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The Isolation and Identification of Precursors and Reaction Products in the Clandestine Manufacture of Methaqualone and Mecloqualone

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ABSTRACT: Abuse of the hypnotic quinazolinone is well recognized and increasing. Clandestine laboratories producing methaqualone (2-methyl-3-*othro*-tolyl-4(3H) quinazolinone) and mecloqualone (2-methyl-3-*othro*-chlorophenyl-4(3H) quinazolinone) have been discovered throughout the United States. These laboratories utilize one of many synthesis routes to produce the illicit quinazolinone. Frequently, the clandestine chemist has little, if any, formal education in chemistry; does not keep notes; and does not label flasks and beakers containing solutions. The forensic chemist may be asked to analyze unmarked reaction mixtures that were seized in a clandestine laboratory raid. As a result, a rapid method of isolation and identification of the precursors and products of such a mixture is presented.

KEYWORDS: toxicology, drug identification, methaqualone, mecloqualone

The drugs methaqualone (2-methyl-3-*ortho*-tolyl-4(3H)-quinazolinone) and mecloqualone (2-methyl-3-*ortho*-chloro-phenyl-4(3H)-quinazolinone) have been manufacturerd in clandestine laboratories in the United States. A rapid method of isolation and identification of the precursors and products of clandestine mixtures is presented. Gas-liquid chromatographic and high pressure liquid chromatographic separations are described. Infrared, nuclear magnetic resonance, and mass spectra of the compounds identified are provided.

The abuse potential of the hypnotic drug methaqualone [*1*] and its chlorinated analogue, mecloqualone [*2*], is recognized. The source of illegal methaqualone is either from legitimate pharmaceutical firms diverted to the illicit market or from clandestine manufacture. Mecloqualone is not available commercially in the United States but has been produced clandestinely. Currently, there are no legitimate manufacturers of either drug in the United States.

Historically, methaqualone (2-methyl-3-*ortho*-tolyl-4(3H)-quinazolinone) was first prepared in 1951 [*3*]. Studies of its metabolism in man were reported in 1960 [*4–6*], and in animals in 1963 [*7*]. Methaqualone was introduced pharmaceutically as a nonbarbiturate, nonaddictive, "sleeping pill" in 1965. Recently (1976) metabolite detection for forensic science purposes has been reported [*8*]. Methaqualone has been controlled in the Federal Comprehensive Controlled Substances Act of 1970 (P.L.91-513) since 4 Oct. 1973 (38 FR27516). As of 27 Aug. 1984, methaqualone has been moved from Schedule II to Schedule I within the Federal Act.

Mecloqualone (2-methyl-3-*ortho*-chlorophenyll-4(3H)-quinazolinone) was first prepared in 1960 [*9*]. Metabolism studies were reported in man in 1974 [*10*]. Since mecloqualone has no

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current medical use in the United States, it has been federally controlled as a Schedule I drug since 10 Sept. 1975 (40 FR28611). In Europe, mecloqualone is available as a hypnotic.

The reported synthetic routes for these quinazolinones are uncomplicated one- or two-step procedures that can be performed in clandestine laboratories without difficulty. Laboratories producing the illicit quinazolinones have been discovered throughout the United States. The forensic chemist frequently is asked to analyze unlabelled reaction mixtures from laboratory seizures. The identification of the precursors and by-products of such a reaction mixture would aid the forensic chemist in determining the synthetic route used in the illicit production.

Synthetic Methods

Two basic methods for the clandestine manufacture of either methaqualone or mecloqualone have been encountered. The first method is a two-step reaction that involves the preparation of *N*-acetyl anthranilic acid (Compound II) (Table I) from anthranilic acid and acetic anhydride followed by condensation with either *o*-toluidine (Compound III) to produce methaqualone (Compound V) or *o*-chloroaniline (Compound IV) to produce mecloqualone (Compound VI). Phosphorus trichloride is used to remove water produced in the reaction [*3*].

The second method is carried out in a one-step reaction by refluxing anthranilic acid (Compound I), *o*-toluidine (Compound III), and acetic acid (or acetic anhydride). Polyphosphoric acid may be added to remove water. Purification is accomplished by dissolving the solid residue in methanol and precipitating the hydrochloride salt from a methanol-diethyl ether solution.

Experimental Procedure

Chromatographic separations of the reactants and by-products were performed by both high pressure liquid chromatography (HPLC) and gas-liquid chromatography (GLC). A Waters Associates HPLC equipped with an ultraviolet (254-nm) detector, fitted with a 30-cm by 3.9-mm inside diameter (ID) Bondapak C_{18} column a mobile phase of 40% methanol-water with 1% acetic acid and methane sulfonic acid (C_1PIC reagent) at a flow rate of 2 mL/min was used. Table 2 gives the retention times of various compounds.

Gas-liquid chromatography was performed on a Hewlett-Packard 5840A equipped with 1.8-m (6-ft) 4-mm ID glass columns packed with 10% OV-101 and 3% OV-17 both on Gas Chrom Q. For the 10% OV-101 column, the initial temperature of 150°C is maintained for 3 min and then programmed to increase at a rate of 20°C per minute until a temperature 280°C is reached. For the 3% OV-17 column, the initial temperature of 150°C is maintained for 1 min, and then programmed to increase at a rate of 10°C per minute until a temperature of 280°C is reached. These somewhat complex programs allow for the elution of both reactants

TABLE 1—*List of compounds.*

Compound	Formula	M.W.	Chemical Name
I	$C_7H_7NO_2$	137	anthranilic acid
II	$C_9H_9NO_3$	179	*N*-acetylanthranilic acid
III	C_7H_9N	107	*o*-toluidine
IV	C_6H_6ClN	127	*o*-chloroaniline
V	$C_{16}H_{14}N_2O$	250	methaqualone
VI	$C_{15}H_{11}ClN_2O$	270	mecloqualone
VII	$C_9H_{10}NO$	149	*o*-methyl acetanilide
VIII	C_8H_8ClNO	169	*o*-chloro acetanilide
IX	$C_{16}H_{12}N_2O_3$	280	2-methyl-3-*o*-carboxyphenyl-4-quinazolinone

TABLE 2—*Retention time (minutes) of methaqualone related compounds.*[a]

Compound	Actual	Relative
I	4.2	0.2
II	6.2	0.29
III	2.0	0.09
V	21.1	1.00
VII	3.7	0.18
IX	15.0	0.71

[a]Bondapak C_{18} column; mobile phase: 40% methanol, 59% water, and 1% acetic acid with methane sulfonic acid (C1 PIC reagent); flow rate 2 mL/min; ultraviolet detector 254 nm.

and by-products. Table 3 gives the actual retention times of the compounds, while Tables 4 and 5 give the relative retention times for the compounds related to methaqualone and mecloqualone, respectively.

Infrared spectroscopy was performed with a Perkin-Elmer 283 spectrophotometer, utilizing the standard KBr disk method. Liquid samples were prepared as thin films between two KBr disks. Figure 1 provides the infrared (IR) spectra of Compounds I to IX. A Finnigan Model 4530 Quadropole gas chromatograph-mass spectrometer (GC/MS/DS) was used to obtain the mass spectra. The chromatographic system used, was 1.8-m (6-ft) 2-mm ID glass column of

TABLE 3—*Retention times (minutes) of Compounds I through IX.*

Compound	10% OV-101[ab]	3% OV-17[ac]
I	5.46	2.90
II	8.19	5.25
III	1.74	0.71
IV	2.20	0.85
V	12.79	10.45
VI	13.71	11.53
VII	5.66	3.13
VIII	5.39	2.54
IX	17.61	14.65

[a]Column is glass, 1.8 m long; injector, 275°C; flame ionization detector, 300°C; nitrogen flow 60 mL/min; support material is 100-120 mesh gas Chrom Q.
[b]Initial temperature 150°C for 3 min; rate 20°C/min; final temperature 280°C.
[c]Initial temperature 150°C for 1 min; rate 10°C/min; final temperature 280°C.

TABLE 4—*Relative retention times (minutes) of some methaqualone related compounds.*

Compound	10% OV-101[a]	3% OV-17[a]
I	0.43	0.28
II	0.64	0.50
III	0.14	0.07
V	1.0	1.0
VII	0.44	0.3
IX	1.38	1.4

[a]Column is glass, 1.8 m long; injector, 275°C; flame ionization detector, 300°C; nitrogen flow 60 mL/min; support material is 100-120 mesh Gas Chrom Q.

TABLE 5—*Relative retention times (minutes) of some mecloqualone related compounds.*

Compound	10% OV-101[a]	3% OV-17[a]
I	0.39	0.25
II	0.6	0.46
IV	0.16	0.07
VI	1.0	1.0
VIII	0.4	0.22
IX	1.28	1.27

[a]Column is glass, 1.8 m long; injector, 275°C; flame ionization detector, 300°C; nitrogen flow 60 mL/min; support material is 100-120 mesh Gas Chrom Q.

