dose on serum level can be defined by comparing the mean serum levels for the two doses at each bleeding time (10). A t test was applied to the mean serum levels and their standard deviations, and the results (Table II) showed that the mean serum levels were significantly different ($p < 0.01$) at each bleeding time.

A t test was also performed between the serum levels following the 11-mg/kg dose and 2.5 times the serum levels following the 4.4-mg/kg dose. There was no significant difference ($p < 0.05$) between the serum levels following the 11-mg/kg dose and 2.5 times the serum levels following the 4.4-mg/kg dose (Table III). These results suggest that serum levels are directly proportional to dose levels.

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Anomalous Chemical Shifts of Methyl Groups of 2,4-Dimethylbenzo[g]quinoline

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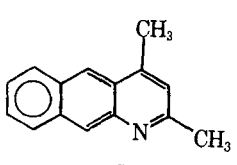
Abstract □ The chemical shifts of the methyl groups of 2,4-dimethylbenzo[g]quinoline are defined with respect to concentration, showing that the methyl resonances are reversed from their expected positions in concentrations normally used in NMR spectroscopy. The phenomenon is explained in terms of the probable "fixation" of bonds in the hetero ring.

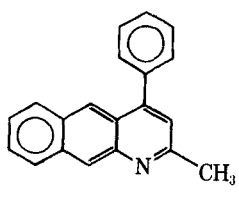
Keyphrases □ 2,4-Dimethylbenzo[g]quinoline—NMR spectrum, chemical shifts of methyl groups defined, effect of concentration □ NMR—spectrum, 2,4-dimethylbenzo[g]quinoline, chemical shifts of methyl groups defined, effect of concentration □ Quinoline, substituted—2,4-dimethylbenzo[g]quinoline, NMR spectrum, chemical shifts of methyl groups defined, effect of concentration

During a study of the possibility of converting 2,4-dimethylbenzo[g]quinoline (I) to benzo[g]cinchoninic acid, large concentration chemical shifts for the methyl groups of I were observed. At low concentrations (3.4×10^{-2} M), the absorptions for the methyl groups appeared as a doublet at δ 2.76 (J = 1.2 Hz) and as a singlet at δ 2.69. As the concentration of I was increased, the expected upfield shifts of the methyl groups occurred, but the downfield methyl resonance showed a larger upfield shift than the methyl resonance at δ 2.69. Therefore, at a concentration of 2.74×10^{-1} M, the two methyl signals had overlapped to produce a single resonance at δ 2.64. When the concentration was increased to 6.4×10^{-1} M, a singlet at δ 2.57 and a doublet at δ 2.5 (J = 1 Hz) were observed.

The classical assignment of the downfield resonance to the 2-methyl of I cannot be accommodated by this information. The chemical shift of the 2-methyl group would be expected to remain relatively constant as the concentration of I is increased while the 4-methyl group would be expected to have the greatest shift due to solute–solute interactions (1). This observation led to assignment of the resonance at δ 2.76 (J = 1.2 Hz) (3.4×10^{-2} M) to the 4-methyl group and at δ 2.69 to the 2-methyl group of I.



I



II

EXPERIMENTAL

Samples were weighed on a microbalance[1] and then diluted to volume with benzene-d_6 or spectrograde carbon tetrachloride containing 1% tetramethylsilane as an internal standard. The NMR spectra were obtained using a 60-MHz spectrometer[2] equipped with a double-resonance accessory.

2,4-Dimethylbenzo[g]quinoline (I) was prepared as reported previously

[1] Cahn RTL.
[2] Perkin-Elmer R12-A.

Table I—Chemical Shifts (δ) of the Protons of I at Various Concentrations [a]

Concentration, M	H_3	H_5	H_{10}	2-CH_3	4-CH_3	$H_{6,7,8,9}$
3.4×10^{-2}	7.02	8.38	8.53	2.69	d, 2.76, J = 1.2 Hz	m, 7.44 and 7.98
2.74×10^{-1}	6.9	8.24	8.48	2.64	2.64	m, 7.42 and 7.98
6.4×10^{-1}	6.77	8.14	8.43	2.57	d, 2.50, J = 1 Hz	m, 7.36 and 7.86
Benzene-d_6	5.8	8.20	8.89	2.58	d, 2.27, J = 0.66 Hz	m, 7.25 and 7.8

[a] Except as noted, spectra were run in carbon tetrachloride; 1% tetramethylsilane was utilized as the internal standard (δ = 0.0) in all samples.

