TECHNICAL NOTE

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The Structural Identification of a Methyl Analog of Methaqualone via 2-Dimensional NMR Techniques

REFERENCE: Angelos, S. A., Lankin, D. C., Meyers, J. A., and Raney, J. K., **"The Structural Identification of a Methyl Analog of Methaqualone via 2-Dimensional NMR Techniques,"** *Journal of Forensic Sciences*, JFSCA, Vol. 38, No. 2, March 1993, pp. 455–465.

ABSTRACT: A submission to the Drug Enforcement Administration North Central Laboratory of a substance believed to be a structural analog of methaqualone hydrochloride precipitated an interest in being able to obtain a rapid and positive identification of such compounds. Both mass spectrometry and proton NMR spectroscopy (1-dimensional) provided evidence to suggest that the structural analog possessed a second methyl group in the molecule, relative to methaqualone, and that the methyl group was attached to the existing methyl-substituted phenyl ring. By application of proton 2-dimensional (2-D) NMR techniques, specifically the homonuclear shift correlation spectroscopy (COSY) and 2-D NOE (NOESY), the precise location of the methyl group in this unknown methaqualone analog was established and shown to have the structure 2.

KEYWORDS: toxicology, methaqualone, mass spectrometry, NMR spectrometry, controlled substances, drug analysis

The ability to provide both rapid identification of the general class of controlled substance as well as determine the exact structure of the analog is becoming an increasingly important task in forensic laboratories across the country. This article describes one approach that has been taken for the identification of a structural analog of methaqualone, 1. It not only uses the complimentary nature of the standard spectroscopic techniques (infrared spectroscopy and mass spectrometry) but also introduces the powerful problem solving capability of 2-dimensional (2-D) NMR spectroscopy [*1–7*].

Experimental Section

The methaqualone analog described in this study was submitted as an exhibit to the Drug Enforcement Administration North Central Laboratory by a state laboratory. The

Received for publication 10 July 1992; revised manuscript received 5 Oct. 1992; accepted for publication 7 Oct. 1992.

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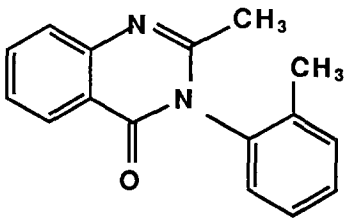


Methaqualone **1**

sample received by the state laboratory for analysis was initially thought to be a sample of methaqualone free-base, 1. The sample was qualitatively identified as a hydrochloride salt by examination of the infrared spectrum of the sample, as received, and the spectrum compared to the infrared spectra of authentic samples of the free base and hydrochloride of authentic methaqualone.

Infrared Spectroscopy

Solid phase infrared spectra were measured on a Perkin-Elmer 1800 FT-IR as KBr pellets. The vapor phase infrared (IR) spectra were obtained on a Hewlett-Packard Model 5865 GC/IRD/MSD. The column used was a 15 m by 0.32 mm DB-1 (1.0 μm loading) and the temperature ramp was from 150° to 260° C at a rate of 10°/min.

Mass Spectrometry

Mass spectra (EI) were obtained on a Hewlett-Packard 5970 GC-MSD using a HP-1, 15 m by 0.20 mm (0.25 μm loading) capillary column run isothermally at 250° C.

Nuclear Magnetic Resonance Spectroscopy

NMR spectra were collected on either a Varian VXR-300 using a 5 mm broad-band switchable probe equipped with the variable temperature accessory regulated at 25° C or a Varian Gemini-300 using a 5 mm ambient temperature (20° C) probe. The proton observation frequency for both instruments was 300 MHz. All samples were run in chloroform-*d* (10 to 20 mg/mL) and were internally referenced to tetramethylsilane (TMS).

Results

The vapor-phase and KBr infrared spectra for both methaqualone, 1, and the methaqualone analog are shown in Figs. 1 and 2, respectively. The results confirm the data initially reported by the state laboratory, the differences observed being more than could be attributed to simple contamination of the sample. The principle differences in the infrared spectra, noted on the figures, are observed in the olefinic/aromatic C-H stretch region (3100 to 3000 cm-1) and the region associated with aromatic substitution pattern (900 to 500 cm-1)

The results obtained from mass spectrometry on both methaqualone, 1 and the methaqualone analog are shown in Figs. 3 and 4, respectively. The fragmentation pattern observed for the methaqualone analog was very similar to and comparable with the data reported earlier for methaqualone [*8*]. The most obvious difference in the two mass spectra was in the molecular ion which indicated a m/z = 264 (M^+) for the methaqualone analog. This difference in mass is consistent with the presence of either an additional methylene unit or the presence of a second methyl group in the methaqualone analog.

