Carbon-13 Nuclear Magnetic Resonance Spectra of Potent Antimalarials: Primaquine and Chloroquine.

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C^{13} Nmr chemical shits of primaquine and chloroquine are reported. The signals are assigned on the basis of substituent effects on benzene shifts, intensities, multiplicities in SFORD and the comparison with structurally related compounds.

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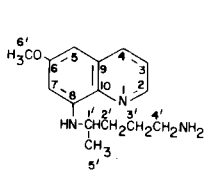
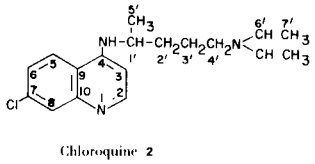
In our continuing efforts to assign C^{13} nmr chemical shifts of potent drugs (1,2), we now wish to report the assignments of C^{13} nmr spectra of the two antimalarials, primaquine **1** and chloroquine **2**. The C^{13} nmr spectra of these compounds are of biological as well as of theoretical interest. Both primaquine and chloroquine have a quinoline ring with an aliphatic side chain. Recently, Wenkert, *et al.*, (3) and Moreland, *et al.*, (4) have reported the C^{13} nmr chemical shifts of the cinchona alkaloids which posses quinoline and quinuclidine rings.

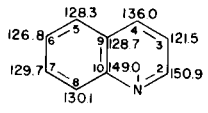
The C^{13} nmr spectra of **1** and **2** were obtained in deuteriochloroform as an internal lock and solvent and tetramethylsilane as a reference. In each case a noise-decoupled and single-frequency off-resonance decoupled (SFORD) spectra were taken. The assignments of the signals were made on the basis of C^{13} nmr chemical shift theory, the multiplicities generated in the SFORD spectra, the intensities of the signals, and the comparision with structurally related compounds.



Primaquine 1



Chloroquine 2



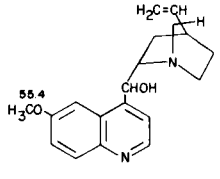
Quinoline 3

Primaquine **1**.

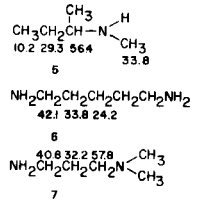
The C^{13} nmr chemical shifts of primaquine obtained from its C^{13} nmr spectra (Figure 1) are recorded in Table 1. The nine separate signals in the 91-160 ppm chemical shift region are assigned to the carbons of the quinoline ring and the six separate signals in the 20-55 ppm region accounted for the side chain carbons relative to tetramethylsilane.

The four low intensity singlets in the C^{13} nmr spectra of **1** are assigned to aromatic carbons 6, 8, 9, and 10 by comparison to signals observed with quinoline **3**. The singlets which occur the farthest downfield at 159.6 ppm and 145.1 ppm are assigned to C-6 and C-8, respectively, since earlier studies have indicated that a directly bonded methoxyl or amino group produces a large downfield shift and the methoxyl group produces greater downfield shift than the amino group (5). The absence of these signals in the C^{13} nmr spectra of **3** (5) further supported these assignments. The remaining singlet resonances at 129.9 ppm and 135.4 ppm are assigned to C-9 and C-10, respectively, on the basis of C^{13} nmr spectra resonances of the corresponding carbons of the quinoline molecule. The chemical shift of C-10 in **1** at a higher field than that of **3** is due to the presence of the imino group at the *ortho* position and a methoxyl group at the *para* position to this carbon which produced a significant shift at higher field (5). Among the remaining carbons of the quinoline ring, C-2 is directly attached to the nitrogen of the ring and, consequently, should show a signal further downfield than C-3 and C-4. Hence the doublet signal at 144.2 ppm is assigned to C-2. The doublet at 91.5 ppm represented C-7 and at 96.7 ppm represented C-5, since the methoxyl and imino groups are known to cause higher field chemical shifts at their *ortho* and *para* positions (5) and that C-5 is *ortho* to the methoxyl group and *para* to the imino group while C-7 is at *ortho* position to both methoxyl and imino groups. In addition, the *ortho* carbon is influenced by the substituent to a greater extent than the *para* carbon. The doublets at 134.7 ppm and 121.7 ppm are assigned to C-4 and C-3, respectively, as have been reported for the corresponding quinoline assignments (5).