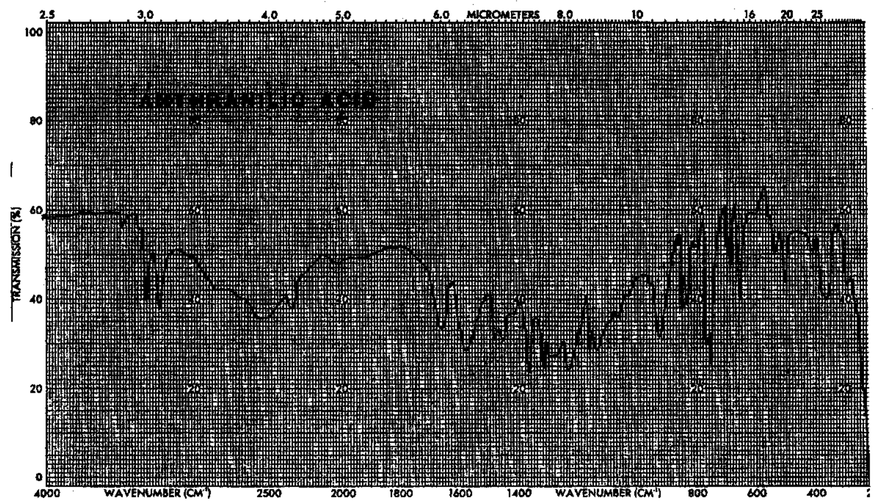
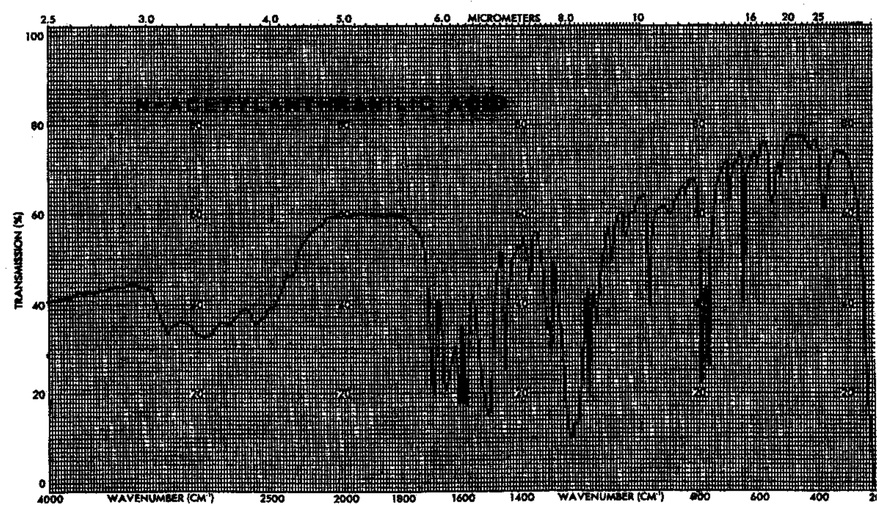


FIG. 1—*Infrared spectra of Compounds I through IX; KBr pellets.*



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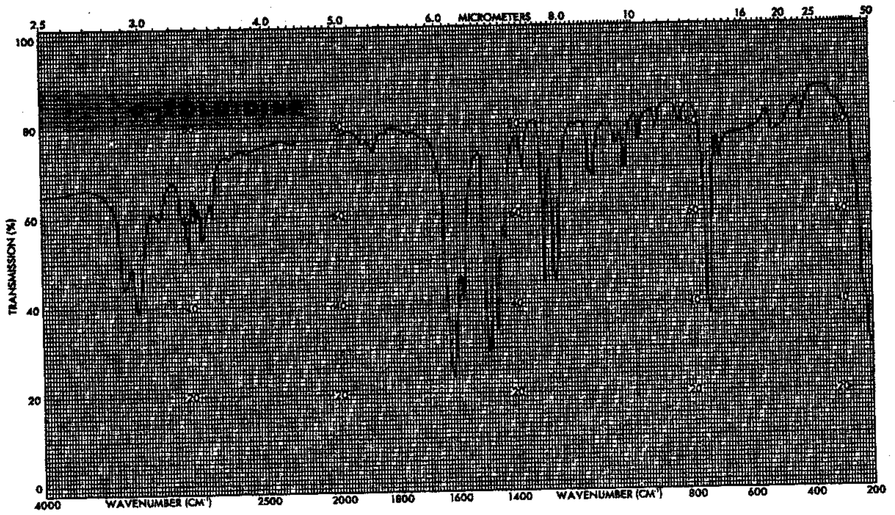

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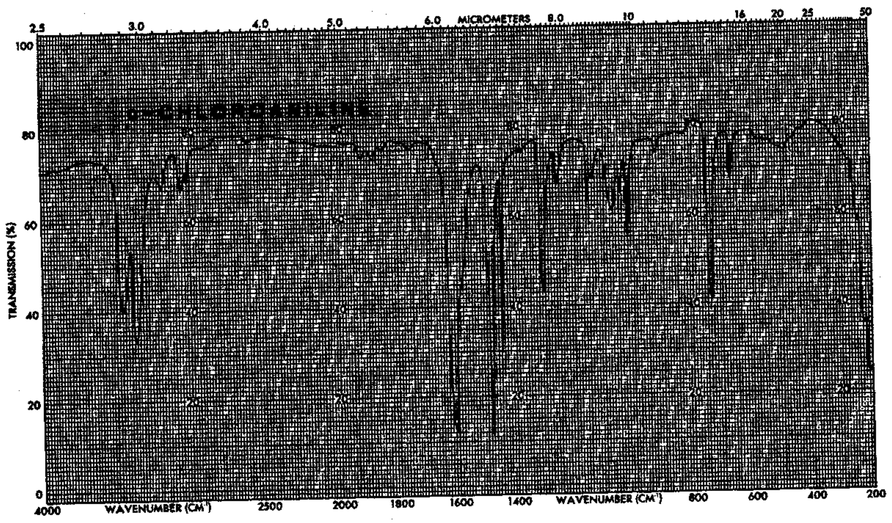

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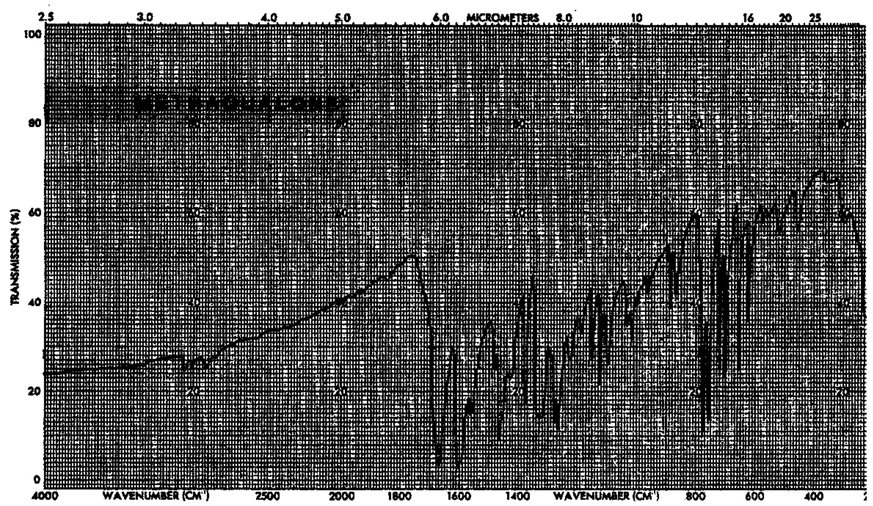

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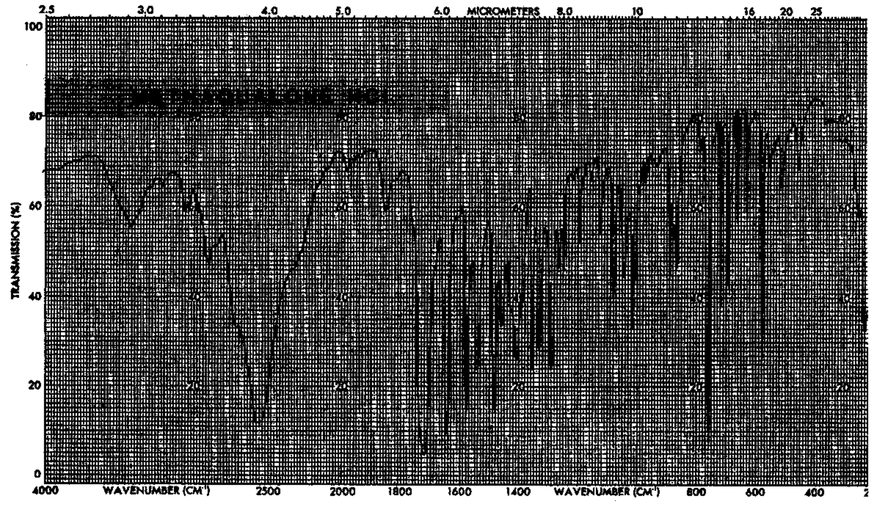

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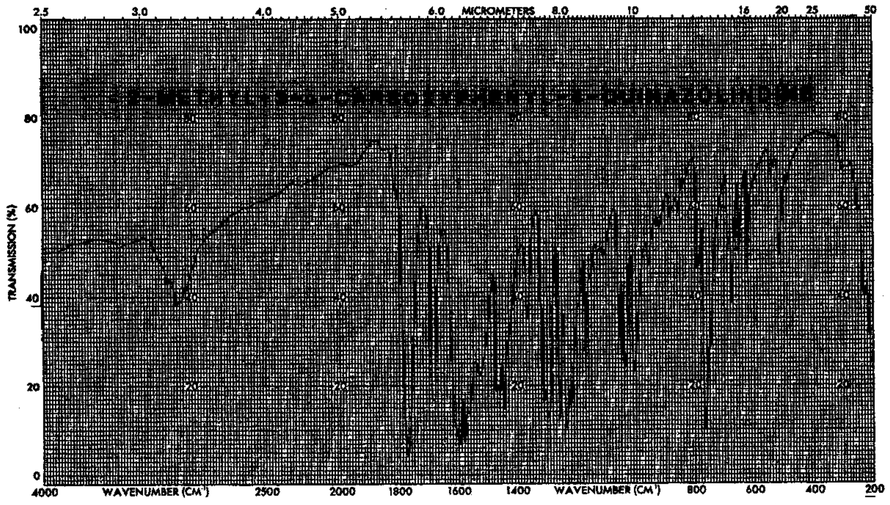


FIG. 1—*continued.*

0.5% OV-101 on Gas Chrom Q, with a temperature program from 100 to 280°C at a rate of 20°C per minute, (Fig. 2).