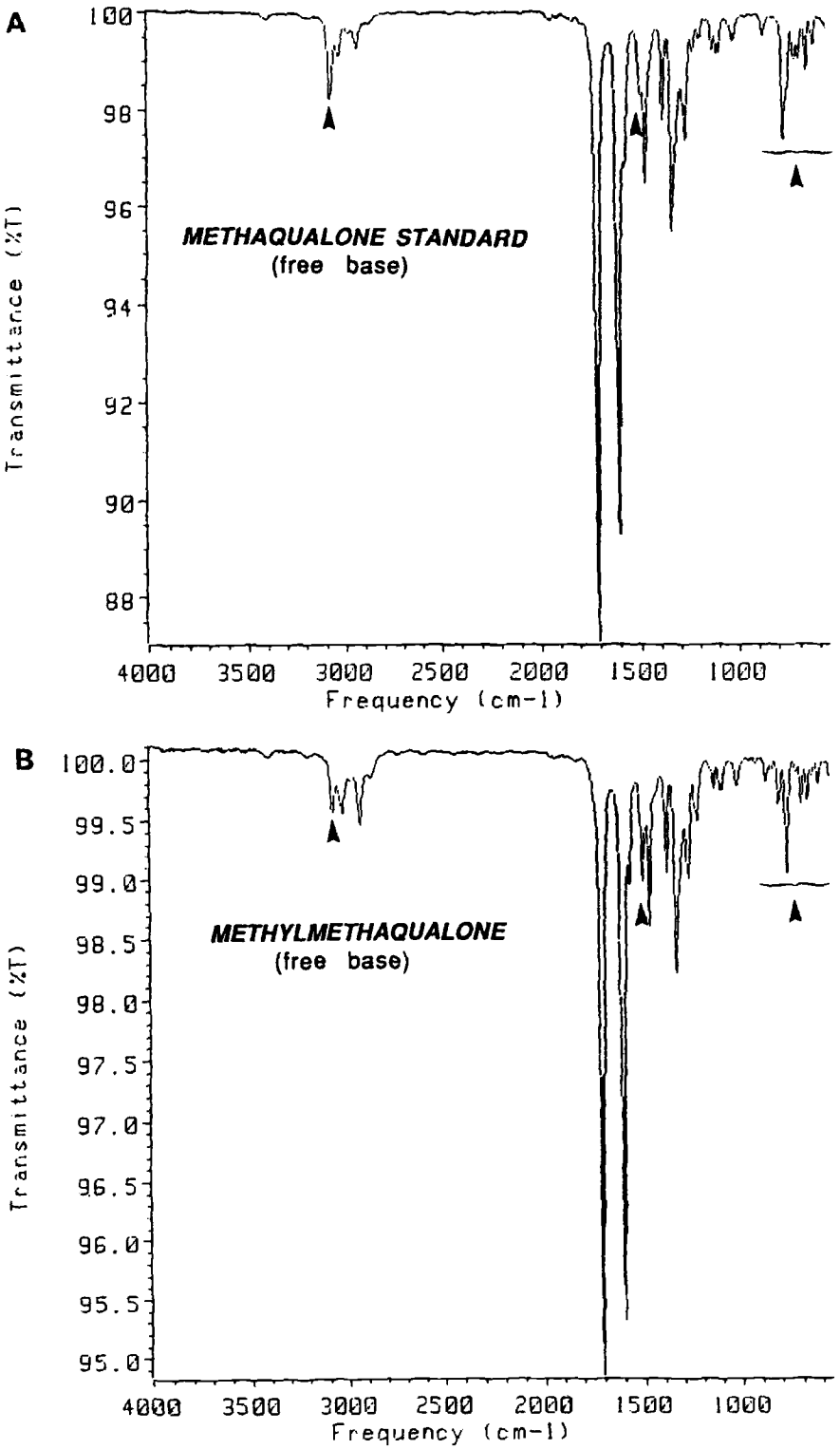


FIG. 1—*Vapor phase infrared spectra of (A) methaqualone I standard (free base) and (B) methylmethaqualone analog (free base).*

