Monatshefte für Chemie 126, 789–794 (1995)

Monatshefte für Chemie
Chemical Monthly

NMR Studies of 4(3*H*)-Quinazolinones and 4(3*H*)-Quinazolinethiones

M. Chakrabarty[1,*], A. Batabyal[1], M. S. Morales-Ríos[2], and P. Joseph-Nathan[2,*]

[1] Chemistry Department, Bose Institute, Calcutta 700 009, India
[2] Departmento de Química, Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, 07000 México City, México

Summary. Unambiguous ^{1}H and ^{13}C NMR assignments for 4(3*H*)-quinazolinones **1–6** and their corresponding 4-thiones **7–12** have been made. This resulted in the revision of the previous assignments for the two benzenoid carbons (C-5 and C-8) of quinazolinones **1,2,4,** and **5**. Thionation of the nucleophilic amides **1–6** has been found to cause a distinct change in the ^{13}C chemical shift of particularly C-4, but also of those of C-4a, C-5, and C-8a. One-bond and several long range heteronuclear coupling constants for the compounds have also been measured.

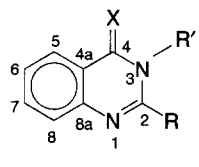
Keywords. 4(3*H*)-Quinazolinones; 4(3*H*)-Quinazolinethiones; ^{1}H NMR; ^{13}C NMR.

Kernresonanzspektroskopie von 4(3*H*)-Chinazolinonen und 4(3*H*)-Chinazolinthionen

Zusammenfassung. Die ^{1}H- und ^{13}C-NMR-Spektren der 4(3*H*)-Chinazolinone **1–6** und ihrer entsprechenden 4-Thione **7–12** wurden zugeordnet. Dabei zeigte sich, daß eine frühere Zuordnung der beiden benzoiden Kohlenstoffe (C-5 und C-8) der Chinazolinone **1,2,4** und **5** falsch war. Ersatz des Sauerstoffs durch Schwefel in den nukleophilen Amiden **1–6** führt insbesondere für C-4, aber auch für C-4a, C-5 und C-8a zu einer deutlichen Änderung der chemischen Verschiebung. Heteronukleare Kopplungskonstanten über eine und über mehrere Bindungen wurden bestimmt.

Introduction

Substituted and annulated 4(3*H*)-quinazolinones constitute an important class of bioactive natural products of plant, microbial, and fungal origin [1–7]. Several synthetic analogues also display a wide range of biological activities [8–10]. However, despite their comprehensive chemistry and biology, structural characterization of this type of compounds by NMR spectroscopy is still scarce in the literature [11–13]. Recently, 2-(α-hydroxyethyl)-4(3*H*)-quinazolinone (chrysogine) [14] has been synthesized [15] and examined by two-dimensional NMR spectroscopy [16]. A survey of the literature also reveals that for 4(3*H*)-quinazolinethiones neither ^{1}H nor ^{13}C NMR spectra have been fully interpreted until now [17]. Therefore we report here the total assignment of the proton and carbon resonances of a series of 4(3*H*)-quinazolinones **1–6** and their thione analogues **7–12**, deduced from 2D and selected 1D NMR techniques.



X = O	1	2	3	4	5	6
X = S	7	8	9	10	11	12
R	H	Me	Ph	CH_2Ph	H	H
R'	H	H	H	H	Me	Ph

Results and Discussion

The assignments of the well resolved ^1H NMR signals of quinazolinones **1–6** and their thione analogues **7–12** were derived from splitting patterns, single-frequency decoupling, and characteristic chemical shift values. The ^1H chemical shifts assignments are collected in Table 1. The data show consistently that the homocyclic proton signal with the lowest field shift in both series of compounds is a doublet with additional fine structure due to further *meta* and *para* couplings. This signal is assigned to H-5 on the basis of the proximity to the carbonyl or thione group. The assignment of H-5 led to the assignment of H-8 by default. In the same spectral region the signal for H-2 is found as a singlet. The signals for protons H-6 and H-7 show two *ortho* couplings. We have assigned the H-7 signal to the lower field one on the basis of proton decoupling experiments performed by irradiating H-5.

