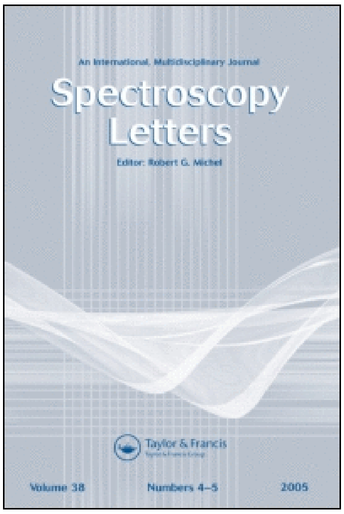

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

N.M.R. Spectral Studies of Some Quinolone Derivatives. Part III.[1] Carbon-13 Magnetic Resonance Spectral Studies of 2- and 4-Quinolone Derivatives

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To cite this Article Claret, Paul A. and Osborne, Alan G.(1976) 'N.M.R. Spectral Studies of Some Quinolone Derivatives. Part III.[1] Carbon-13 Magnetic Resonance Spectral Studies of 2- and 4-Quinolone Derivatives', Spectroscopy Letters, 9: 3, 167 — 175

To link to this Article: DOI: 10.1080/00387017608067425

URL: http://dx.doi.org/10.1080/00387017608067425

SPECTROSCOPY LETTERS, 9(3), 167-175 (1976)

N.M.R. SPECTRAL STUDIES OF SOME QUINOLONE DERIVATIVES. Part III.[1] CARBON-13 MAGNETIC RESONANCE SPECTRAL STUDIES OF 2- AND 4-QUINOLONE DERIVATIVES

KEY WORDS : CMR, chemical shifts, quinolone, shielding effects

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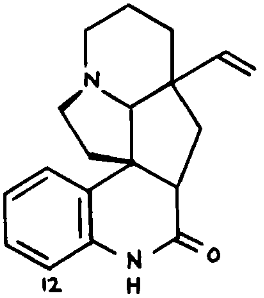
Abstract : The ^{13}C n.m.r. spectra of a series of 2- and 4-quinolone derivatives are presented and discussed. A characteristic high field signal for C-8 was observed which should prove useful for the identification of substituted quinolones.

Recently Carbon-13 magnetic resonance spectral studies of pyridone derivatives has attracted some interest.[2-5] However, as far as we are aware no similar studies have yet been reported for the quinolone series, we now wish to present some initial studies on these compounds. Recently, a report of the ^{13}C n.m.r. spectra of some condensed quinolone alkaloids, including meloscine (I), has appeared.[6]



(I)

Due to their limited solubility the solvent previously employed for the measurement of the ^{1}H n.m.r. spectra of quinolone derivatives was not suitable for the ^{13}C studies; it was therefore found necessary to employ a solvent mixture comprising 9:1 DMSO-d_6 : $CDCl_3$ for the studies. This solvent mixture was suitable for both the 2- and 4- quinolone series. For proton decoupled ^{13}C n.m.r. spectra about 2000 scans were necessary for the most soluble compounds and about 15000 scans for the majority of samples. However, the least soluble derivative (4,6,8-trimethyl-2-quinolone) required about 60000 scans. Low solubility prevented the use of off-resonance spectra except in a few specific cases. The results obtained are shown in Tables 1 and 2 and also in Figure 1 where a comparison of the chemical shifts for pyridine, pyridone, quinoline and quinolone is presented.

Assignments of the resonances were made by comparison with the respective pyridine, pyridone and quinoline shieldings where appropriate, and also by selective methyl substitution with the use of substituent chemical shifts. In this manner all of the signals for 2-quinolone could be assigned, except that for C-3 which was accordingly assigned by default. A limited number of compounds from the 4-quinolone series have also been examined and some preliminary results for these compounds are included.

2-Quinolones

The signal for the carbonyl group appeared at 162.0δ and showed little variation with changes of substitution. We have recently noted[9] that the ^{1}H chemical shift of the N<u>H</u> proton in 2-quinolones is effected by substitution at the 8-position due to inhibition of hydrogen bonding. Subsequently it was proposed[1] that the dominant factor which appeared to contribute to to the observed chemical shift of the N<u>H</u> proton was the degree of π-hydrogen bonding present. Since this type of bonding would not be expected to effect the ^{13}C chemical shift of the carbonyl group to any significant extent, the