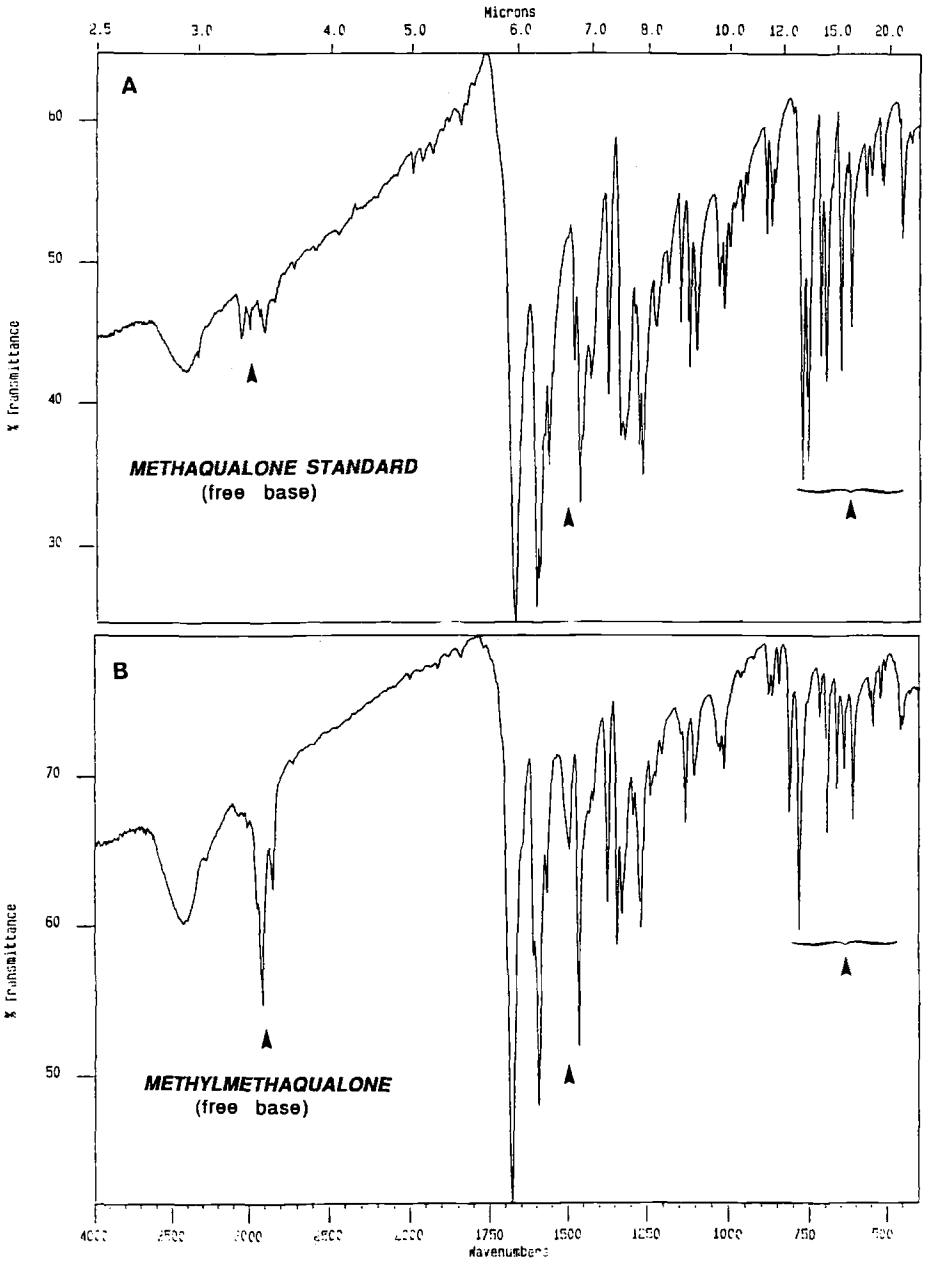


FIG. 2—*Infrared spectra (KBr) of (A) methaqualone 1 standard (free base) and (B) methylmethaqualone analog (free base).*