The change in functionality from a carbonyl to a thione group results in a deshielding effect at the H-5 resonance of *ca.* 0.5 ppm, reflecting the greater electron density of the sulfur atom. The remaining homocyclic chemical shift values in **7–12** are close to those of the corresponding carbonyl compounds. It is known that in

Table 1. ^1H NMR chemical shifts (ppm) in *DMSO*-d_6

Compound	H-2	H-5	H-6	H-7	H-8	R and R'
1	8.19	8.20	7.57	7.86	7.73	12.32 (NH)
2	-	8.12	7.48	7.79	7.61	12.23 (NH), 2.40 (Me)
3	-	8.19	7.54	7.84	7.76	12.47 (NH), 8.22 (*o*), 7.57 (*m*), 7.60 (*p*)
4	-	8.10	7.48	7.78	7.62	12.42 (NH), 7.40 (*o*), 7.34 (*m*), 7.26 (*p*), 3.96 (CH_2)
5	8.37	8.17	7.55	7.82	7.68	3.54 (Me)
6	8.37	8.21	7.60	7.89	7.75	7.59–7.53 (Ph)
7	8.19	8.58	7.63	7.91	7.74	13.85 (NH)
8	-	8.57	7.55	7.85	7.64	13.75 (NH), 2.50 (Me)
9	-	8.65	7.62	7.91	7.80	13.92 (NH), 8.19 (*o*), 7.58 (*m*). 7.61 (*p*)
10	-	8.60	7.56	7.85	7.69	14.01 (NH), 7.44 (*o*) 7.36 (*m*), 7.27 (*p*), 4.15 (CH_2)
11	8.69	8.66	7.61	7.87	7.72	3.91 (Me)
12	8.54	8.71	7.67	7.93	7.80	7.62–7.52 (Ph)

Average coupling constants (in Hz)

	J_{ortho}			J_{meta}		J_{para}
1–6	$H_5,H_6 = 7.9$	$H_6,H_7 = 7.1$	$H_7,H_8 = 8.2$	$H_5,H_7 = 1.6$	$H_{6,8} = 1.2$	$H_5,H_8 = 0.5$
7–12	$H_5,H_6 = 8.2$	$H_6,H_7 = 7.0$	$H_7,H_8 = 8.2$	$H_5,H_7 = 1.6$	$H_{6,8} = 1.3$	$H_5,H_8 = 0.5$

Table 2. ^{13}C NMR chemical shifts (ppm) *DMSO*-d_6

Compound	C2	C4	C4a	C5	C6	C7	C8	C8a	R and R′
1	145.4	160.8	122.7	125.9	126.7	134.2	127.2	148.8	
2	154.3	161.8	120.6	125.7	125.8	134.2	126.5	148.9	21.4 (Me)
3	152.3	162.2	121.0	125.8	126.5	134.4	127.4	148.7	132.8 (*i*), 127.7 (*o*), 128.5 (*m*), 131.3 (*p*)
4	155.9	161.8	120.6	126.6	126.1	134.3	126.8	148.8	136.5 (*i*), 128.8 (*o*), 128.4 (*m*), 126.7 (*p*), 40.7 (CH_2)
5	148.3	160.6	121.4	125.8	126.8	134.0	127.1	148.1	33.5 (Me)
6	147.1	159.9	121.9	126.4	127.4	134.6	127.3	147.7	137.6 (*i*), 129.2 (*o*), 127.5 (*m*), 128.7 (*p*)
7	143.7	185.7	128.8	129.2	128.3	135.3	128.1	144.2	
8	152.9	186.7	127.0	129.0	127.1	135.1	127.3	144.6	21.1 (Me)
9	151.4	187.8	127.6	129.3	127.9	135.3	128.1	144.2	132.1 (*i*), 128.4 (*o*), 128.4 (*m*), 131.4 (*p*)
10	154.6	187.1	127.3	129.1	127.5	135.2	127.7	144.6	136.4 (*i*), 128.9 (*o*), 128.5 (*m*), 126.8 (*p*), 40.1 (CH_2)
11	146.8	185.8	128.5	129.3	128.3	134.3	127.8	142.5	41.9 (Me)
12	145.9	187.3	129.0	130.0	128.8	135.0	128.1	142.4	142.1 (*i*), 129.5 (*o*), 127.8 (*m*), 129.1 (*p*)

benzo-fused heterocyclic rings the magnitude of the *ortho* coupling constants $^3J_{1_H,1_H}$ can be influenced by the hetero atom [18]. This influence is apparent in the quinazolinone compounds which show the following trend. $^3J_{6,7} < {}^3J_{5,6} < {}^3J_{7,8}$ (see Table 1). The observed value of $^3J_{7,8}$ which is greater than $^3J_{5,6}$ further supports the assignments.

