Carbon-13 Nuclear Magnetic Resonance Spectrum of Methaqualone

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^{13}C nmr chemical shifts of methaqualone, 2-methyl-3-propyl-4-quinazolone, 2-methyl-3-phenyl-4-quinazolone and their precursor, acetanthranil, are reported. The signals are assigned on the basis of substituent effects on benzene shifts, intensities, multiplicities in SFORD, and comparison with structurally related compounds.

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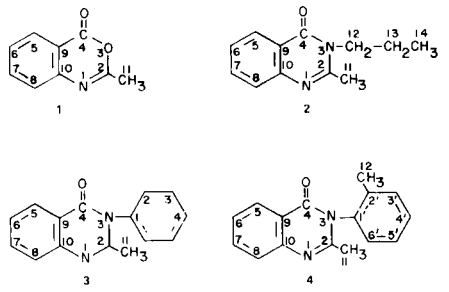
Our continuing interest on the metabolism of methaqualone (2-methyl-3-*ortho*-tolyl-4-quinazolone) **4** towards elucidation of the biochemical mechanism of action of its sedative, hypnotic and anticonvulsant properties (1), prompted us to study ^{13}C nmr spectra of **4**. In the present investigation we have also studied the ^{13}C nmr spectra of acetanthranil **1**, 2-methyl-3-propyl-4-quinazolone **2** and 2-methyl-3-phenyl-4-quinazolone **3** as model compounds for assigning the various carbon resonances of **4**. The ^{13}C nmr spectra of **1**, **2**, **3** and **4** were run in DMSO-d_6, using tetramethylsilane as a reference and the deuterium resonance of DMSO-d_6 as an internal lock signal, on a JEOL FX-60 spectrometer.



The ^{13}C nmr spectra of **1**, **2**, **3** and **4** are recorded in Tables I, II, III and IV, respectively. In all cases, a noise decoupled and a single-frequency off-resonance decoupled (SFORD) spectra were taken (Figures 1, 2, 3 and 4). The multiplicities generated in SFORD spectra exhibited the distinction between various types of carbon resonances. The interpretation of ^{13}C nmr spectra of **3** and **4** are complicated because all the chemical shifts of the aromatic carbon resonances are assigned in the 120-148 ppm region. The SFORD spectrum is unable to differentiate between the resonances of some of the aromatic carbons. The various assignments of signals in the ^{13}C nmr spectra of **1**, **2**, **3** and **4** were made on the basis of chemical shift theory, verification by multiplicities in the SFORD spectra, intensity of signals, and comparison with some structurally related compounds.

Acetanthranil (**1**).

The ^{13}C nmr of **1** exhibited nine separate signals in the 25-170 ppm chemical shift region (Table I), as compared to internal reference, tetramethylsilane. The SFORD spectrum showed one quartet, four singlets, and four doublets.

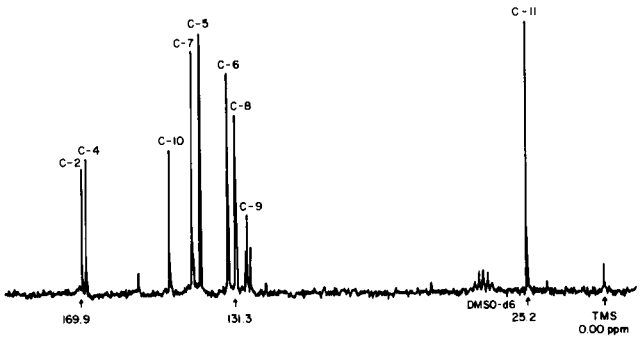


Figure 1. The proton noise decoupled ^{13}C nmr spectrum of acetanthranil.

