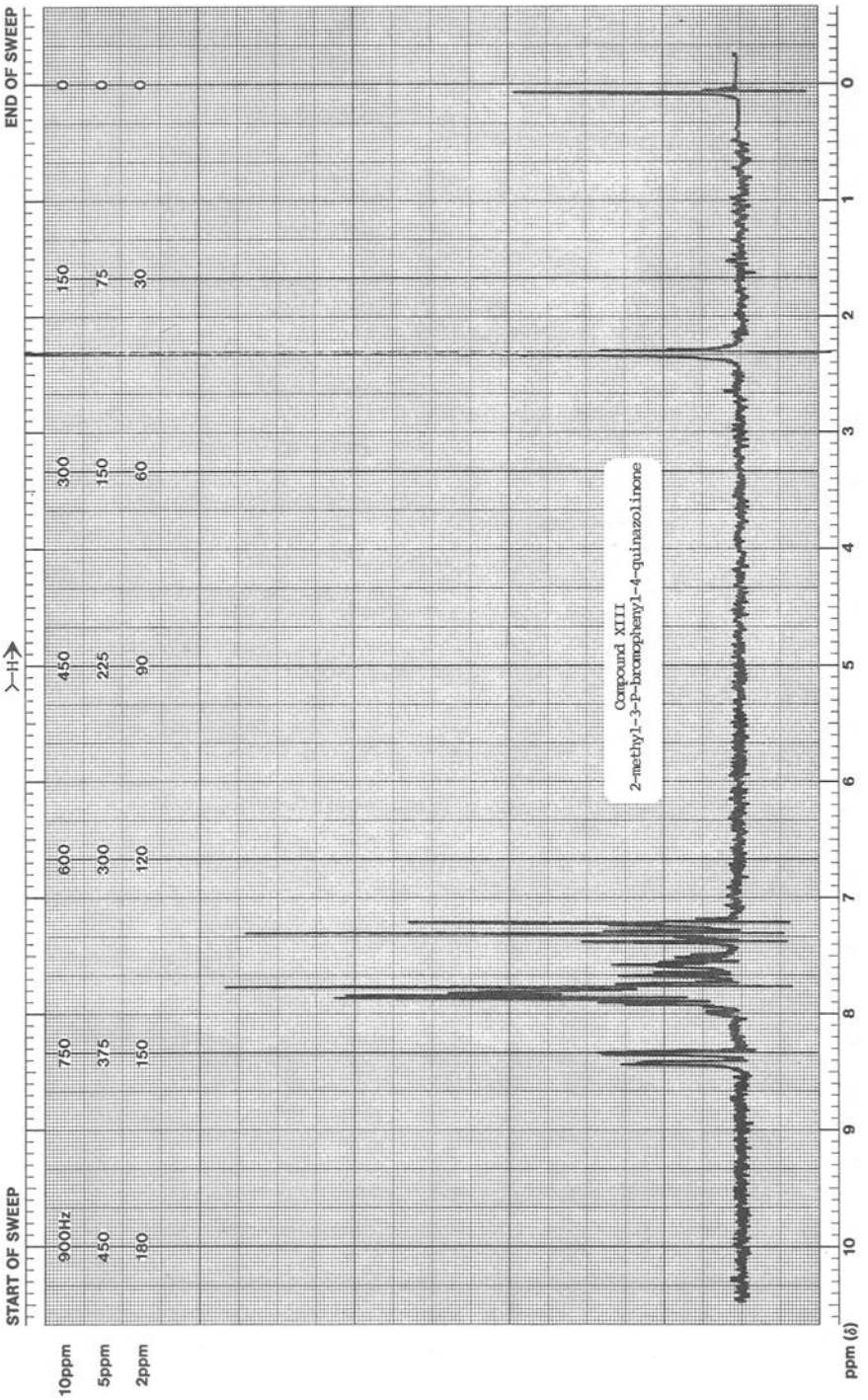


FIG. 5—*Continued.*

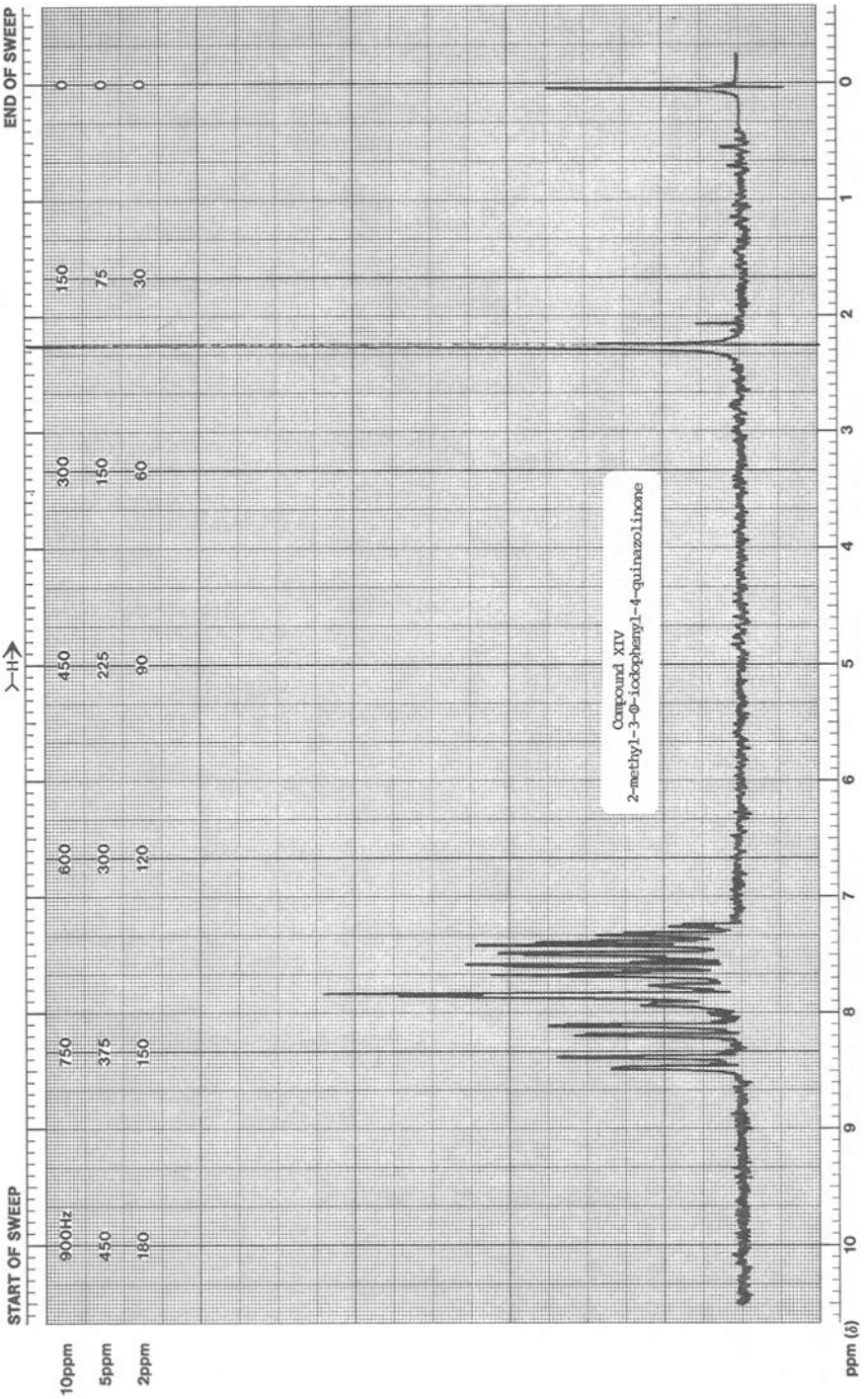


FIG. 5—*Continued.*

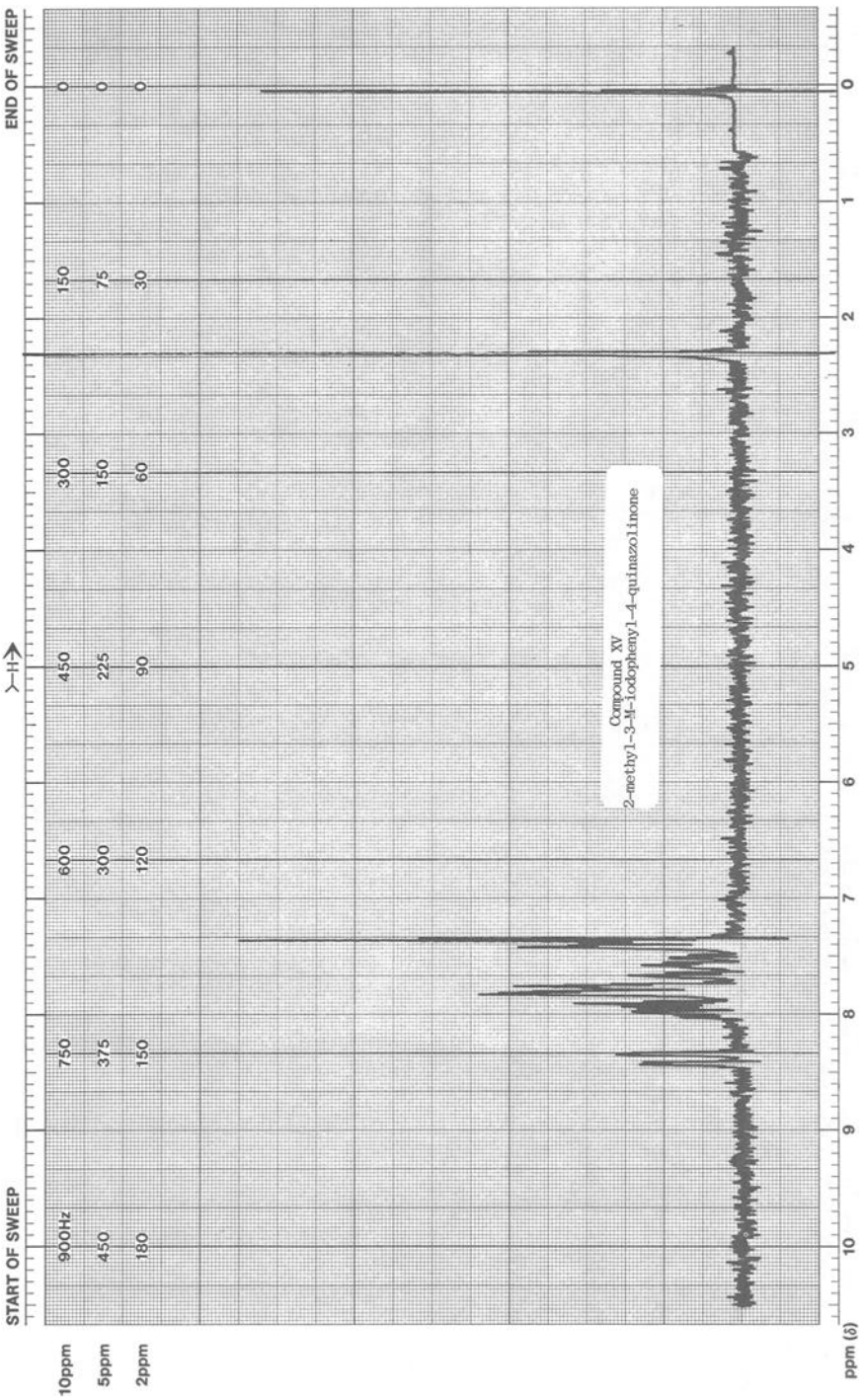


FIG. 5—*Continued.*

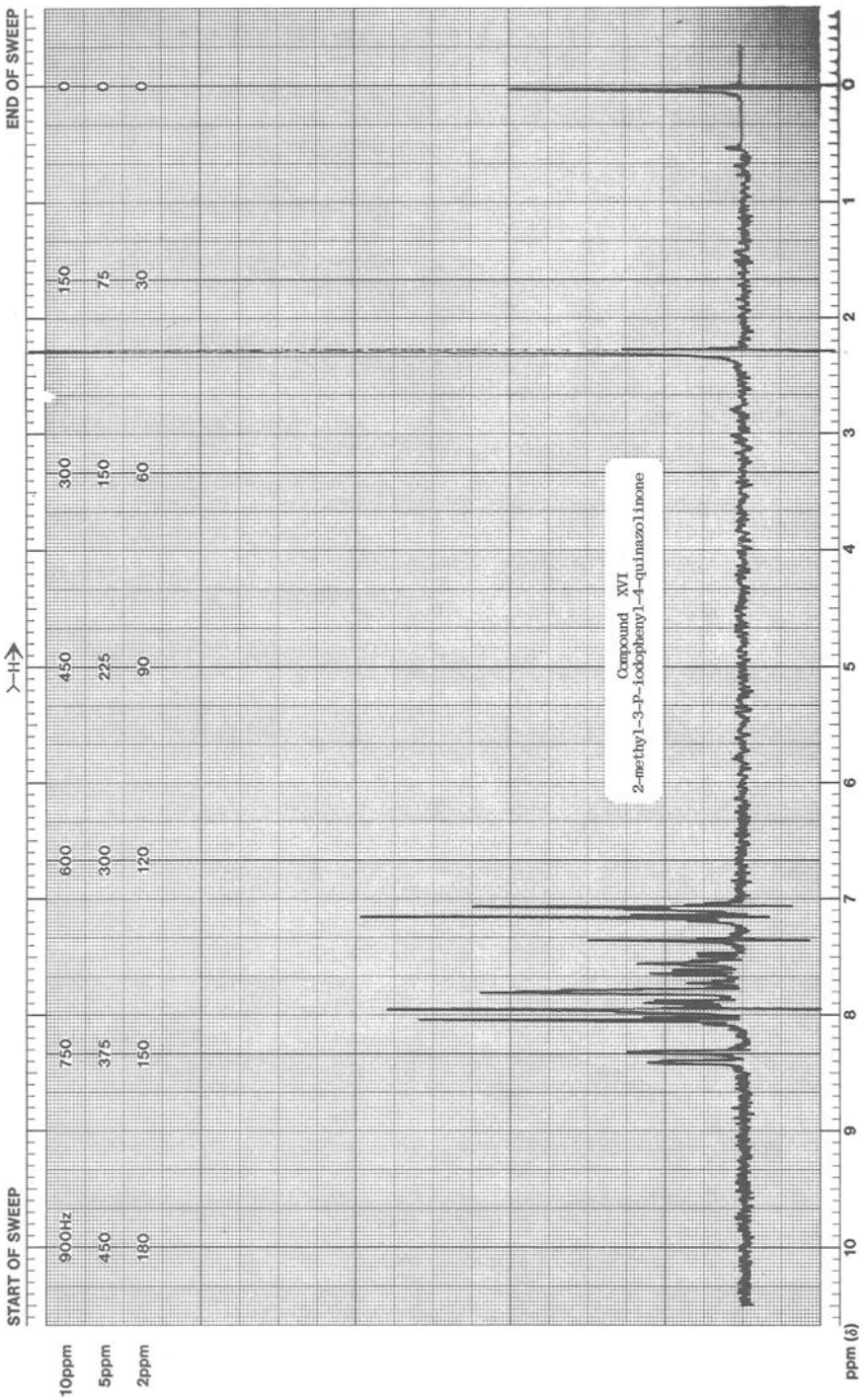


FIG. 5—*Continued.*

ation of the synthesized compounds. Whereas GLC may be used to indicate the probable identity of these 16 quinazolinone compounds and should be employed as a screening technique, UV spectroscopy provides evidence of the quinazolinone structure, and after the compound has been conclusively identified it may serve as a quantitative tool. However, TLC, using the systems examined, has no value as an identification tool since R_f values vary so little among the 16 compounds. In instances where sufficient amounts of pure material are available (10 to 15 mg), NMR spectroscopy may be used to identify the compound.

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