(2). The chemical shifts for the protons of I at various concentrations are shown in Table I.

Compound I, 150 mg, was refluxed for 15 min in 4 ml of methyl alcohol-d_1, to which had been added 200 mg of metallic sodium. The reaction was then treated with 25 ml of water, the mixture was extracted with ether, and this extract was dried with magnesium sulfate. The residue remaining after evaporation under vacuum was recrystallized from petroleum ether, mp 92–93° [lit. (2) mp 92–93°], and the NMR spectrum was determined in benzene-d_6. The downfield methyl resonance contained 26% less protons than the upfield 4-methyl group.

2-Methyl-4-phenylbenzo[g]quinoline (II) was prepared as described by Huisgen (3). The product melted at 110° [lit. (3) mp 110°]; NMR: δ 8.58 (s, 1H), 8.27 (s, 1H), 8.14 (m, 9H), 7.09 (s, 1H), and 2.76 (s, 3H). No appreciable change in the spectrum was found when the concentration of II was changed.

DISCUSSION

The lack of coupling between proton H_3 and the methyl group of 2-methylquinoline and the fact that the methyl protons of 4-methylquinoline were observed as a doublet (J = 0.95 Hz) (4) supported the discussed assignment of the methyl resonances of I. In addition, the methyl resonance of II was a singlet. To show that the doublet of I was the result of coupling to proton H_3 rather than to a long-range interaction, proton H_3 was irradiated to produce a singlet for the 4-methyl resonance of I. The ability of benzene to produce larger upfield chemical shifts for methyl groups on the 4-position of quinoline or pyridine is well documented (1), and the same physical phenomenon should result in an upfield shift for the 4-methyl of I.

When the spectrum of I was run in benzene-d_6, the methyls appeared as expected as a singlet at δ 2.58 and as a doublet at δ 2.27 (J = 0.66 Hz). When I was treated with sodium methoxide–methyl alcohol-d_1, the downfield resonance as observed in benzene-d_6 exchanged more rapidly than the upfield resonance, showing that the downfield resonance in benzene-d_6 was due to the more acidic 2-methyl group (5).

The finding of Clar and MacKay (6) that the splitting between methyl-substituted anthracenes and aromatic protons was directly related to the extent of double bond fixation has application to the benzo[g]quinoline system. Since the resonance energy of benzo[g]quinoline is 21.2 kcal/mole less than anthracene, the possibility of even greater bond localization exists with I than with anthracene. The lack of coupling between proton H_3 and the 2-methyls of I and II substantiated the localization of bonds in the hetero ring of benzo[g]quinolines as shown in Structures I and II.

The localization of the bonds in the hetero ring results in less paramagnetic shielding for the 2-methyl group because it is removed from the aromatic naphthalene ring. The 4-methyl group is affected by the paramagnetic shielding of the naphthalene section of the molecule, resulting in its downfield position with respect to the 2-methyl in dilute solutions where solute–solute interactions are minimized. In more concentrated solutions, increased shielding of the 4-methyl group due to solute–solute interactions produces a spectrum that conforms to the classical absorption pattern.

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Quantitative Determination of Phenol by High-Pressure Liquid Chromatography

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Abstract □ High-pressure liquid chromatography was used with a 5-μm silica gel column to quantitate the phenol in phenolated calamine lotion USP and a commercial antiseptic solution. This method requires less than 10 min/assay, and other compounds present in the products analyzed did not interfere.

Keyphrases □ Phenol—high-pressure liquid chromatographic analysis, pharmaceutical preparations □ High-pressure liquid chromatography—analysis, phenol in pharmaceutical preparations □ Antipruritics—phenol, high-pressure liquid chromatographic analysis in pharmaceutical preparations

Methods for the quantitative analysis of phenol include a bromometric analysis (1), a colorimetric analysis based on the reaction of phenol with copper sulfate (2), and, most recently, a colorimetric analysis based on the reaction of phenol with ferric chloride (3). This report describes a rapid quantitative method for the analysis of the phenol