Proton magnetic resonance spectra were run on the free base compounds dissolved in deuturated dimethylsulfoxide (DMSO) using a 90-MHz Varian EM 390 spectrometer (Fig. 3).

Discussion

Clandestine laboratory operators generally spend little or no time purifying the "final product," thus, many impurities and side products can be identified in the forensic science labora-

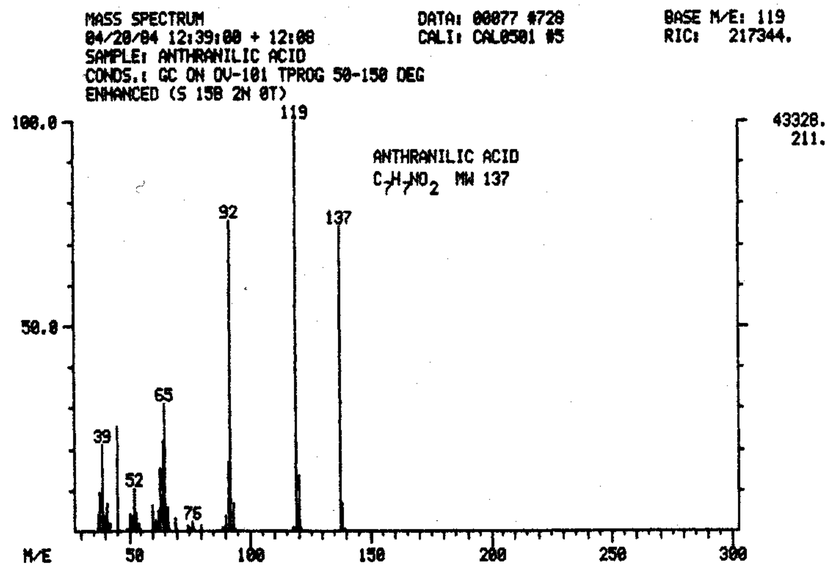
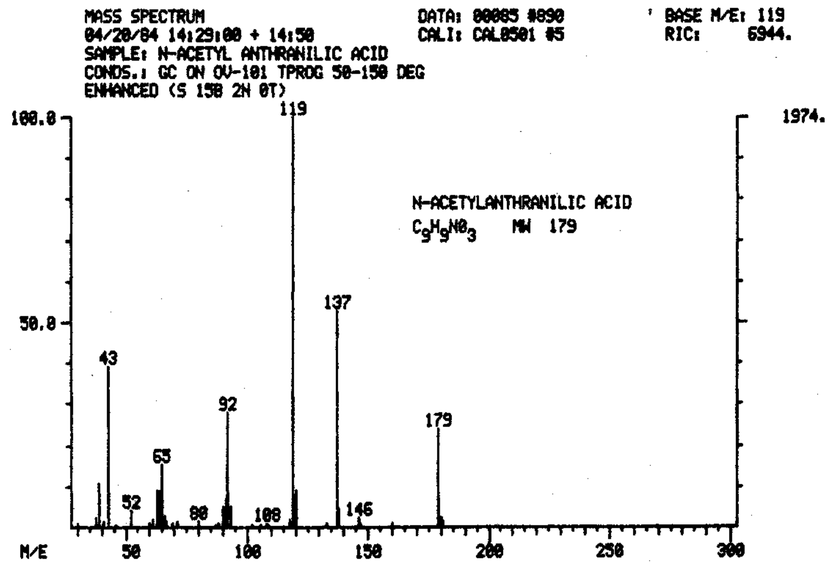


FIG. 2—*Normalized 80 eV, EI, mass spectra of Compounds I through IX.*



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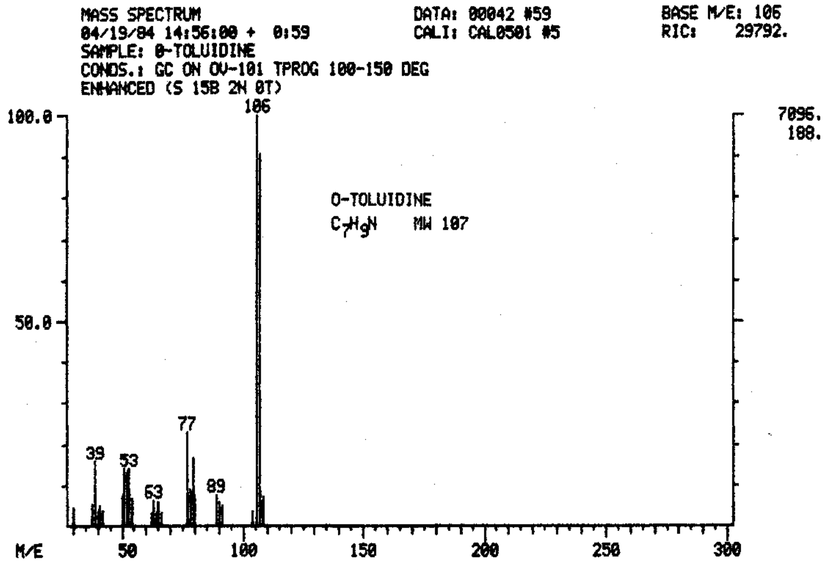

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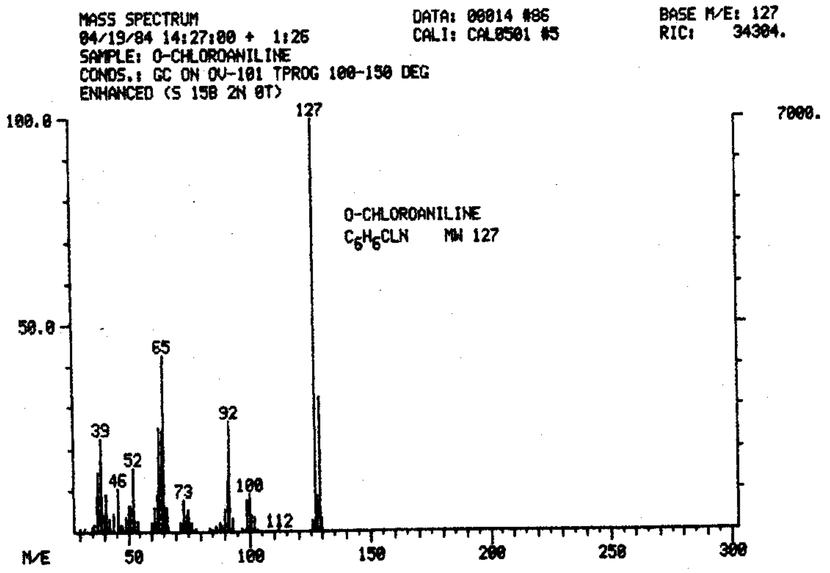

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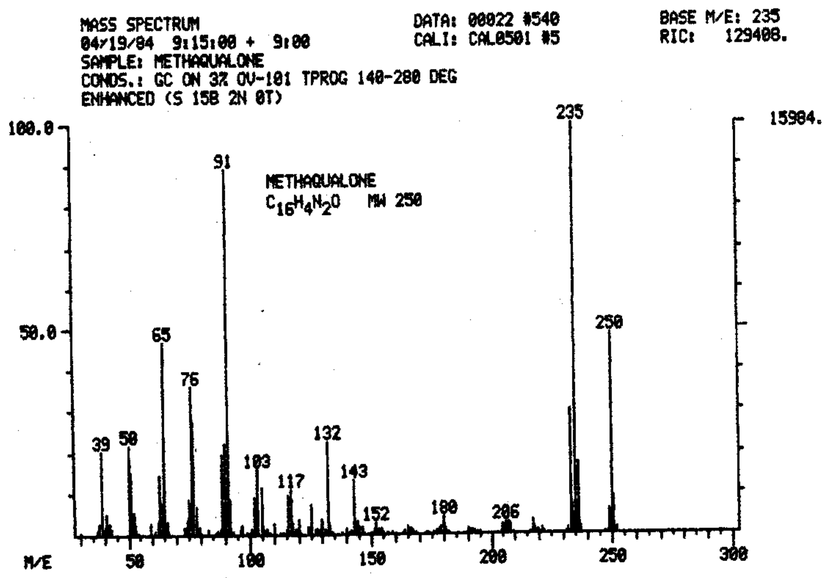

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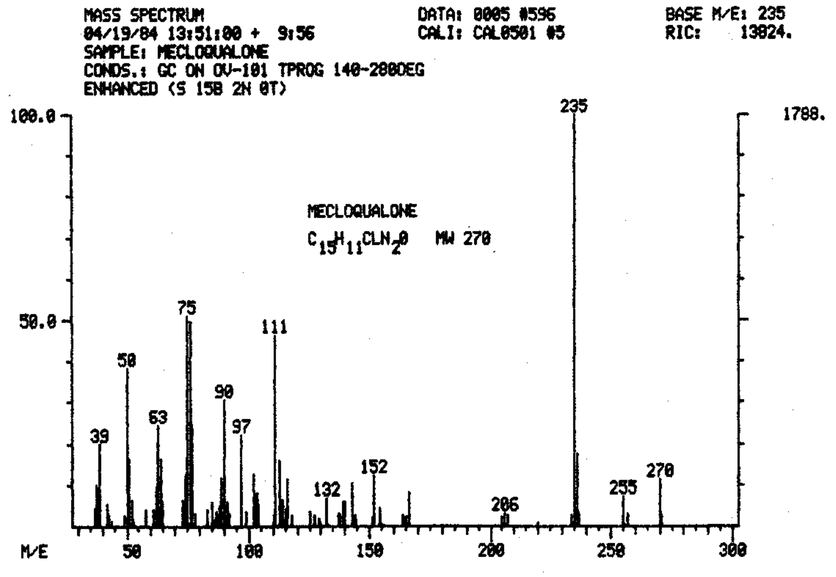

