^{13}C NMR Study of 1-Substituted 2-Thioxo-4(1*H*,3*H*)-quinazolinones Employing the 1D and 2D Methods

[a]J. IMRICH, [a]T. BUŠOVÁ, [a]D. KOŠČIK, and [b]T. LIPTAJ

[a]*Department of Organic Chemistry, Faculty of Natural Sciences, P. J. Šafárik University, CS-041 67 Košice*

[b]*Department of Physical Chemistry, Faculty of Chemical Technology, Slovak Technical University, CS-812 37 Bratislava*

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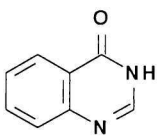
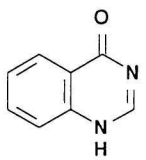
The ^{13}C and ^{1}H NMR spectra of the title compounds and their 2-oxo analogue were studied by one- and two-dimensional methods COSY and INEPT. The chemical shifts were unambiguously ascribed to compounds under investigation and the coupling constants J(H,C) of the 4-quinazolinone ring system were determined by the 2D-J selective INEPT. Relationship between localization of the multiple bond in the diazine ring and the ^{13}C chemical shift values is discussed. The obtained values allowed us to deduce the SCS increments of 2-thioxo-4(1*H*,3*H*)-quinazolinon-1-yl grouping on the aromatic ring.

The ^{13}C NMR spectroscopy has successfully been used in the last decade for structure elucidation of compounds possessing the 4-quinazolinone ring system, as *e.g.* alkaloids [1, 2] and other biologically active substances [3]. The ^{13}C spectra of 4(3*H*)-quinazolinones *I* were best examined; the known sedative 2-methyl-3-(2-methylphenyl)-4(3*H*)-quinazolinone (Methaqualone) also belongs to this group [2—7]. Less attention has been paid to 4(1*H*)-quinazolinones *II* [1, 2].

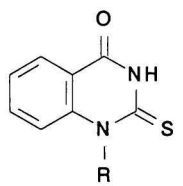


I

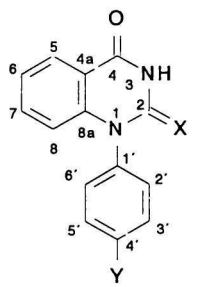


II

This paper presents the utilization of ^{13}C NMR spectroscopy for structure confirmation of 1-substituted 2-thioxo-4(1*H*,3*H*)-quinazolinones and 2,4(1*H*,3*H*)-quinazolinedione *IIIa*—*IIIi*, having, in contrast to compounds *I* and *II*, no endocyclic multiple bond in the diazine ring of the quinazolinone.



IIIa, IIIb
R = C_2H_5 (*a*), $C_6H_5CH_2$ (*b*)



IIIc—IIIi
X = S, Y = CH_3O (*c*), CH_3 (*d*), H (*e*), Cl (*f*), Br (*g*), NO_2 (*h*)
X = O, Y = CH_3O (*i*)

^{13}C NMR spectra of quinazolinones of this type were studied in more detail only with 3-substituted 2,4(1*H*,3*H*)-quinazolinediones [8]. The controversial assignment of some carbon atoms [1, 8] prompted us to investigate the resolution of chemical shifts ^{13}C, ^{1}H and coupling constants J(H,C), J(H,H) by the 2D-COSY correlation and the 2D-J selective INEPT in addition to the noise-decoupled and "off-resonance" spectra.

Table 1. ^{13}C NMR Chemical Shifts (δ) for Derivatives *IIIa*—*IIIi*

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-4a	C-8a
IIIa	174.7	157.5	127.0	123.8	135.1	115.5	117.7	139.9
IIIb	176.6	158.0	127.0	124.4	135.2	116.5	117.9	140.5
IIIc	176.4	157.9	126.5	123.6	134.4	116.3	116.9	142.8
IIId	176.1	157.9	126.5	123.8	134.4	116.2	116.9	142.5
IIIe	176.0	158.0	126.6	123.7	134.5	116.1	116.9	142.5
IIIf	176.6	158.7	127.3	124.3	134.9	116.5	117.5	142.7
IIIg	176.2	158.7	127.0	124.3	135.1	116.6	117.2	142.6
IIIh	176.0	158.7	127.1	124.5	135.1	116.4	117.3	142.3
IIIi	149.7	161.7	126.9	122.2	134.4	115.0	115.1	142.7