The signal occurring at 55.0 ppm on **1** is a quartet and is assigned to C-6 methoxy-methyl group since the methoxy-methyl signal of quinine **4** occurs at 55.4 ppm. The C-1′ directly linked to imino and C-4′ to amino group are represented by signals at 47.9 ppm and 41.9 ppm, respectively, on the basis of multiplicities and comparison with the anologous chemical shifts observed in compounds



Quinine 4



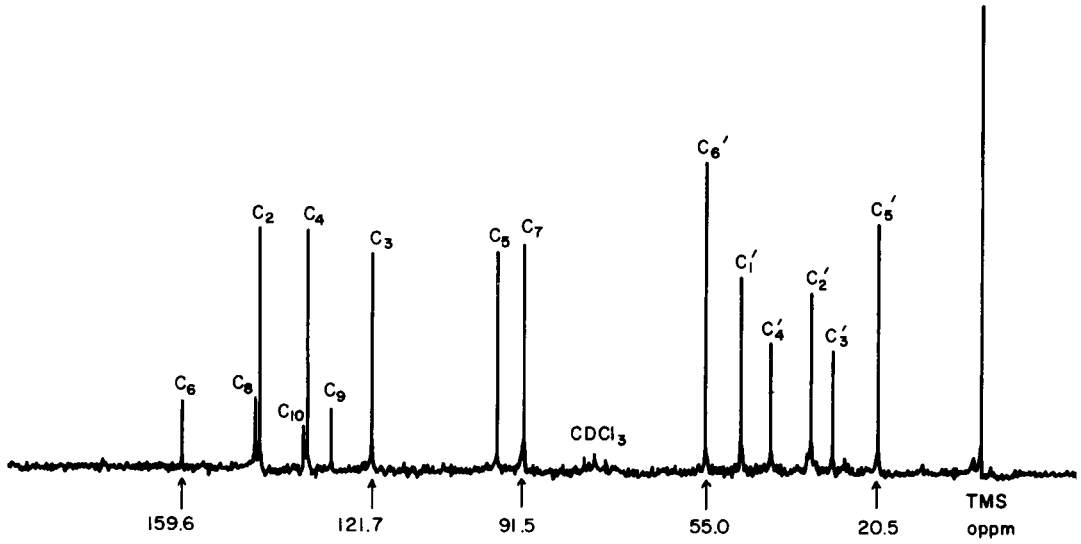


Figure 1. The proton noise decoupled C^{13} Nmr spectrum of primaquine

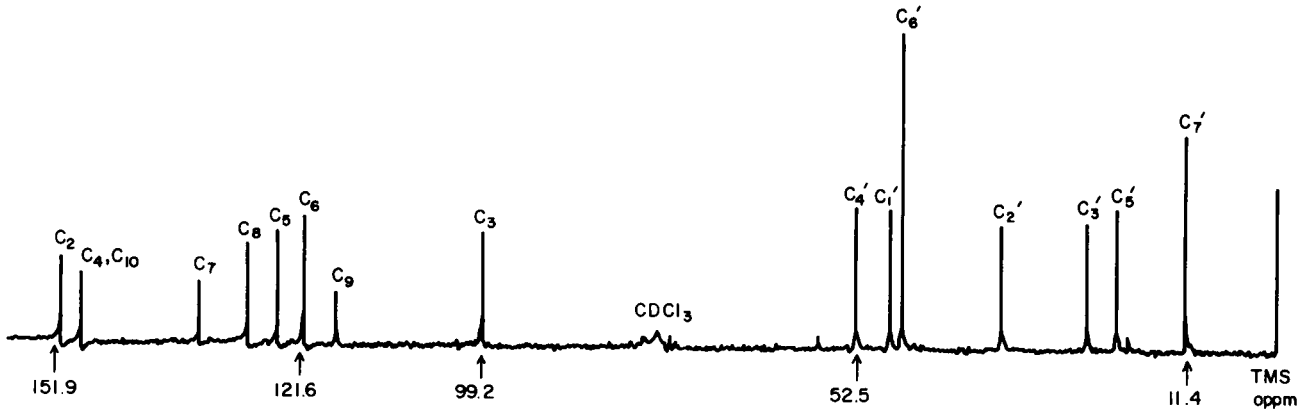


Figure 2. The proton noise decoupled C^{13} Nmr spectrum of chloroquine

5, **6**, and **7** (5). The chemical shifts at 29.7, 34.1, and 20.5 ppm are assigned to C-2′, C-3′ and C-5′, respectively, as has been reported earlier for compounds **5**, **6**, and **7** (5).