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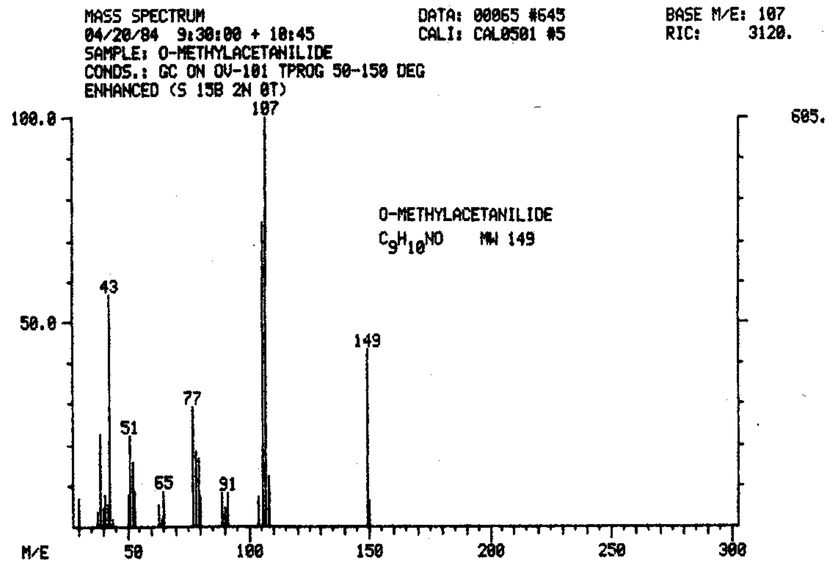

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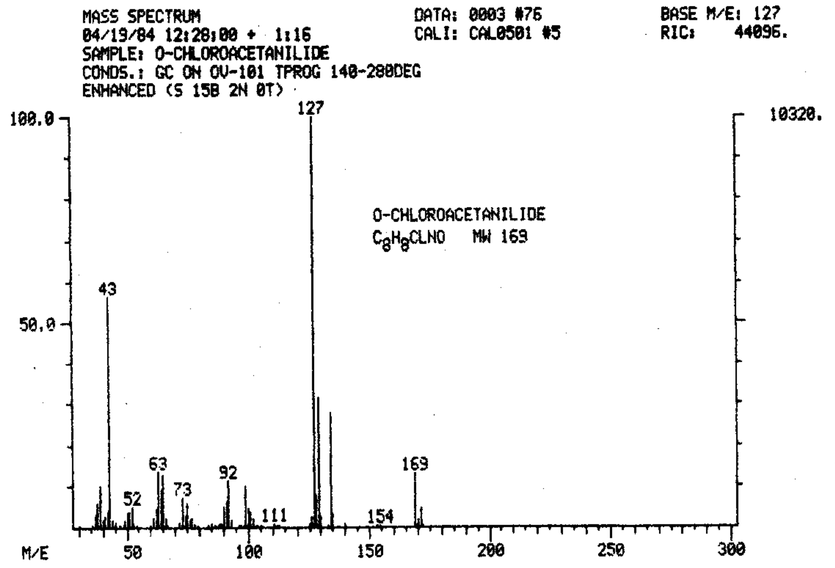

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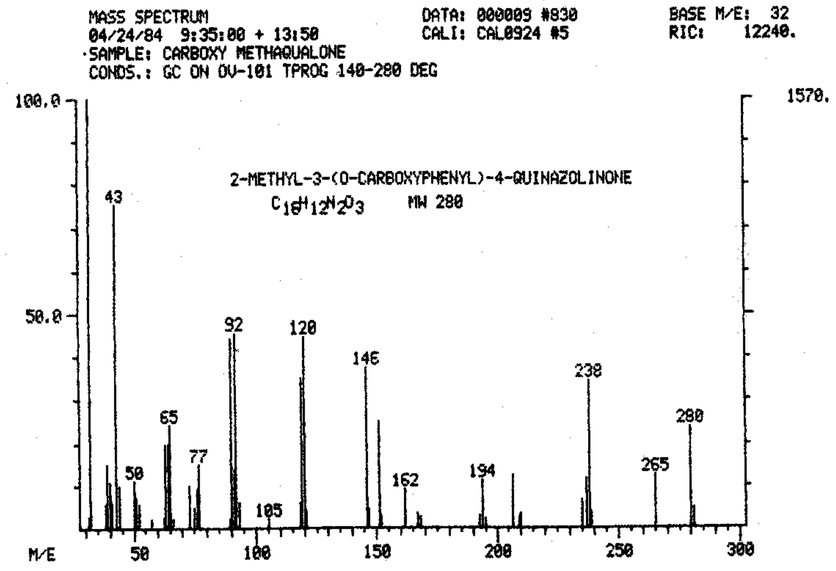

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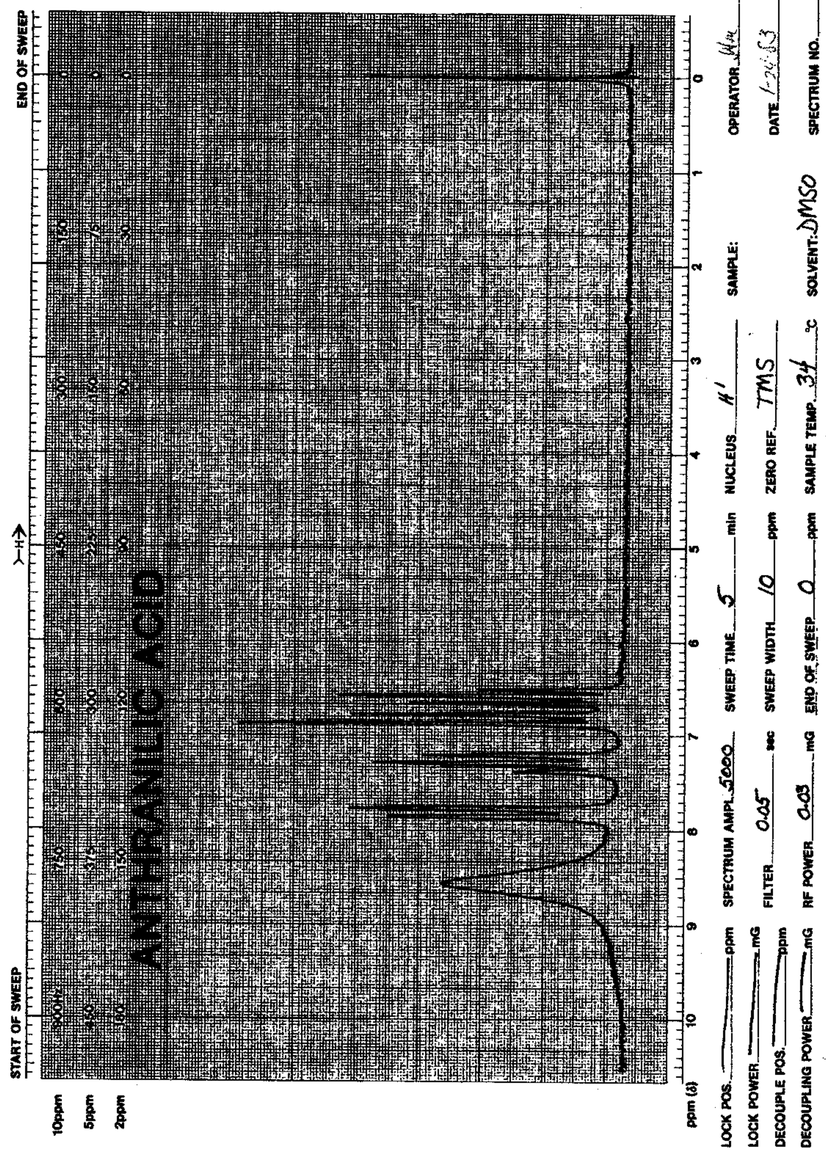
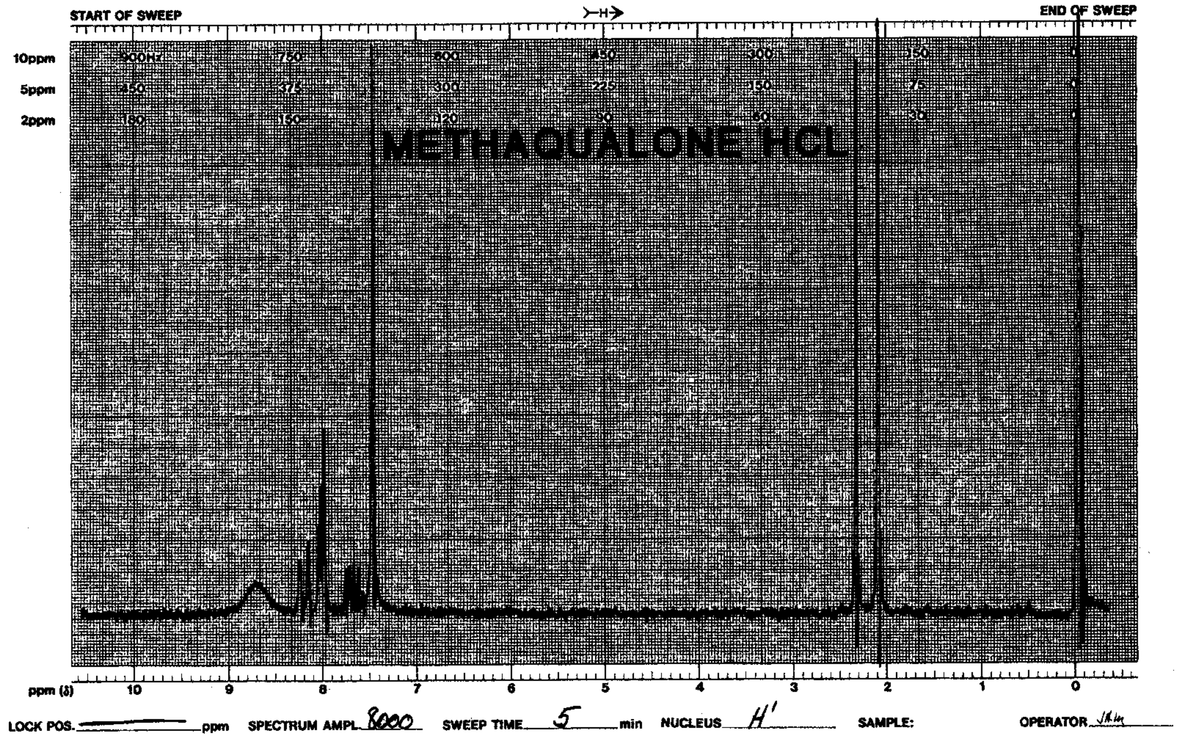