Chemical shift values and coupling constants of compounds under study are listed in Tables 1—3, respectively and in Experimental. The ^{13}C NMR spectra of compounds *IIIa—IIIh* contain a pair of signals with a high chemical shift value $\delta \approx 176$ and $\delta \approx 157$ corresponding to the thiocarbonyl C-2 and carbonyl C-4 carbons, respectively. Resolution of carbons C-2 and C-4 follows from the proton-coupled ^{13}C spectra of *IIIc* and *IIIi*, in which the C-2 signal contains only J(H,C) coupling constant with the N-3 proton (*IIIc*), whereas the C-4 signal is a doublet with J(H-5,C-4) = 4.2 (4.1) Hz. The presence of C=S group signals at $\delta \approx 176$ provides an unequivocal proof for the thioxoquinazolinone and not the isomeric 2-imino-1,3-benzothiazine structure, for which the C-2 chemical shift value has to be by $\delta \approx 10$ lower [9]. On the other hand, the chemical shift value of C-2 for 2-oxo derivative *IIIi* δ = 149.7 is consistent with that reported by *Petridou-Fischer* [8] for 3-substituted 2,4(1*H*,3*H*)-quinazolinediones (δ = 149.8—150.2). Relationship between the thioxo and oxo analogues was expressed by *Kalinowski* [10] by the equation

$$\delta_{C=S} = 1.45\ \delta_{C=O} - 46.5 \qquad (1)$$

according to which the $\delta_{C=S}$ value 170.6 would correspond to $\delta_{C=O}$ value 149.7; as seen, this represents a one-order agreement with the C-2 chemical shifts of compounds *IIIa—IIIh*.

As known [2], the C-4 chemical shift value for 4-quinazolinones indicates localization of the double bond in the diazine ring for 3*H* tautomer *I* and 1*H* one *II* at ≈ 161 and ≈ 168, respectively. Derivatives *IIIa—IIIh* (Table 1) disclose lower chemical shift values for C-4 (δ = 157.5—158.7) when compared with compounds *I* and *II*. Replacement of 2-C=S group by 2-C=O one (*IIIi*) resulted in the increase of C-4 chemical shift value to δ = 161.7, this being in a very good accordance with the appropriate C-4 value of the unsubstituted 2,4(1*H*,3*H*)-quinazolinedione (δ = 162.6) and its 3-substituted derivatives (δ = 161.5—162.2) [8]. As follows, the sub-

Table 2. ^{13}C NMR Chemical Shifts (δ) of the Substituent in Position 1 for Compounds *IIIa—IIIi* and Calculated SCS Increments Z for 2-Thioxo-4(1*H*,3*H*)-quinazolinon-1-yl and 2,4(1*H*,3*H*)-Quinazolinedion-1-yl on the Aromatic Ring

Compound	^{13}C Chemical shifts						SCS increments			
	C-1′	C-2′ C-6′	C-3′ C-5′	C-4′	CH_2	CH_3	Z_I	Z_o	Z_m	Z_p
IIIa					43.1	11.0				
IIIb	135.1	126.0	128.5	127.2	51.4					
IIIc	131.9	129.8	114.8	159.0		55.0	11.5	0.4	1.0	0.3
IIId	136.7	128.2	129.9	138.0		20.1	11.3	− 0.3	0.8	0.2
IIIe	139.3	128.6[a]	129.5[a]	128.4			10.8	−	−	− 0.1
IIIf	138.2	130.3[a]	130.9[a]	134.3			11.7	−	−	− 0.6
IIIg	138.9	131.4	133.0	122.1			11.4	0.7	1.2	− 1.0
IIIh	145.2	131.1	125.4	147.4			10.7	1.8	2.2	− 0.7
IIIi	128.5	130.0	115.0	159.2		55.2	8.1	0.6	1.2	0.5

a) The values can be interchanged.