Table 1

^{13}C n.m.r. spectra of 2- and 4- quinolone derivatives. (ring carbons)

substituted quinolone	Chemical shift (δ, p.p.m. from T.M.S.)								
2-Q (a)	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
nil	162.0	121.7*	140.1	127.8	121.9*	130.2	115.2	139.0	119.1
nil (b)	164.8	121.5	141.0	127.7	122.6	130.6	116.3	138.7	120.0
4-Me	161.6	120.9	147.7	124.5	121.5	130.1	115.4	138.7	119.6
4,6-Me_2	161.5	120.8	147.4	124.1	130.4	131.3	115.4	136.6	119.5
4,7-Me_2	161.9	119.8	147.7	124.4	123.0	140.2	115.2	138.8	117.6
4,8-Me_2	161.8	120.6	148.1	122.5	121.2	131.4	123.5	137.0	119.7
4,5,7-Me_3	161.0	121.6	149.4	135.9	127.2	140.5	114.4	139.0	116.9
4,6,7-Me_3	161.6	119.7	147.3	124.5	129.8	139.3	115.8	136.9	117.7
4,6,8-Me_3	161.7	120.6	147.9	122.1	130.1	132.7	123.4	135.0	117.6
4-Q (a)									
nil	139.5	108.8	177.2	-	-	-	118.4	140.1	125.9
2-Me	149.5	108.4	176.8	-	-	-	117.7	140.2	124.6
2,8-Me_2	149.9	108.7	177.0	-	-	-	125.8	138.8	124.8

(a) - Q : Quinolone.

(b) - determined in $CDCl_3$ only.

* - assignments may be reversed.

near constant nature of this parameter would also appear to lend support to our proposal.[1] The chemical shift of the carbonyl group was very similar to that observed for 2-pyridone.[3]

Table 2

^{13}C n.m.r. spectra of 2- and 4- quinolone derivatives. (methyl carbons)

Substituted quinolone	Chemical shift (δ, p.p.m. from T.M.S.)[a]		
2-Quinolones			
4-Me	18.4 (4)		
4,6-Me_2	18.5 (4)	20.6 (6)	
4,7-Me_2	18.4 (4)	21.2 (7)	
4,8-Me_2	17.3 (8)	18.7 (4)	
4,5,7-Me_3	20.7	24.2	24.9
4,6,7-Me_3	18.4 (4)	19.0	19.6
4,6,8-Me_3	17.2 (8)	18.8 (4)	20.4 (6)
4-Quinolones			
2-Me	19.5 (2)		
2,8-Me_2	17.5 (8)	19.8 (2)	

(a) - assignments of methyl groups shown in parenthesis.

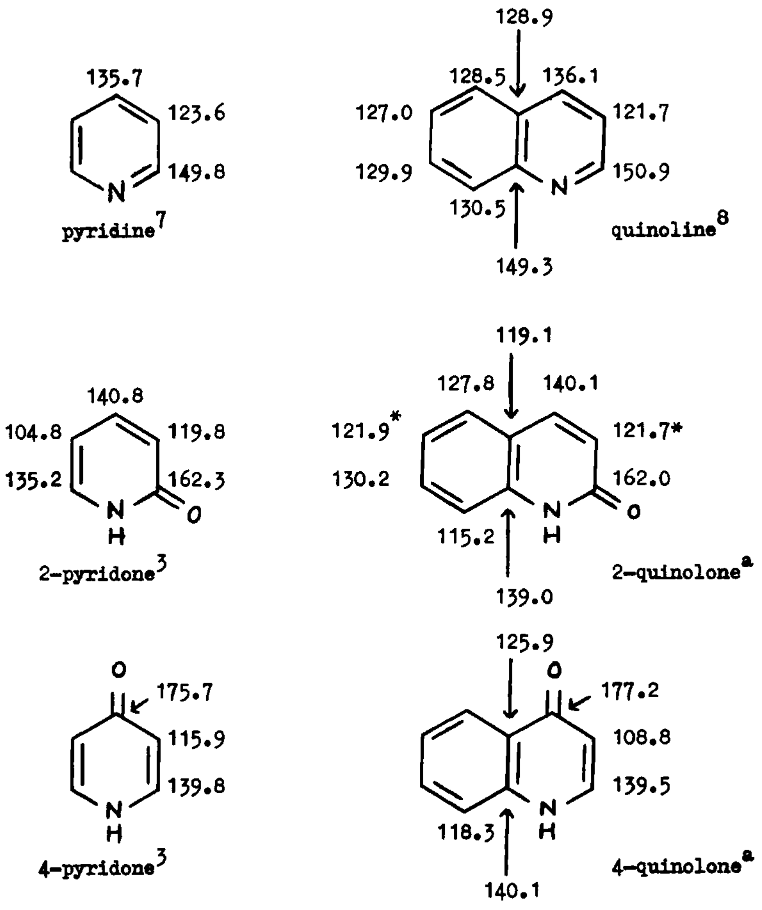
The signals for C-3 and C-4 appeared at 121.7(121.9) and 140.1δ respectively and were also similar to those observed for C-3 and C-4 in 2-pyridone.[3]

The signal for C-5 appeared at 127.8δ in 2-quinolone and at 124.5δ in the 4-methyl- derivative, hence a pronounced *peri* shielding occurred. The signal was also further shielded when additional *para* substitution was present in accordance with similar effects found in methylbenzene derivatives.[10]

Figure 1

^{13}C Chemical shifts for pyridine and quinoline derivatives

(δ, p.p.m. from T.M.S.)