FIG. 3—*Nuclear magnetic resonance spectra of Compounds I through IX; in deutero-dimethyl sulfoxide.*



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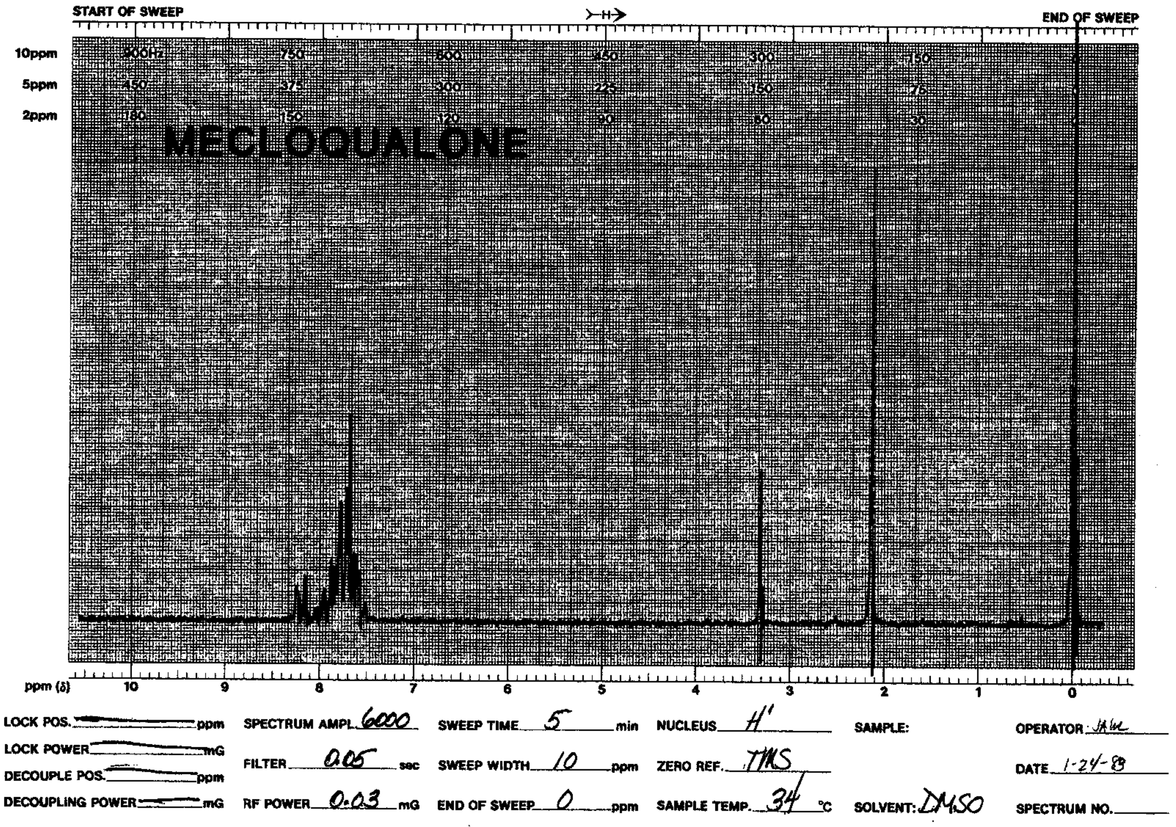

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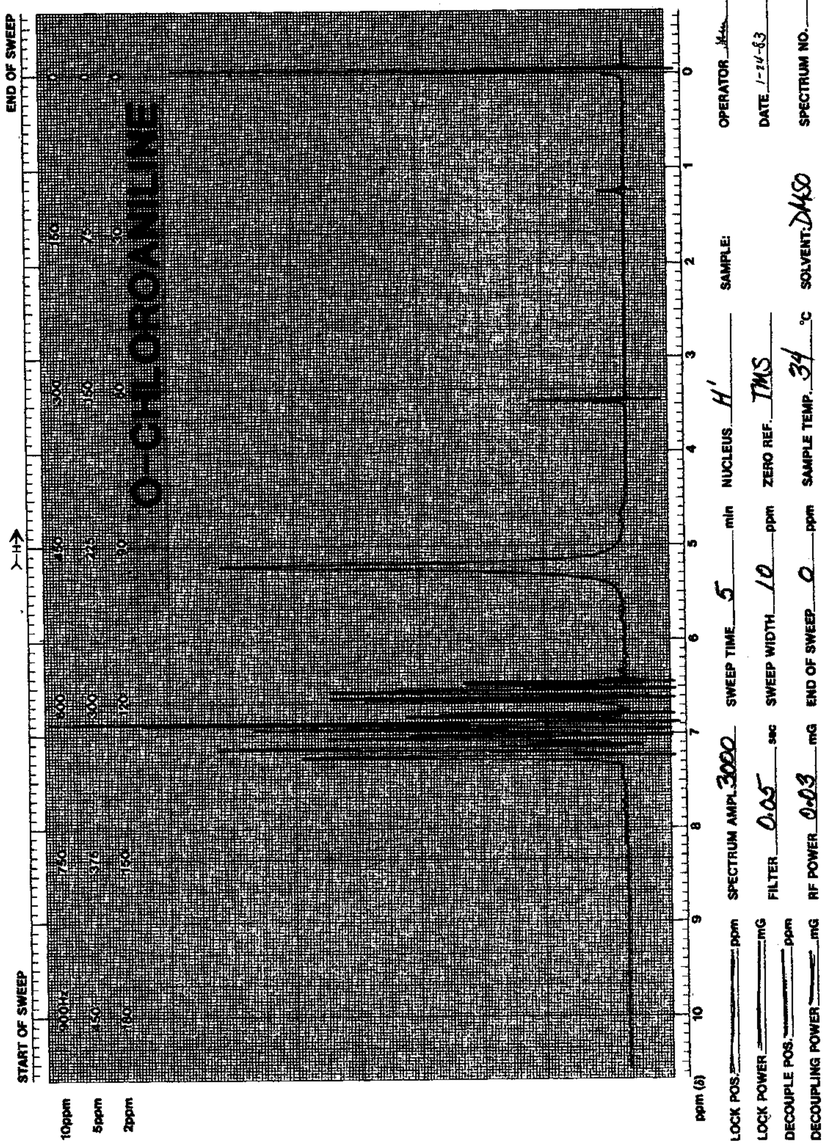

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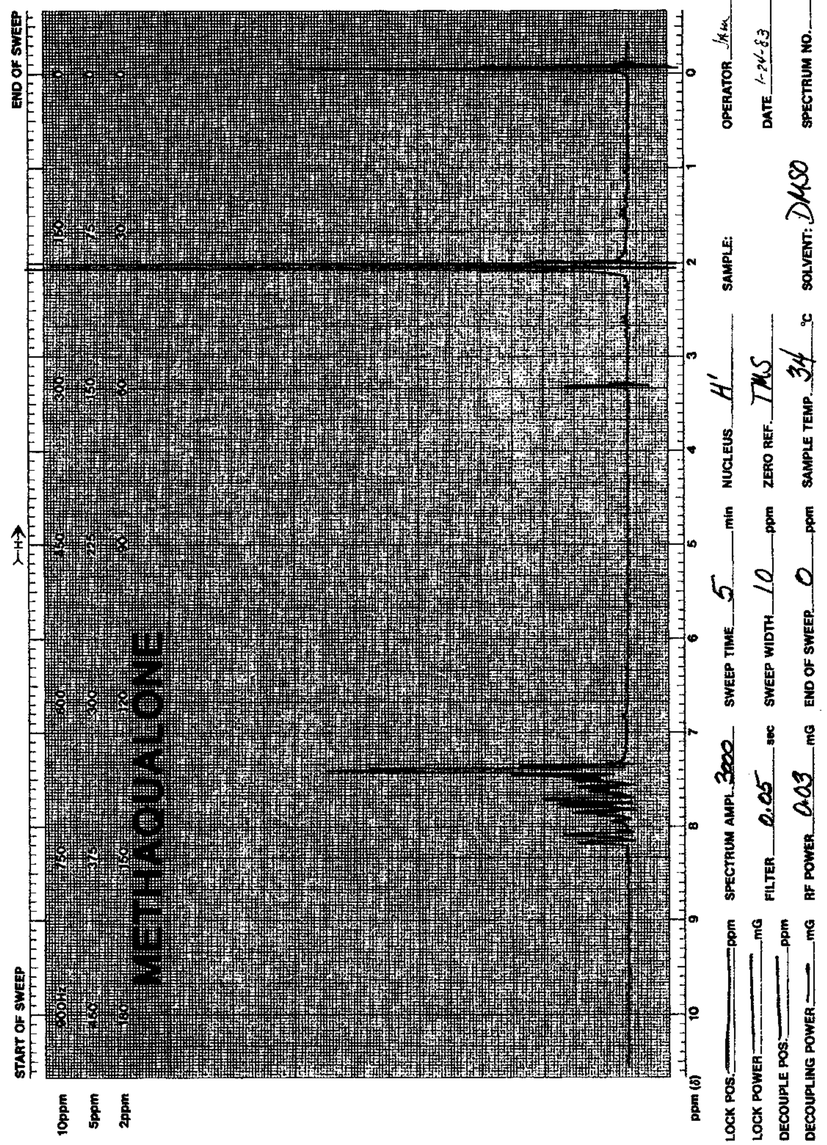