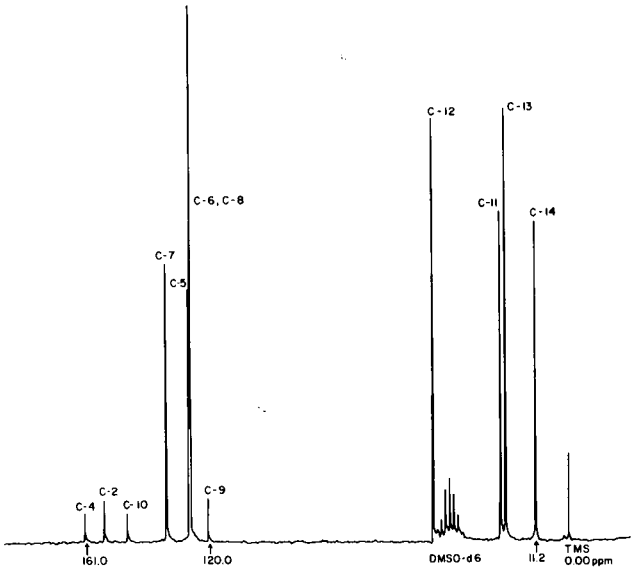
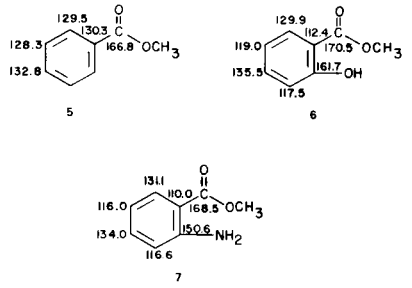


Figure 2. The proton noise decoupled ^{13}C nmr spectrum of 2-methyl-3-propyl-4-quinazolone.

Because of its chemical shift and splitting pattern, the quartet centered at the 25.2 ppm is assigned to the C-11 methyl group. The four singlets represent C-2, C-4, C-9 and C-10 resonances. The signals at 168.6, 141.5 and 116.7 ppm are assigned to C-4, C-10 and C-9, respectively, by analogy to the assignments of ^{13}C nmr of methyl benzoate **3**, methyl salicylate **4**, and methyl anthranilate **5**, (2). By difference, the C-2 signal is represented by a chemical shift to 169.9

ppm, and since C-2 is directly attached to nitrogen and oxygen it would be expected to have a downfield chemical shift (3). The assignments of C-2 and C-4 may be interchanged. The doublets centered at 134.1, 131.3, 122.5 and 119.9 ppm chemical shifts represented assignments for C-7, C-5, C-6, and C-8, respectively, on the basis of the chemical shift theory and comparison with C^{13} nmr spectra of **5**, **6**, and **7**, although the C-6 and C-8 assignments could possibly be interchanged.



2-Methyl-3-Propyl-4-Quinazolone (**2**).

There are eleven signals in the ^{13}C nmr spectrum of **2** in the region of 11-161 ppm chemical shifts. The assignments of the chemical shifts of these signals are recorded in Table II and illustrated in Figure 2. The carbonyl resonances of amides are normally found in the region of 160-180 ppm (3) and the amidic carbon signal of **8** is at 162.1 ppm (3). Therefore, the resonance at 161.0 ppm chemical shift is assigned to C-4. The C-2 and C-10, are directly attached to tetiary nitrogen atom and, therefore, have downfield shift (3) compared to other carbons. The C-2 signal has shifted more downfield compared to C-10, since C-2 is also attached to another nitrogen atom. On the basis of these observations and comparing the ^{13}C nmr spectra of **1**, **6** (2), **7** (2) and quinoline **9** (3), the three singlets at 154.6, 147.0 and 120.0 ppm represent the resonances of C-2, C-10 and C-9, respectively. The doublet centered at 134.0 ppm is attributed to the carbon resonance of C-7 which is well comparable with the chemical shift of the corresponding carbon of **1**, **5**, **6** and **7**. As is evident by the signal intensities from Figure 2, the chemical shifts at 126.5 and 125.9 represent one and two carbon resonances, respectively.

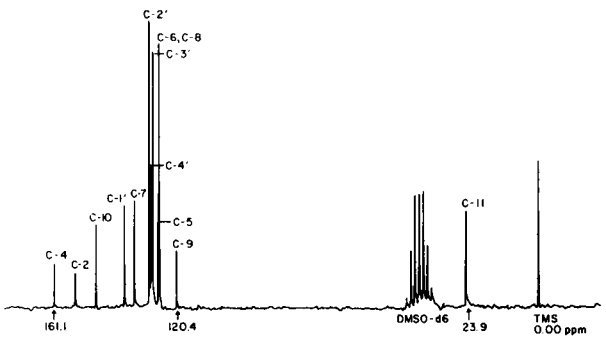


Figure 3. The proton noise decoupled ^{13}C nmr spectrum of 2-methyl-3-phenyl-4-quinazolone.