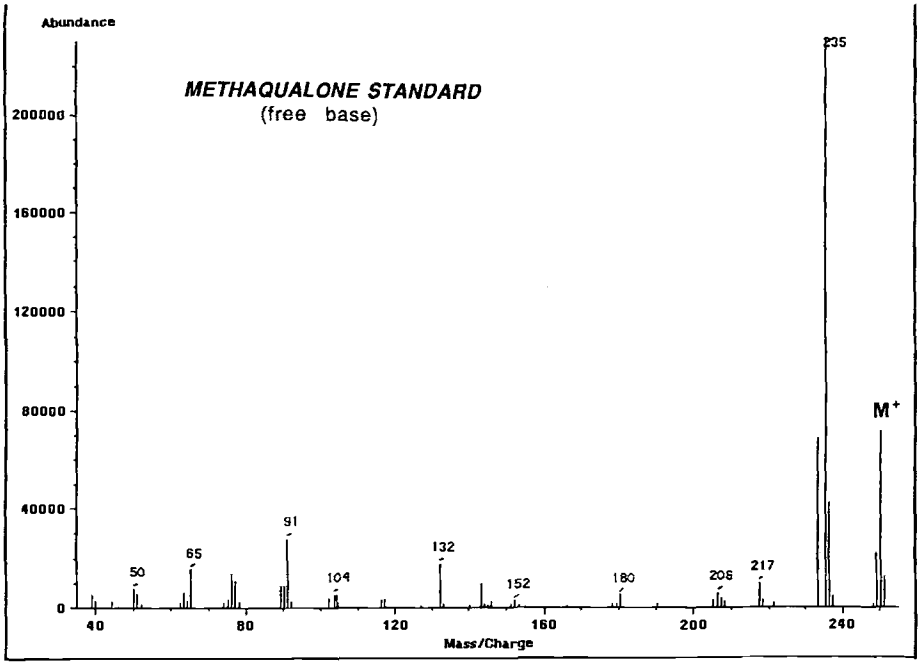


FIG. 3—*The mass spectrum of methaqualone 1 standard (free base).*

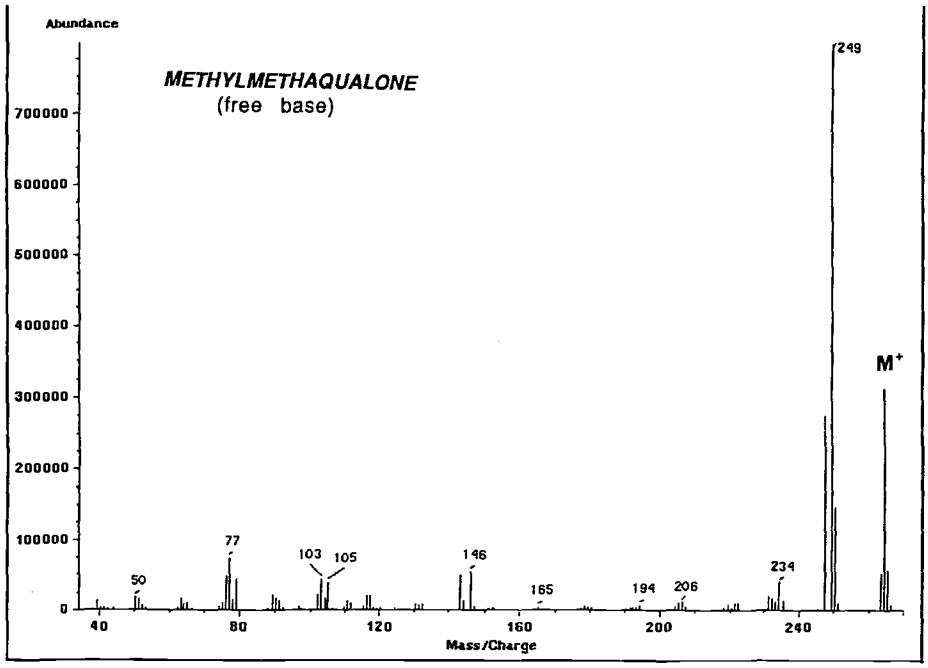
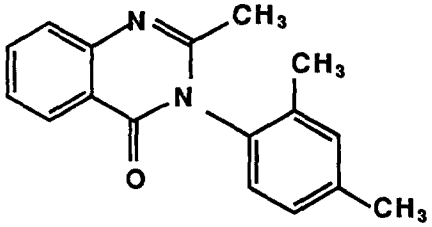


FIG. 4—*The mass spectrum of methaqualone 1 analog (free base).*

The proton NMR spectra (300 MHz), obtained for comparison, of the hydrochloride salts of both methaqualone standard and the methaqualone analog, are shown in Figs. 5 and 6. The data clearly indicates the presence of an additional 3-proton signal at ≈2.3 ppm in the proton spectrum of the methaqualone analog. Examination of the aromatic region (7.0 to 9.0 ppm) of the proton NMR spectra, shown in the expansion in Fig. 7, of the methaqualone analog, indicates that its spectrum integrates for one less aromatic proton than methaqualone and that the aromatic substitution pattern for the N-phenyl moiety for the two substances are different. The data indicates that an additional methyl group is present in the methaqualone analog and that it resides on the methyl-bearing N-phenyl ring moiety. Additional examination of the aromatic proton substitution pattern for the phenyl ring in the NMR spectrum of the methaqualone analog, suggests that the ring is 1,2,4 trisubstituted. Only two structural arrangements possessing the 1,2,4-trisubstituted aromatic pattern and lacking an element of symmetry that would render the ring methyls chemically nonequivalent are possible for the methaqualone analog: either 2 and 3. To unambiguously resolve this structural question, the application of 2-D NMR spectroscopy was used. Figures 8 and 9 depict the COSY [*9*] and NOESY [*10*] data, respectively, obtained for the methaqualone analog.