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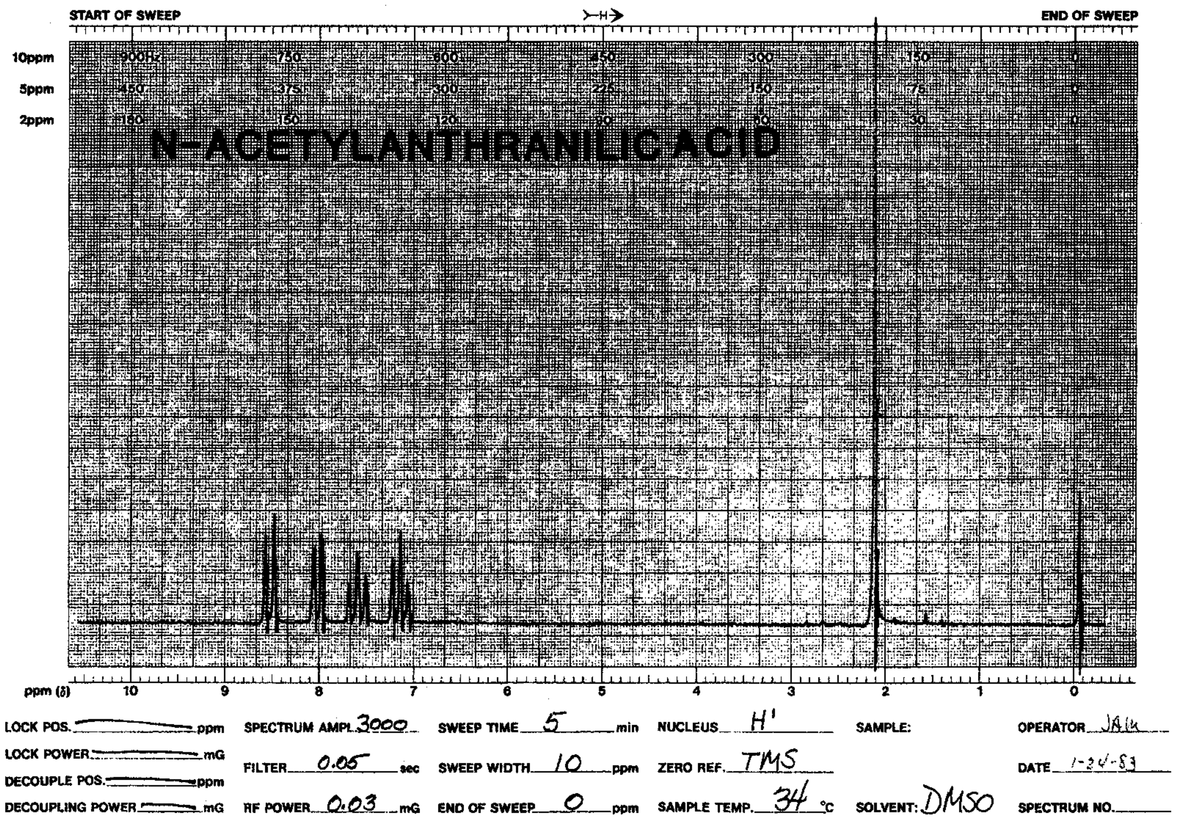

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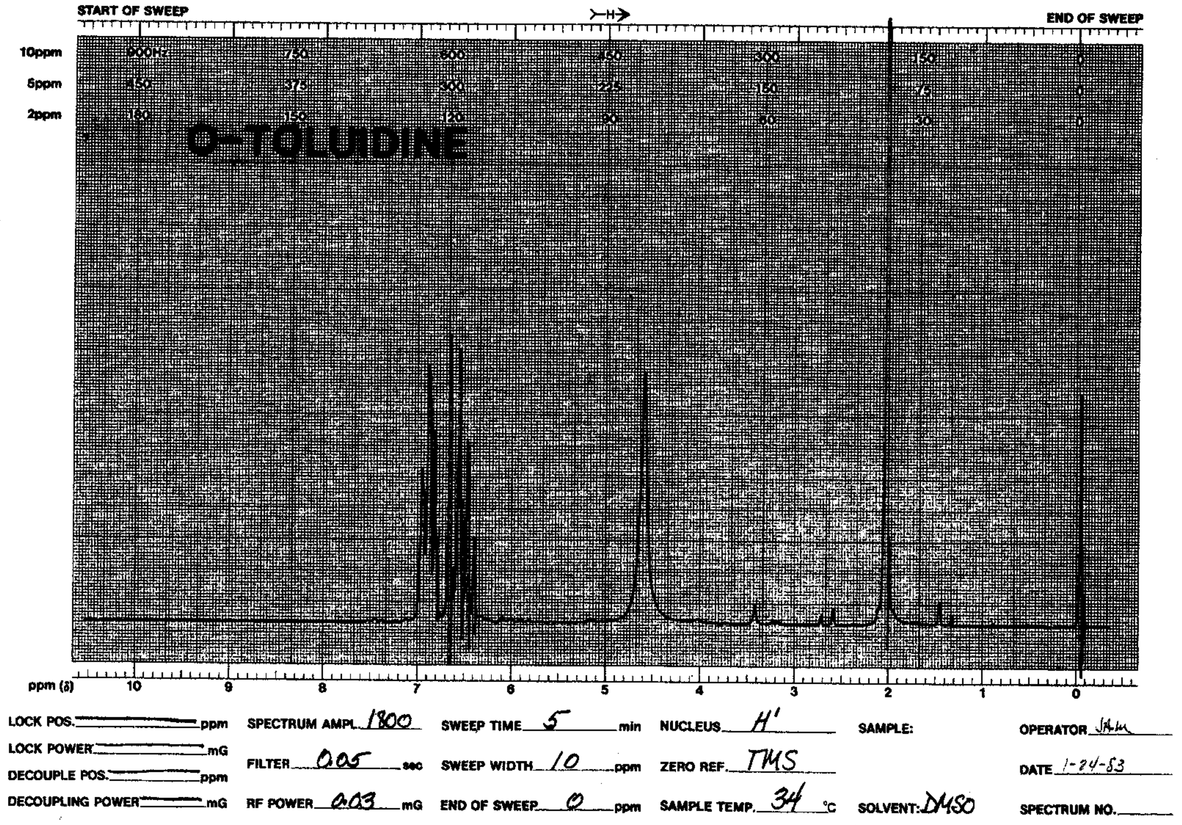

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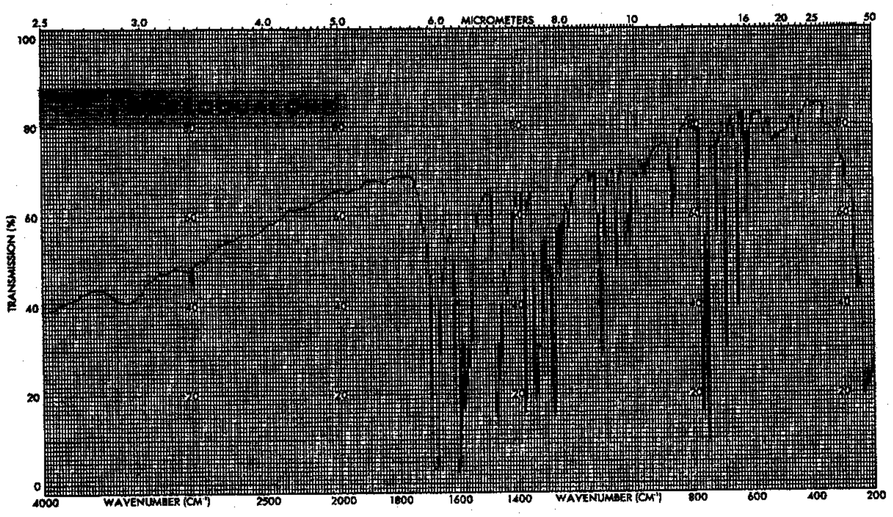

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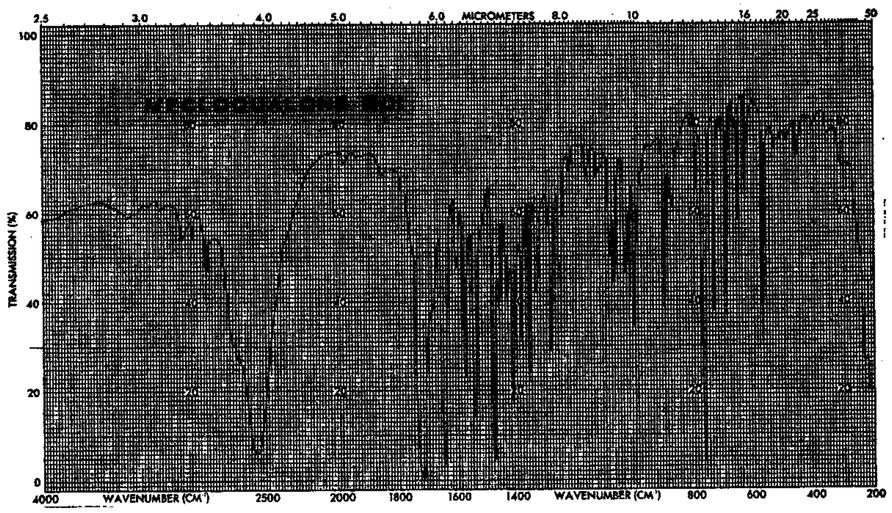