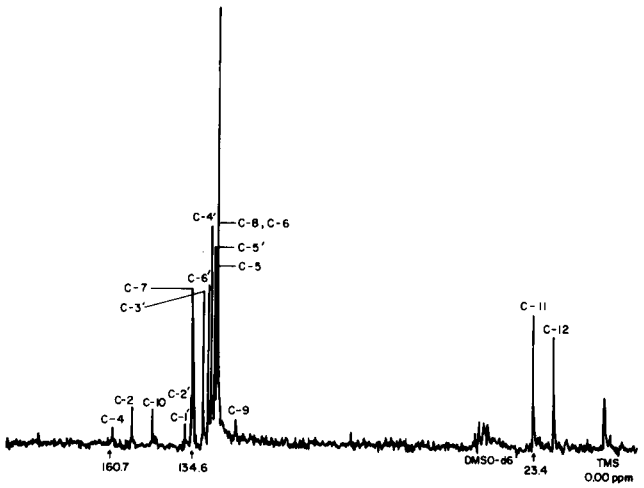
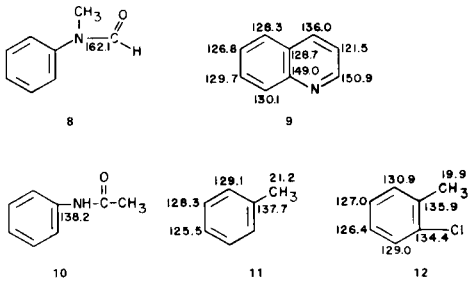


Figure 4. The proton noise decoupled ^{13}C nmr spectrum of methaqualone.

These two signals are due to the carbon resonances of C-5, C-6 and C-8. Since these signals are so close to each other, a definite assignment is not possible. The four signals in the higher field region are accounted to the carbon resonances of C-11, C-12, C-13 and C-14. Since α and β carbons cause about 9 ppm downfield shift and nitrogen produces 20 ppm downfield shift to its α-carbon (3), the signals at 21.3 and 45.3 ppm are attributed to C-13 and C-12, respectively. The two quartets at 22.7 and 11.2 ppm are assigned to the carbon resonances of C-11 and C-14, respectively, as compared to C-11 of **1**. The assignments of C-13 and C-11 may be interchanged because it is difficult to say that the quartet in the SFORD spectrum of **2** is due to the signal at 21.3 or 22.7 ppm.

2-Methyl-3-Phenyl-4-Quinazolone (**3**).

The ^{13}C nmr spectrum of **3** represented twelve separate signals for its fifteen carbon resonances. The chemical shifts of various carbon resonances are recorded in Table III and represented in Figure 3. The farthest upfield signal at 23.9 ppm chemical shift is assigned to C-11 on the basis of chemical shift theory and the multiplicity generated in SFORD spectrum of **3**. This assignment is also comparable with the chemical shift of methyl carbon of **1**. The singlets at 161.1, 154.1, 147.3, 120.4 ppm and a doublet centered at 134.4 ppm chemical shift are represented to the carbon resonances of C-4, C-2, C-10, C-9 and C-7, respectively, by the same analogy for assigning the chemical shift of **2** and are in agreement with the chemical shift of corresponding carbons of **2**. The signal observed at 126.6 ppm is attributed to C-5 and at 126.2 ppm to C-6 and C-8 on the basis of signal intensities and comparing the chemical shift of corresponding carbons of **2**. These may be interchanged. Since an amidic nitrogen attached to benzene ring produces a downfield shift at its ipso carbon atom, the singlet at 137.8 ppm is assigned to C-1'. This assignment is also supported by the corresponding carbon chemical shift of acetanilide



8 9

10 11 12

10 (2). The remaining signals at 129.5, 128.8 and 128.3 could be assigned to C-2′, C-4′ and C-3′ on the basis of their signals intensities (Figure 3). The carbon resonances for C-2′ and C-3′ may be interchanged.