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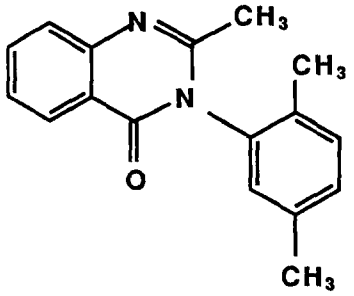
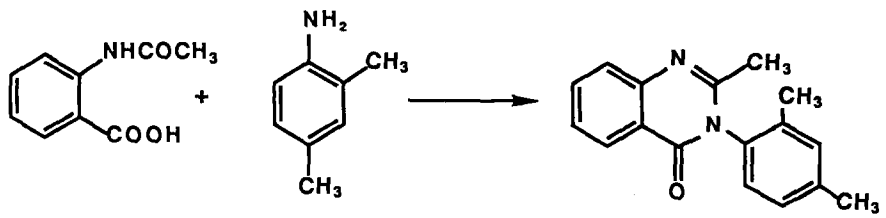


3

Possible Analogs of Methyl Methaqualone

The COSY (*CO*rrelation *S*pectroscop*Y*) data provides evidence for homonuclear J-coupling of spins and shows that the aromatic proton displaying only meta type coupling to other aromatic protons is J-coupled to both methyl groups attached to the ring. Additionally, the NOESY (*N*uclear *O*verhauser *E*nhancement correlation *S*pectroscop*Y*)