Chloroquine **2**.

The C^{13} nmr spectra of chloroquine is recorded in Table 2 and illustrated in Figure 2. The eight signals in the region of 99 to 152 ppm, relative to tetramethylsilane, and seven signals at 11-55 ppm represented the carbons of the quinoline ring and side chain carbons, respectively.

The three singlet signals at 149.3, 134.7, and 117.5 ppm are assigned to the aromatic C-4, C-7, C-9, and C-10. The singlet at 134.7 ppm is assigned to C-7 by comparison to the C^{13} nmr of chlorobenzene **8** (6) which, however, is not affected by the presence of the nitrogen atom at the *meta* position (5). The C-9, *ortho* to imino group and *para* to chlorine atom, is more highly shielded than it is in **3** and hence exhibits its signal at a higher field of 117.5 ppm than that of C-10. The unresolved singlet resonance at 149.3 ppm represents assignments for both C-4 and

Table 1

Carbon-13 Chemical Shifts of Primaquine (a)

Assignments (b)	Multiplicity (c)	Chemical Shift
C-6	s	159.6
C-8	s	145.1
C-2	d	144.2
C-10	s	135.4
C-4	d	134.7
C-9	s	129.9
C-3	d	121.7
C-5	d	96.7
C-7	d	91.5
C-6′	q	55.0
C-1′	d	47.9
C-4′	t	41.9
C-3′	t	34.1
C-2′	t	29.7
C-5′	q	20.5

(a) Chemical shifts are expressed in ppm relative to tetramethylsilane. (b) Numbering of carbon is shown in the structure **1**. (c) Signal multiplicity obtained from SFORD; s = singlet, d = doublet, t = triplet, q = quartet.

Table 2

Carbon-13 Chemical Shifts of Chloroquine (a)

Assignments (b)	Multiplicity (c)	Chemical Shift
C-2	d	151.9
C-4, C-10	s	149.3
C-7	s	134.7
C-8	d	128.5
C-5	d	124.8
C-6	d	121.6
C-9	s	117.5
C-3	d	99.2
C-4′	t	52.5
C-1′	d	48.3
C-6′	t	46.8
C-3′	t	34.5
C-2′	t	23.8
C-5′	q	20.1
C-7′	q	11.4

(a) Chemical shifts are expressed in ppm relative to tetramethylsilane. (b) Numbering of carbon is shown in the structure **2** (c) Signal multiplicity obtained from SFORD; s = singlet, d = doublet, t = triplet, q = quartet.

C-10 on the basis of the substituent effects, intensity of the signal, and comparison with C^{13} nmr of quinoline (5). The lower field signal at 151.9 ppm represents the aromatic C-2, and differs from C-2 of the quinoline (5) since it is directly attached to tertiary nitrogen and is at the *meta* position to imino group. The resonance at 99.2 ppm is assigned to C-3 because it is more shielded than the C-5, C-6, and C-8 due to an *ortho* effect of the imino group. The doublets centered at 128.5, 124.8, and 121.6 ppm represents assignments for C-8, C-5, and C-6, respectively, since the chlorine atom does not significantly affect its *ortho*, *meta*, and *para* positions.

The resonance at 52.5, 48.3, 46.8, 20.1, and 11.4 ppm are assigned to the side chain C-4′, C-1′, C-6′, C-5′, and C-7′, respectively, on the basis of their intensities, splitting patterns and comparison with C^{13} nmr chemical shifts of **5**, **7**, and **9** (5,6). The signals at 34.5 and 23.8 ppm are assigned to the side chain C-2′ and C-3′, respectively.

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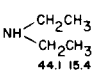

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EXPERIMENTAL

The C^{13} nmr spectra of both the antimalarials, primaquine and chlorquine, were recorded on a JEOL FX 60 spectrometer operating at 15.03 KHz. The samples were run in 10 mm tubes using deuteriochloroform (concentration 30% w/v) as an internal lock and tetramethylsilane as reference. The spectrometer setting during experiment was as following: spectra width 36.00 Hz, pulse width 4 μ sec (90°), repetition rate 1 sec., and data points 8K.

Primaquine and chloroquine were obtained as their hydrochlorides from Sigma Chemical Co., St. Louis, MO. The free bases were obtained by neutralizing the hydrochloride with 10% sodium carbonate solution and subsequent extraction with ether.

Acknowledgement.

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