Table I

Carbon-13 Chemical Shifts of Acetanthranil (a)

Assignment	Multiplicity	Chemical Shift
C-2 (b)	s	169.9
C-4 (b)	s	168.6
C-10	s	141.5
C-7	d	134.1
C-5	d	131.3
C-6 (c)	d	122.5
C-8 (c)	d	119.9
C-9	s	116.3
C-11	q	25.2

(a) Chemical shifts are in parts per million relative to tetramethylsilane. Numbering of carbon is shown in the structure. Signal multiplicity was obtained from single-frequency off-resonance experiment. (b) (c) May be interchanged. s = singlet, d = doublet, q = quartet

Table II

Carbon-13 Chemical Shifts of 2-Methyl-3propyl-4-quinazolone (a)

Assignments	Multiplicity	Chemical Shift
C-4	s	161.0
C-2	s	154.6
C-10	s	147.0
C-7	d	134.0
C-5 (b)	d	126.5
C-6, C-8 (b)	d	125.9
C-9	s	120.0
C-12	t	45.3
C-11 (c)	q	22.7
C-13 (c)	-	21.3
C-14	q	11.2

(a) See footnote in Table 1. (b) (c) May be interchanged.

Methaqualone (**4**).

The ^{13}C nmr spectrum of **4** gave fifteen signals for the sixteen carbons relative to the internal reference tetramethylsilane (Table IV and Figure 4). The two signals which are located at higher field at 23.4 and 16.7 ppm chemical shift represent the C-11 and C-12, respectively, on the basis of their multiplicity in SFORD spectrum and comparing with the chemical shift of C-11 in **1**, **2**, and **3**. The four singlets at 160.7, 154.2, 147.2 and 120.3 ppm chemical shift are assigned to the carbon resonances of C-4, C-2, C-10 and C-9, respectively, on the basis of same arguments which were made for assigning the various carbon resonances of **2**. These assignments are further supported by comparing the chemical shifts of corresponding carbons in **2** and **3**. The C-1′ and C-2′ are attached to amidic nitrogen and methyl group, respectively, which are known to produce deshielding effect at their ipso carbon (3). On this basis and comparing the corresponding carbon chemical shift of **1** to **3** and **11** (2), the signal at 136.8, 135.0, and

Table III

Carbon-13 Chemical Shifts of 2-Methyl-3-phenyl-4-quinazolone (a)

Assignments	Multiplicity	Chemical Shift
C-4	s	161.1
C-2	s	154.1
C-10	s	147.3
C-1′	s	137.8
C-7	d	134.4
C-2′ (b)	-	129.5
C-4′	-	128.8
C-3′ (b)	-	128.3
C-5 (c)	-	126.6
C-6, C-8 (c)	-	126.2
C-9	s	120.4
C-11	q	23.9

(a) See footnote in Table 1. (b) (c) May be interchanged.

Table IV

Carbon-13 Chemical Shifts of Methaqualone (a)

Assignments	Multiplicity	Chemical Shift
C-4	s	160.7
C-2	s	154.2
C-10	s	147.5
C-1′ (b)	-	136.8
C-2′ (b)	-	135.0
C-7 (b)	-	134.6
C-3′ (c)	-	131.0
C-6′ (c)	-	129.3
C-4′ (c)	-	128.3
C-5′ (c)	-	127.3
C-5 (d)	-	126.8
C-6, C-8 (d)	-	126.4
C-9	s	120.3
C-11	q	23.4
C-12	q	16.7

(a) See footnote on Table I. (b) (c) (d) May be interchanged.

134.6 ppm are attributed to C-1′, C-2′ and C-7, respectively, which however, could be interchanged. By comparing the signal intensities and the assignments of **2** and **3**, the signal at 126.8 ppm is represented by C-5 and the signal at 126.4 ppm by C-6 and C-8, which could be interchenged. The signals at 131.0, 129.3, 128,3 and 127,3 ppm are assigned to the carbon resonance of C-3′, C-6′, C-4′ and C-5′, respectively, by comparison with the ^{13}C nmr spectra of **3**, **11** (2) and **12** (2). These assignments may be interchanged.

EXPERIMENTAL

The ^{13}C nmr spectra were recorded on a JOEL FX-60 multinuclear spectrometer equipped with a Fourier transform system. The synthesis of **1**, **2**, **3** and **4** was carried out in our laboratory by methods reported earlier (4). The samples were run at 32° in 10 mm tubes, using DMSO-d_6 as an internal lock and tetramethylsilane as a reference. The concentrations of **1**, **2**, **3** and **4** were 20% (w/v). The conditions for measurements were as follows: pulse width 18 μ sec, repetition time 1.5 sec, spectral width 400 HZ, and data points 4 K. All chemical shifts are expressed in ppm downfield.

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