Table 3. Coupling Constants ^nJ(H,C)/Hz of the Derivatives *IIIc* and *IIIi*

Locant	*IIIc*[a]				*IIIi*			
	H-5	H-6	H-7	H-8	H-5	H-6	H-7	H-8
C-2	0	0	0	0	0	0	0	0
C-4	4.2	*b*	*b*	*b*	4.1	*b*	*b*	*b*
C-4a	*b*	8.0	*b*	4.8	4.6	7.9	1.3	5.2
C-5	164.9	*b*	8.1	*b*	164.7	1.8	7.9	*b*
C-6	*b*	167.1	*b*	7.6	*b*	164.5	2.2	7.8
C-7	8.7	*b*	165.7	*b*	8.6	2.9	161.1	*b*
C-8	*b*	7.6	*b*	165.3	*c*	7.3	*c*	*c*
C-8a	7.7	*b*	9.5	*b*	7.5	1.5	9.4	1.5
	H-2′	H-3′	H-5′	H-6′	H-2′	H-3′	H-5′	H-6′
C-1′	2.9	9.5	9.5	2.9	2.7	9.3	9.3	2.7
C-2′	163.9	*b*	*b*	6.1	163.4	*b*	*b*	6.2
C-3′	*b*	162.6	5.3	*b*	*b*	162.4	5.3	*b*
C-4′	*b*	*b*	*b*	*b*	9.3	2.8	2.8	9.3
C-5′	*b*	5.3	162.6	*b*	*b*	5.3	162.4	*b*
C-6′	6.1	*b*	*b*	163.9	6.2	*b*	*b*	163.4

a) ^2J(H-3,C-2) = 1.9 Hz; *b*) J(H,C) not estimated; *c*) The C-8 signals are overlapped by C-3′ and C-5′ signals.

stitution effects from positions 1 and 3 of derivatives *III* are almost identical and negligibly low. It could be, therefore, concluded that the exocyclic 2-C=S group of derivatives *IIIa—IIIh* lowers the electron density at C-4 (mediated by the lone electron pair of N-3) in a lower extent than does the endocyclic N-1=C-2 bond of 4(3*H*)-quinazolinones *I*.

The H-5 to H-8 chemical shifts were assigned unequivocally by the 2D-COSY experiment. Then, by means of the selective 1D-INEPT [11], it was possible to attribute undoubtedly the resonances of carbons C-5 to C-8 of the quinazoline ring system to *IIIi* and *IIIc* (Table 1). Chemical shifts of these carbons are virtually independent either of the substituent in position 1, or of the replacement of 2-C=S group by the 2-C=O one; they well correspond with the values for C-5 to C-8 of 3-substituted 2,4(1*H*,3*H*)-quinazolinediones [8]. Comparison of chemical shifts of carbon C-8 of *IIIa—IIIi* with that of 4(3*H*)-quinazolinones *I* shows that the former resonates at lower δ values ($\approx$ 116) than the latter ($\approx$ 124—127) [2]. This finding evidences the existence of N-1 nitrogen of an amino type with a great shielding effect on C-8 [12] in derivatives *IIIa—IIIi* in contrast to an imino type N-1 with the lower shielding effect on C-8 [13] in derivatives *I*.

The chemical shift values of the considerably polarized C-4a=C-8a bond of *IIIa—IIIh* correspond better with those of 4(1*H*)-quinazolinones *II* ($\delta \approx 120$ for C-4a, $\delta \approx 141$ for C-8a) than of 4(3*H*)-quinazolinones *I* ($\delta \approx 120$ for C-4a, $\delta \approx 149$ for C-8a) [2]. This can probably be due to an analogous interaction of the amine nitrogen N-1 with the aromatic system of 4-quinazolinone so with derivatives *II* [2] as with our compounds *IIIa—IIIi*. The C-8a chemical shift value is, therefore, a further localization indicator of the double C=N bond in the 4-quinazolinone ring. Table 3 presents the ^nJ(H,C) coupling constants of derivatives *IIIi* and *IIIc* as obtained with the 300 MHz spectrometer by 2D-J selective INEPT experiment [14]. The C-4a and C-8a carbon signals are split by spin-spin interactions with four protons H-5 to H-8 confirming thus regularity of their identification. The experimental chemical shift values for C-2 and C-8a, which are in line with those reported in [8], let us conclude that assignments of C-2 (δ = 140.4) and C-8a (δ = 150.7) chemical shifts for 2,4(1*H*,3*H*)-quinazolinedione and its 3-(2-phenylethyl) derivative given in paper [1] have to be revised and these assignments should be done in an opposite order.