(a) - present work.

* - assignments may be reversed.

The signals for C-6 and C-7 appeared at 121.9(121.7) and 130.2δ respectively, that for C-6 being more shielded than its comparative position

(127.0δ) in quinoline,[8] an upfield shift similarly occurred in the aromatic model compound, acetanilide, for the para carbon.[11]

The signal for C-8 appeared at 115.2δ and exhibited a 15.3 p.p.m. upfield shift from its position in quinoline. Substitution of a methyl group at position 8 caused a characteristic deshielding effect, in accordance with the effect found in methylbenzene derivatives,[10] which confirmed the assignment. Similar upfield shifts to that observed for C-8 in 2-quinolone have also been reported for the condensed quinolone alkaloids, such as C-12 in meloscine,[6] and also for the ortho carbons in the aromatic model compound, acetanilide.[11] This characteristic high field signal should prove to be of use for the identification of 8-substituted 2-quinolones by ^{13}C n.m.r.

The signal for C-9 appeared at 139.0δ, an upfield shift of 10.3 p.p.m. compared to its position in quinoline. The chemical shift of C-9 may be compared with that for C-6 in 2-pyridone, since both carbons are meta to the carbonyl group and are seen to be shielded to about the same extent.

The other bridgehead carbon, C-10, appeared at 119.1δ, an upfield shift of 9.8 p.p.m. compared to its value in quinoline. The chemical shift of C-10 may likewise be compared with that for C-5 in 2-pyridone since both are para to the carbonyl group, each experiences a pronounced shielding effect of the carbonyl group, but the quinolone carbon is shielded to a lesser extent, possibly since it is quaternary.

The respective assignments of the bridgehead carbons were confirmed by assessment of shielding effects, particularly those due to para methyl groups.[12] Thus C-9 experienced such an upfield shift when a 6-methyl group was present whilst C-10 experienced a similar shift in the presence of a 7-methyl group.

4-Quinolones

We have also undertaken some preliminary studies on selected 4-quinolone derivatives.

The carbonyl group appeared at 177.2δ, similar to the shift observed for the carbonyl group in 4-pyridone. Like 2-quinolone the chemical shift of the carbonyl group showed little variation upon introduction of substitutents.

The signal for C-2 appeared at 139.5δ, a similar shift to that observed with 4-pyridone.[3]

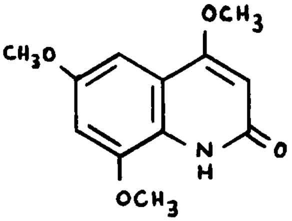
The signal for C-3 appeared at 108.8δ, the assignment being confirmed by a specific proton decoupling experiment, likewise the signal for C-3 in 4-pyridone also appeared at high field (115.9δ).[3]

The signal for C-8 appeared upfield (118.3δ), the shift being similar to that observed for 2-quinolone, again the identification of 8-substituted 4-quinolones may readily be achieved by ^{13}C n.m.r.

The signal for C-9 appeared at 140.1δ, an upfield shift of 9.2 p.p.m. compared to its position in quinoline.[8] The chemical shift may be compared with that for C-2 in 4-pyridone, since both carbons are <u>meta</u> to the carbonyl group and are seen to be shielded to about the same extent.

The other bridgehead carbon, C-10, appeared at 125.9δ, and exhibited a comparatively small shift of 3.0 p.p.m. compared to its position in quinoline.[7] Introduction of the carbonyl group in 4-pyridone resulted in shielding of both C-3 carbons by 7.7 p.p.m., a total shielding effect of 15.4 p.p.m. In 4-quinolone, C-3 is shielded by 12.9 p.p.m. and C-10 by 3.0 p.p.m., a total shielding effect of 15.9 p.p.m. on the <u>ortho</u> carbons. Although the total effect is similar the distribution of the effect is different, this may be due to the quaternary nature of C-10 or there may be some other mechanism operative since it should be noted that the C-3 carbons in 2-pyridone and in 2-quinolone, although <u>ortho</u> to a carbonyl group, are only shielded to a small extent.

The ^{13}C n.m.r. spectra of 2- and 4- quinolone derivatives are similar to those previously obtained for the corresponding pyridone derivatives, except that a characteristic high field signal is observed for C-8. This latter effect should prove useful for the identification of 8-substituted quinolone derivatives, such as halfordamine (II)[12] in the alkaloid field.



(II)

Spectra were determined, for samples dissolved in a mixture of 9:1 DMSO-d_6 : $CDCl_3$ in the presence of T.M.S., on a Bruker HX90E spectrometer operated in the Fourier Transform mode at 22.63 MHz, with broad band proton decoupling. Spectra were determined by the Physico Chemical Measurements Unit, Harwell to whom we are indebted.

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Received: 12-15-75
Accepted: 12-19-75