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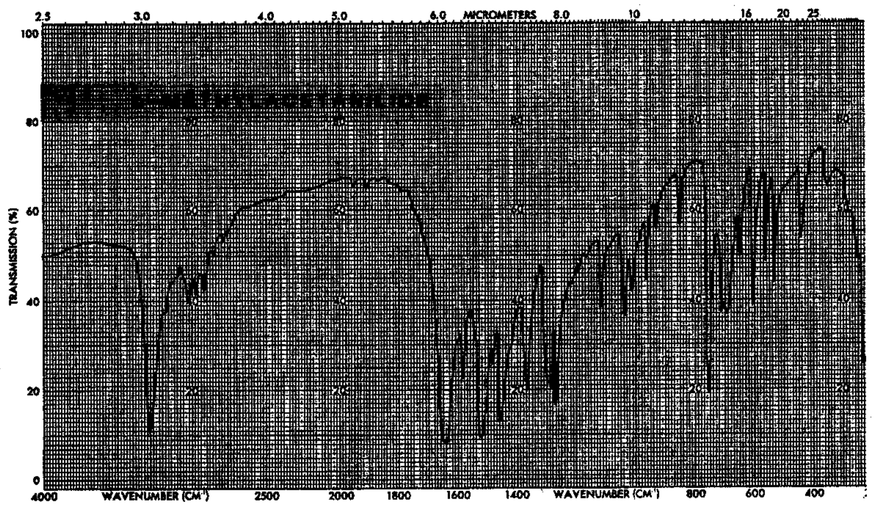

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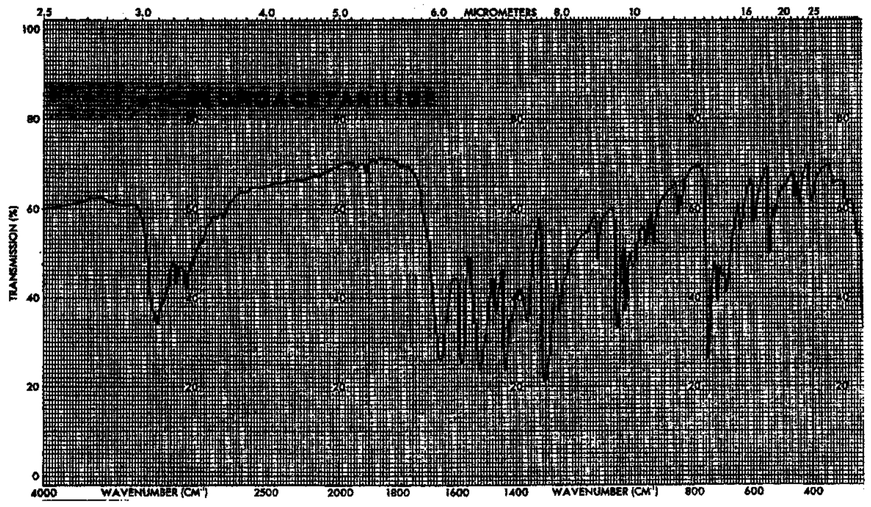

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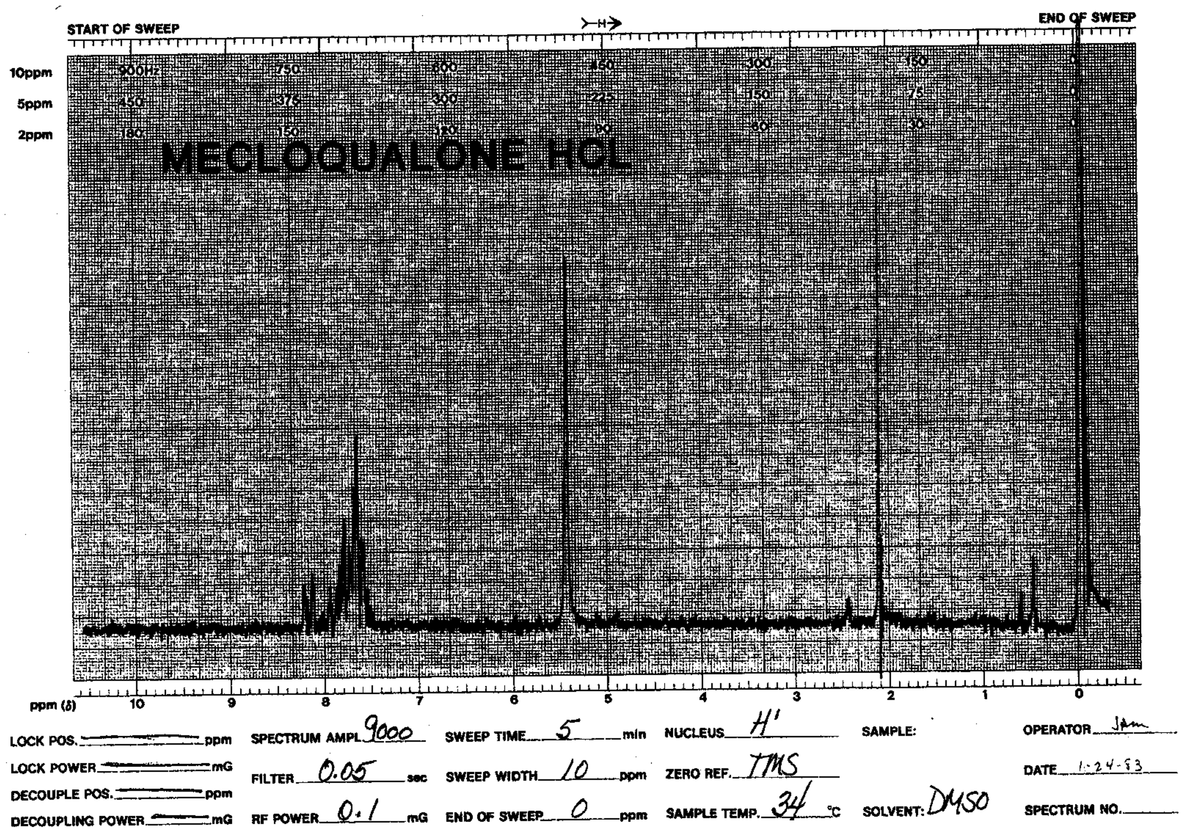

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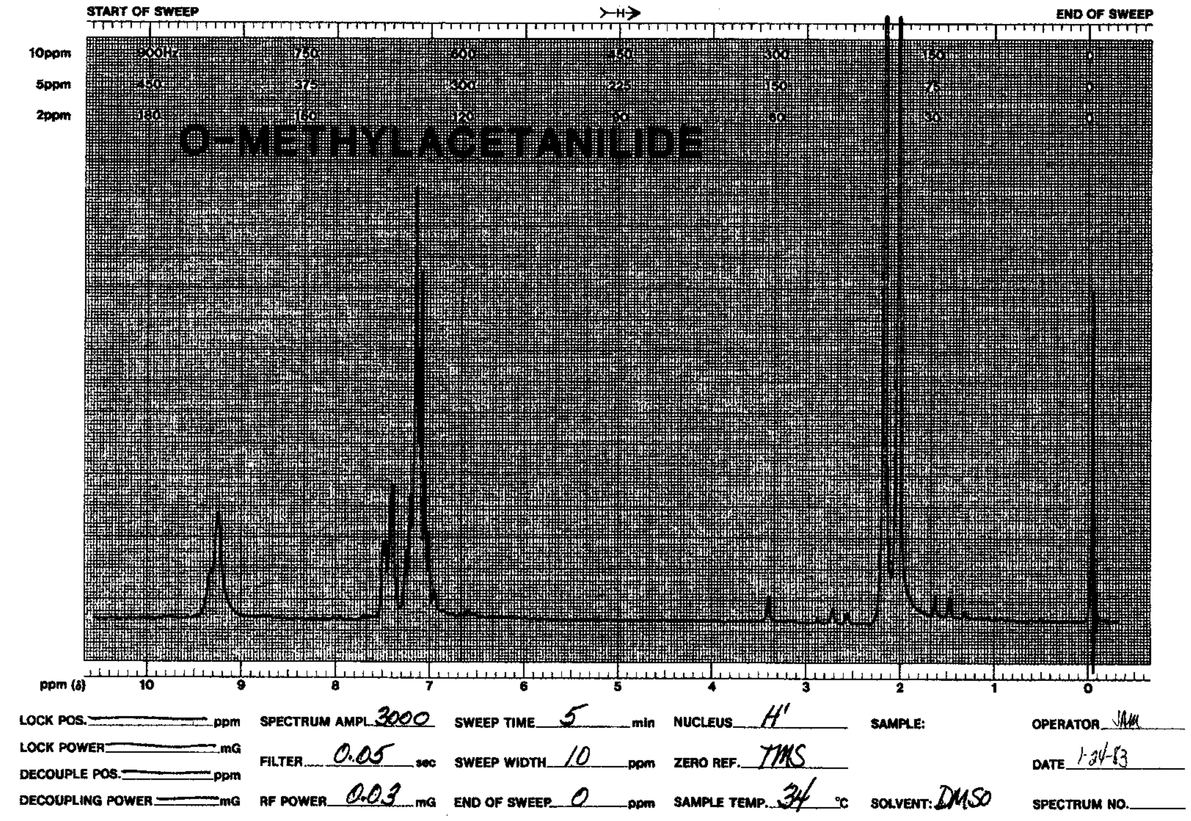