Scheme 1



N-Acetyl-anthranilic Acid

2,4-Xylidine

2

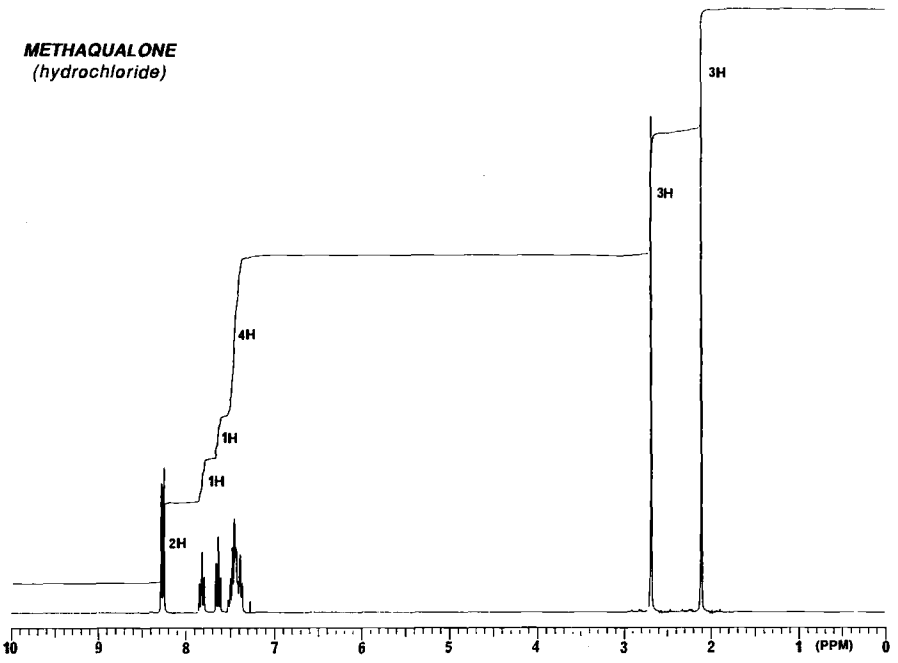


FIG. 5—*The proton NMR spectrum of methaqualone 1 (hydrochloride).*

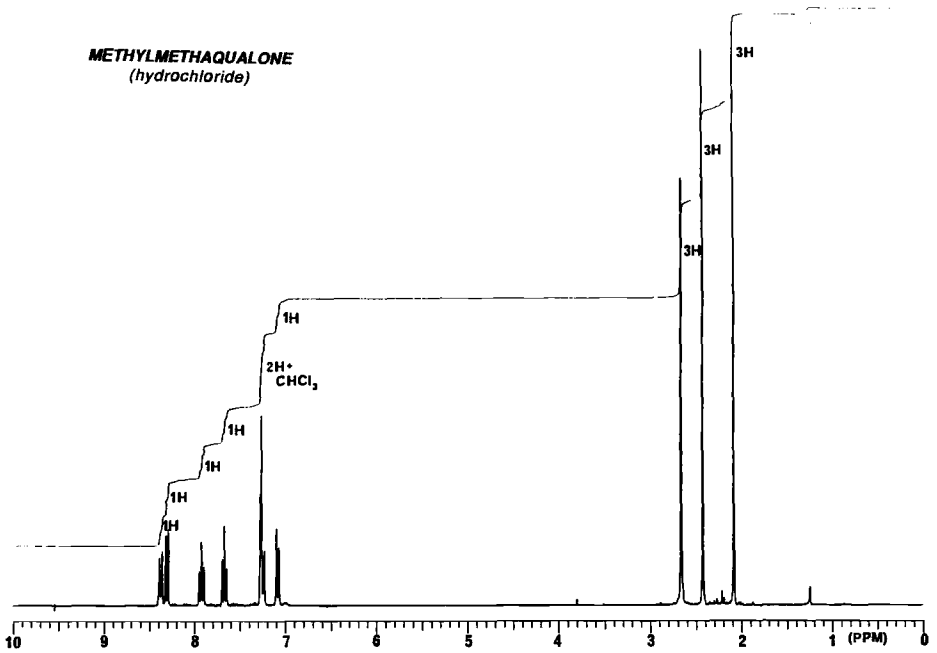


FIG. 6—*The proton NMR spectrum of methylmethaqualone 2 (hydrochloride).*

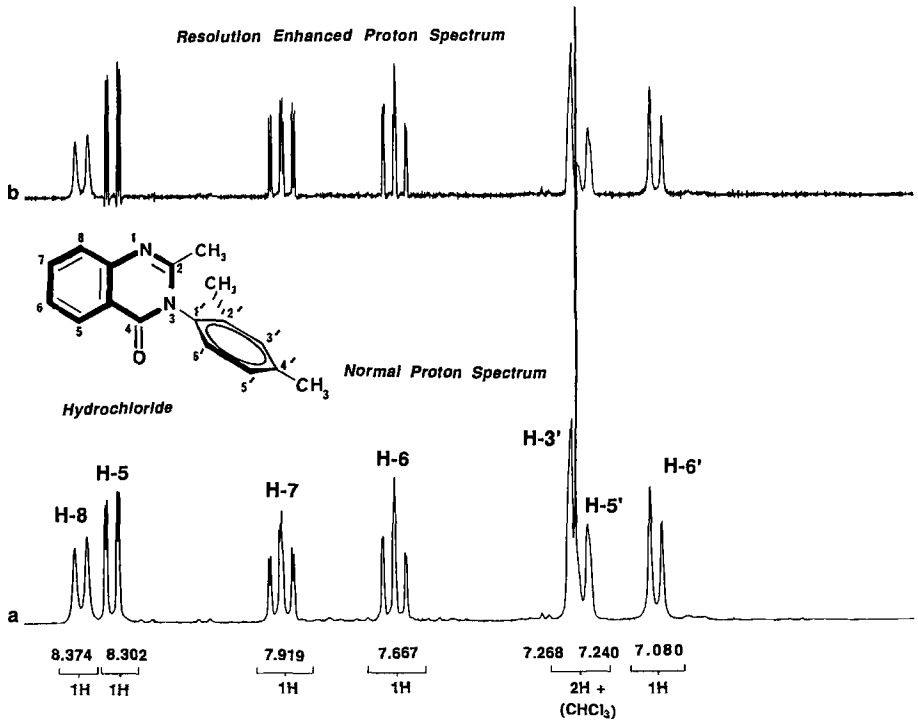


FIG. 7—*Expansion of the proton NMR spectrum of methylmethaqualone (hydrochloride) 2 showing the details of the aromatic region: (A) normal spectrum; (B) resolution enhanced spectrum.*

data, which renders information about the protons which are close to one another in space, shows the existence of cross-peaks between the meta-coupled aromatic proton to both methyl groups. This indicates that this meta-coupled proton is spacially proximate to and lies between the two methyl groups on the aromatic ring. The data from both 2-dimensional NMR techniques are consistent with the methaqualone analog possessing structure 2. Verification of this method of analog identification was confirmed by independent syntheses of 2 [*11*] (Scheme 1). A summary of the proton chemical shifts and coupling constants obtained for methaqualone 1 and the methyl analog 2 appears in Tables 1 and 2, respectively.