Signals of C-5 to C-8 carbons are split always by spin-spin interactions with three protons of the quinazolinone ring. The experimental section also presents the *J*(H,H) coupling constants between hydrogens H-5 to H-8 for derivatives *IIIi* and *IIIc*. These values are in a good accordance with those (*J*(H,C) [7] and *J*(H,H) [15, 16]) for quinazolines and extend them by the hitherto not published *J*(H,C) long-range constants. The ^{13}C SCS (substituent chemical shift) increments *Z* of the 2-thioxo-4(1*H*,3*H*)-quinazolinon-1-yl substituent at the benzene ring (Table 2) were calculated from chemical shifts of carbons of the aromatic ring in position 1 of derivatives *IIIc—IIIh*. The average values of the calculated increments *Z* (± the standard deviation) are as follows: Z_{ipso} = 11.2 ± 0.4, Z_{ortho} = 0.7 ± 0.9, Z_{meta} = 1.3 ± 0.6, Z_{para} = − 0.3 ± 0.5. The ^{13}C SCS increments for 2,4(1*H*,3*H*)-quinazolinedion-1-yl grouping presented in Table 2 for derivative *IIIi* have an approximative value only (with regard to one compound considered), but still they are close to values for 2,4(1*H*,3*H*)-quinazolinedion-3-yl (Z_i = 7.2, Z_o = 0.5, Z_m = 0.2, Z_p = − 0.5 [8].

EXPERIMENTAL

Synthesis of compounds *III* was published elsewhere [17]. The ^{13}C and ^{1}H NMR spectra of hexadeuterodimethyl sulfoxide solutions were measured with a Tesla BS 567 (25 MHz for ^{13}C) and Varian VXR-300 (75 MHz for ^{13}C; 300 MHz for ^{1}H) spectrometers at room temperature (*IIIb*, *IIIc*, *IIIf—IIIi*) and 90 °C (*IIIa*, *IIId*, *IIIe*). Chemical shift values in the ^{1}H and ^{13}C NMR spectra were determined from the DMSO-d_6 signal (δ = 39.4 for ^{13}C and δ = 2.50 for ^{1}H) against that of TMS. Measurement conditions (25 MHz): Spectral width 7600 Hz, 30° pulse, relaxation interval 3 s, 8 K; (75 MHz): 18 000 Hz, 30°, 3 s, 32 K; (300 MHz): 6000 Hz, 45°, 3 s, 16 K. Selective pulses employed in the selective 1D-INEPT and selective 2D-J INEPT experiments were realized by means of a soft rectangular pulse with a $\gamma B_2/2\pi$ = 25 Hz amplitude.

1-(4-Methoxyphenyl)-2-thioxo-4(1*H*,3*H*)-quinazolinone (*IIIc*)

^{1}H NMR spectrum, δ: 8.05 (dd, 1H, H-5, $J_{5,6}$ = 7.8 Hz, $J_{5,7}$ = 1.5 Hz), 7.35 (dd, 1H, H-6, $J_{6,7}$ = 7.5 Hz), 7.61 (m, 1H, H-7, $J_{7,8}$ = 8.6 Hz), 6.45 (d, 1H, H-8), 7.13 (m, 2H, H-2′, H-6′), 7.27 (m, 2H, H-3′, H-5′), 3.85 (s, 3H, CH_3O), 12.79 (s, 1H, NH).

1-(4-Methoxyphenyl)-2,4(1*H*,3*H*)-quinazolinedione (*IIIi*)

^{1}H NMR spectrum, δ: 8.04 (dd, 1H, H-5, $J_{5,6}$ = 8.0 Hz, $J_{5,7}$ = 1.7 Hz), 7.22 (dd, 1H, H-6, $J_{6,7}$ = 7.1 Hz), 7.53 (m, 1H, H-7, $J_{7,8}$ = 8.4 Hz), 6.51 (d, 1H, H-8), 7.13 (m, 2H, H-2′, H-6′), 7.31 (m, 2H, H-3′, H-5′), 3.85 (s, 3H, CH_3O).

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