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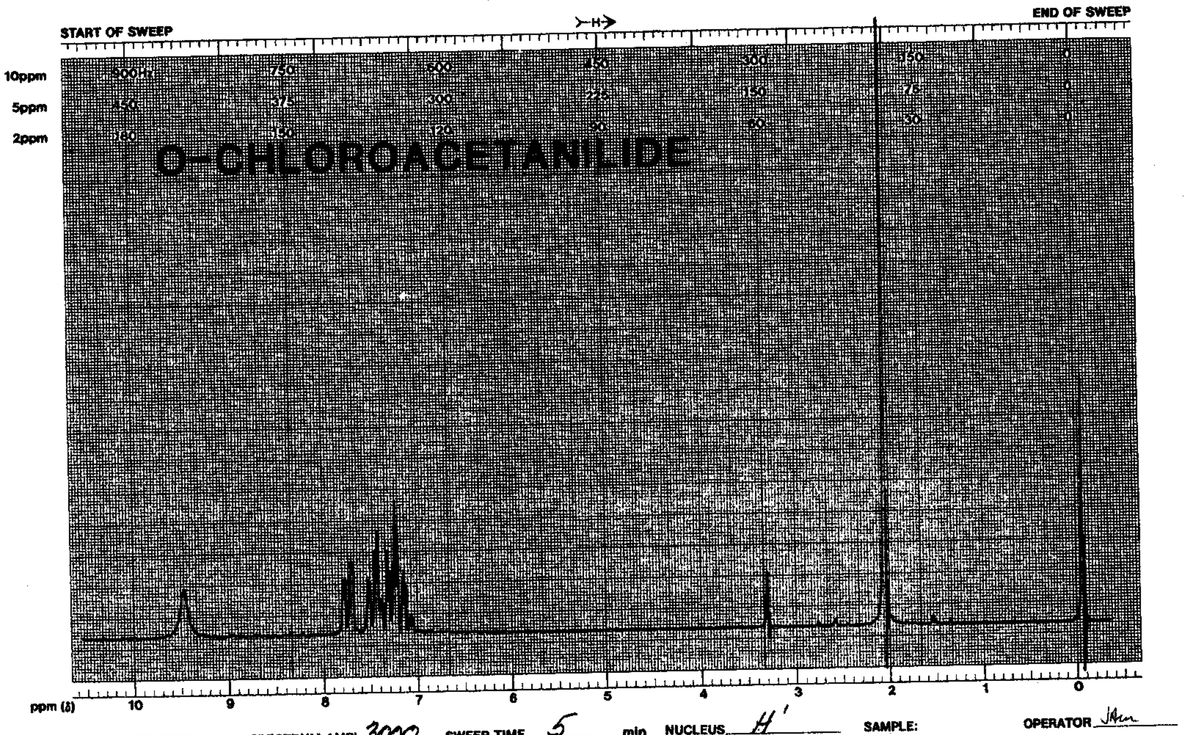

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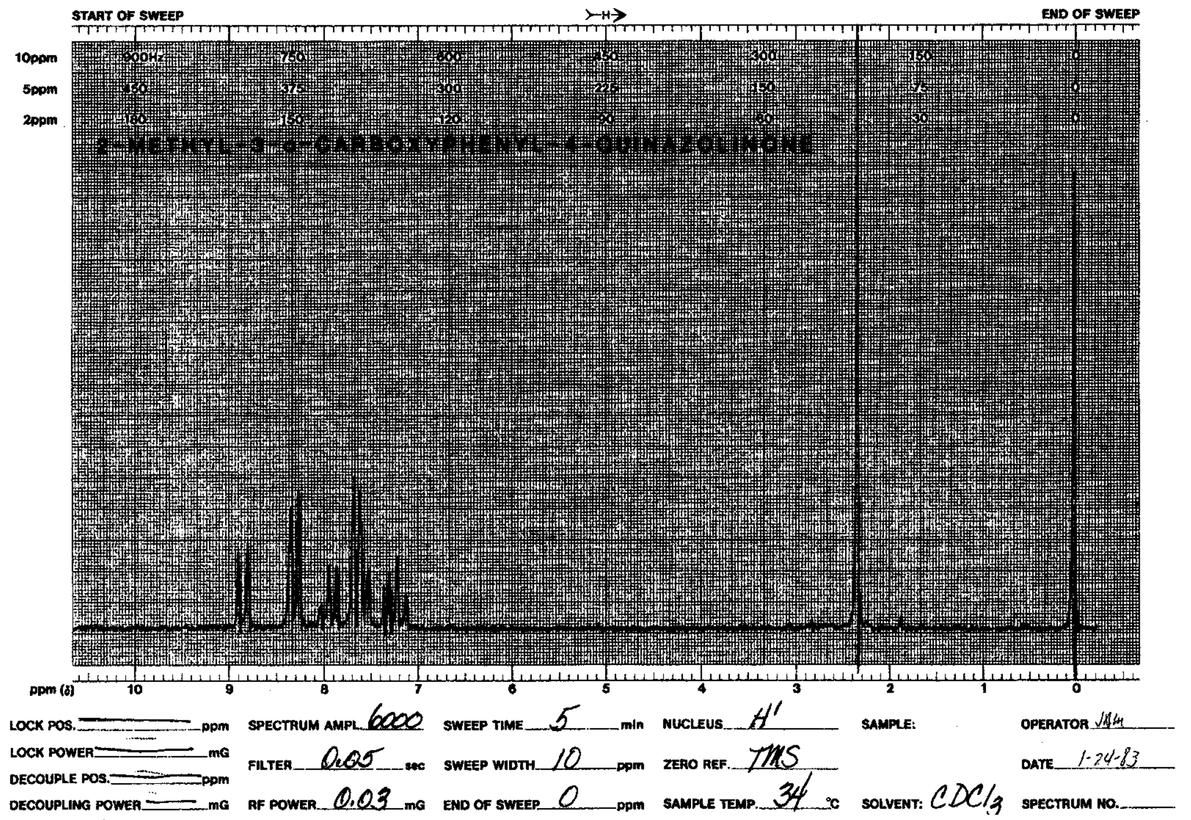

FIG. 3—*continued.*

tories. The starting reactants anthranilic acid (Compound 1) and *o*-toluidine (Compound III) in the case of methaqualone (Compound V) would be present. Normally *o*-toluidine is found in relatively large amounts. Additionally the intermediate *N*-acetyl anthranilic acid (Compound II) can be used as an indicator of the success of the reaction, in that a large amount in the sample would imply a low yield of the quinazolinone.

The intermediates and by-products found in a clandestine mixture are useful in identifying the synthesis route. For example, *o*-methyl acetanilide would only be found in a reaction mixture of anthranilic acid, *o*-toluidine, and acetic anhydride. If *n*-acetyl-anthranilic acid is produced, isolated, and then reacted with *o*-toluidine, the *o*-methyl acetanilide would not be formed. Because of the reactivity of acetic anhydride, several other compounds can be predicted, as any basic compound will undergo nucleophilic substitution with the unreacted acetic anhydride. Initially, there would be a competition between anthranilic acid and *o*-toluidine, for the available acetic anhydride which would determine the extent of the formation of these by-products. If the original reaction was not shifted towards the product *n*-acetyl anthhranilic acid, the yield of methaqualone would be appreciably reduced. Additionally, the production of *o*-methyl acetanilide gives rise to additional by-products and further reduces the yield of methaqualone by removing *o*-toluidine from the reaction.

The by-product 2-methyl-3-(*o*-carboxyphenyl)-4-quinazolinone is formed by the condensation of anthranilic acid and *N*-acetyl-anthranilic acid. This carboxy analogue can be formed whether methaqualone is being produced, and is in competition with its formation. The presence of this analogue would indicate the synthesis route starting with anthranilic acid. Mixtures of methaqualone, mecloqualone, or the carboxy analogue cannot be differentiated by ultraviolet spectroscopy (UV), which could result in an error if UV is used for quantitation.

Methanolic solutions of actual clandestine methaqualone reaction mixtures were used in the gas chromatograph-mass spectrometry study. The solutions were found to contain large amounts of methaqualone, moderate amounts of *o*-methyl acetanilide (Compound VII) and 2-methyl-3-ocarboxyphenyl-4(3H)-quinazolinone (Compound IX), and small amounts of *o*-toluidine.

Conclusions

The methods described can be very important tools to successful prosecution of an illicit drug manufacturer. Consideration should also be given to application of these methods on the finished product, "street samples."

Since the final product of clandestine laboratories can vary from a purified drug to a combination of starting ingredients, by-products, and the desired drugs it may be important to identify as many components as possible in the sample. This can give an indication of the synthesis route employed or the sophistication of the "chemist" or both. The results of the analysis can be used for intelligence purposes as a possible basis for comparison with other samples, which could lead, in turn, to identification of trafficking routes and possible sources of illicit drugs.

References

[1] Pascarelli, E. F., *Journal of the American Medical Association*, Vol. 224, No. 11, June 1973, pp. 1512-1514.
[2] Drug Enforcement Administration, *Federal Register*, Vol. 40, No. 131, June 1975, p. 28611.
[3] Kacher, I. K. and Zaheer, S. H., *Journal of the Indian Chemical Society*, Vol. 28, No. 6, 1951, pp. 344-346.
[4] Preuss, Fr. R., Hassler, H. M., and Kopf, R., *Arzneimittel Forschung* (*Drug Research*), Vol. 16, No. 3, March 1966, pp. 395-401.
[5] Preuss, Fr. R., Hassler, H. M., and Kopf, R., *Arzneimittel Forschung* (*Drug Research*), Vol. 20, No. 17, Dec. 1970, pp. 1920-1922.
[6] Preuss, Fr. R., Hassler, H. M., and Kopf, R., *Arzneimittel Forschung* (*Drug Research*), Vol. 16, No. 3, March 1966, pp. 401-407.

[7] Akagi, M., Oketani, Y., and Yamane, S., *Chemical and Pharmaceutical Bulletin*, Vol. 11, No. 9, Sept. 1963, pp. 1216-1217.
[8] Permisohn, R. C., Hilpert, L. R., and Kozyak, L., *Journal of Forensic Sciences*, Vol. 21, No. 1, Jan. 1976, pp. 98-107.
[9] Jackman, G. V., Petrow, V., and Stephenson, O., *Journal of Pharmacy and Pharmacology*, Vol. 12, No. 9, Sept. 1960, pp. 528-529.
[10] Daenens, P. and Van Boven, M., *Arzneimittel Forschung* (*Drug Research*), Vol. 24, No. 2, Feb. 1974, pp. 195-202.

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