Conclusions

A contemporary approach to analog identification employing the power of 2-dimensional NMR spectroscopy, illustrated by the identification of the methyl analog of methaqualone as 2, can result in rapid and unambiguous confirmation of structure. This necessarily reduces the need to synthesize all of the possible structural combinations and permutations of a given analog for authentic comparison except for the structure or structures indicated by the appropriate 1- and 2-dimensional NMR experiments. This approach can contribute to a significant reduction in the time required to deal with a particular unknown analog identification and greatly enhance the overall productivity and efficiency of the laboratory operation, while expediting the legal procedure for its control.

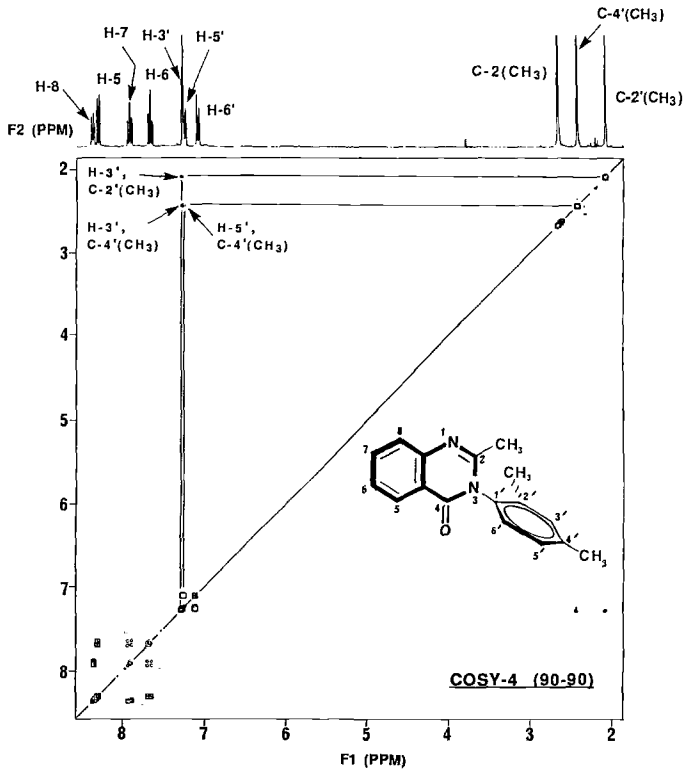


FIG. 8—*The COSY spectrum (absolute value) of the methylmethaqualone analog (hydrochloride) 2 showing cross-peak correlations of the two methyl groups to the same aromatic ring proton.*

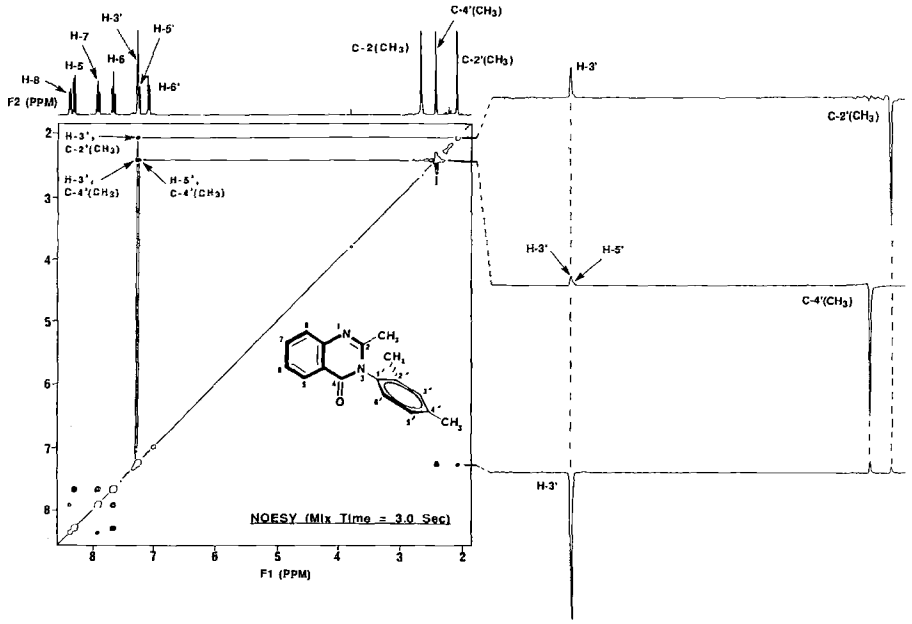


FIG. 9—*The phase-sensitive NOESY spectrum of the methylmethaqualone analog (hydrochloride) 2 showing cross-peak correlations of the two methyl groups to the same common ring proton.*

TABLE 1—*The proton NMR chemical shifts of methaqualone and the methyl methaqualone analog, free bases (A) and hydrochloride salts (B) (300 MHz, $CDCl_3$ solution, 20° C).*

Proton Assignment	Compound			
	1(A)	1(B)	2(A)	2(B)
H-5	8.247 dd	8.261 d	8.252 dd	8.302 dd
H-6	7.424 td	7.632 td	7.431 td	7.667 td
H-7	7.730 td	7.814 td	7.738 td	7.919 ddd
H-8	7.650 br d	8.262 br d	7.652 br d	8.374 br d
H-3′	┐	┐	7.173 br s	7.268 br s
H-4′	7.37–7.29 m	7.32–7.44 m	- - - -	- - - -
H-5′	┘	┘	7.131 br d	7.240 br d
H-6′	7.122 br d		6.988 d	7.080 br d
C-2(Me)	2.139 s	2.686 s	2.157 s	2.664 s
C-2′(Me)	2.801 br s	2.109 s	2.043 br s	2.085 br s
C-4′(Me)	- - - -	- - - -	2.362 br s	2.426 br s

The proton chemical shifts are expressed in ppm(δ) relative to tetramethylsilane (TMS), δ = 0.00 ppm. The following abbreviations are used: s = singlet; d = doublet; t = triplet; m = multiplet; dd = doublet-of doublets; td = triplet-of-doublets; br s = broadened singlet; br d = broadened doublet; ddd = doublet-of-doublet-of-doublets.

TABLE 2—*Proton-proton coupling constants of methaqualone and the methyl methaqualone analog, free bases (A) and hydrochloride salts (B) (300 MHz, $CDCl_3$ solution, 20° C).*

Coupling Constant (J, Hz)	Compound			
	1(A)	1(B)	2(A)	2(B)
J (5,6)	8.0	8.0	8.1	8.1
J (6,7)	6.9	7.4	7.1	7.4
J (7,8)	6.9	8.3	8.0	8.6
J (5,7)	1.6	1.5	1.5	1.5
J (6,8)	1.1	1.1	1.2	1.0
J (3′,4′)			- - -	- - -
J (4′,5′)			- - -	- - -
J (5′,6′)	6.8		8.0	7.2
J (4′,6′)			- - -	- - -
J (3′,5′)	NR		NR	NR

NR = not resolved.

References

[1] Derome, A. E., *Modern NMR Techniques for Chemistry Research*, Pergamon Press, New York, NY, 1987.

[2] Friebolin, H., *Basic One- and Two-Dimensional NMR Spectroscopy*, VCH Publishers, New York, NY, 1991.

[3] Croasman, W. R. and Carlson, R. M. K., *Two-Dimensional NMR Spectroscopy: Applications for Chemists and Biochemists*, VCH Publishers, New York, NY, 1987.
[4] Shoolery, J. N., "Recent Developments in ^{13}C- and Proton NMR," *Journal of Natural Products*, Vol. 47, No. 2, 1984, pp. 226–259.
[5] Benn, R. and Gunther, H., "Modern Pulse Methods in High-Resolution NMR Spectroscopy," *Angewandte Chemie International*, Edition in English, Vol. 22, No. 5, pp. 350–380.
[6] Kriwacki, R. W. and Pitner, T. P., "Current Aspects of 2-Dimensional (2-D) Nuclear Magnetic Resonance (NMR) Spectroscopy: Applications to Structure Elucidation," *Pharmaceutical Research*, Vol. 6, No. 7, pp. 531–554.
[7] Jelinski, L. W., "Modern NMR Spectroscopy," *Chemical and Engineering News*, November 5, 1984, pp. 26–47.
[8] Angelos, S. A. and Meyers, J. A., "The Isolation and Identification of Precursors and Reaction Products in the Clandestine Manufacture of Methaqualone and Mecloqualone," *Journal of Forensic Sciences*, Vol. 30, No. 4, Oct. 1985, pp. 1022–1047.
[9] Martin, G. E. and Zektzer, A. S., *Two-Dimensional NMR Methods for Establishing Molecular Connectivity*, pp. 58–161. VCH Publishers, New York, NY, 1988.
[10] Neuhaus, D. and Williamson, M., *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, VCH Publishers, New York, NY, 1989.
[11] Kacker, I. K. and Zaheer, S. H., "Potential Analgesics, Part 1—Synthesis of Substituted 4-Quinazolones," *Journal of the Indian Chemical Society*, Vol. 28, No. 6, 1951, pp. 344–346.

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