The ^{13}C chemical shift values are given in Table 2. All ternary resonances were assigned from the corresponding proton resonances using a 2D ^1H-^{13}C HETCOR correlation experiment. This technique permitted the unequivocal assignment of the closely spaced C-5, C-6, and C-8 signals which appeared in the range of 125.6–127.4 ppm in the quinazolinone series and of 127.1–130.0 ppm in the thione series. The signal sequence in order of increasing chemical shifts in **1–5** is C-5 < C-6 < C-8. This analysis allows us to reverse the assignments for C-5 and C-8

Table 3. Heteronuclear coupling constants (Hz)

Compound	C2	C4	C4a	C5	C6	C7	C8	C-8a
1	^1J_d204.2	s[b]	-	^1J_d163.6	^1J_d162.8	^1J_d160.3	^1J_d163.6	-
			^3J_t6.4[a]	^3J_d 7.7	^3J_d 8.9	^3J_d 9.0	^3J_d 6.7	^3J_q8.1[a]
						^2J_d 3.2		
2	-	s[b]	-	^1J_d162.5	^1J_d162.5	^1J_d160.2	^1J_d163.0	-
	^2J_q 6.8		^3J_t6.4[a]	^3J_d 8.6	^3J_d 8.8	^3J_d 8.2	^3J_d 6.6	^3J_t6.5
						^2J_d 2.7		
3	s[b]	-	-	^1J_d163.6	^1J_d162.5	^1J_d160.2	^1J_d163.6	-
		^3J_d3.2	^3J_t6.5[a]	^3J_d 7.5	^3J_d 8.3	^3J_d 8.7	^3J_d 6.7	^3J_t7.6
						^2J_d 2.7		
4	-	s[b]	-	^1J_d163.3	^1J_d162.6	^1J_d160.4	^1J_d163.1	-
	^2J_t 7.2		^3J_t6.4[a]	^3J_d 7.9	^3J_d 8.1	^3J_d 9.1	^3J_d 7.0	^3J_t7.6
						^2J_d 2.7		
5	^1J_d206.2	s[b]	-	^1J_d163.7	^1J_d162.9	^1J_d159.9	^1J_d164.1	-
	$3J_q$ 3.8		^3J_t6.6[a]	^3J_d 7.6	^3J_d 8.3	^3J_d 8.8	^3J_d 7.2	$^3J_{dt}$9.6, 5.3
						^2J_d 2.8		
6	^1J_d208.7	-	-	^1J_d164.1	^1J_d163.4	^1J_d160.6	^1J_d163.6	-
		^3J_t4.3	$^3J_{dd}$8.3,5.3	^3J_d 7.8	^3J_d 7.9	^3J_d 8.5	^3J_d 7.1	$^3J_{dt}$9.0, 7.0
						^2J_d 3.2		
7	^1J_d207.7	-	-	^1J_d164.2	^1J_d163.8	^1J_d161.2	^1J_d165.0	-
		^3J_t4.8	$^3J_{dd}$8.1, 5.3	^3J_d 7.1	^3J_d 8.5	^3J_d 8.9	^2J_d 7.3	$^3J_{dt}$10.3, 6.6
						^2J_d 3.3		
8	-	-	-	^1J_d163.8	^1J_d162.9	^1J_d161.4	^1J_d164.6	-
	^2J_q 7.0	^3J_d4.6	^3J_t6.3[a]	^3J_d 7.4	^3J_d 8.1	^3J_d 8.7	^3J_d 7.4	^3J_t 7.7
						^2J_d 3.3		
9	-	s[b]	-	^1J_d163.6	^1J_d162.9	^1J_d161.5	^1J_d164.2	-
	^3J_t 3.7		$^3J_{dd}$7.8, 5.3	^3J_d 7.1	^3J_d 8.2	^3J_d 9.1	^3J_d 6.3	^3J_t 7.8
						^2J_d 2.3		
10	-	s[b]	c	^1J_d165.0	^1J_d162.9	^1J_d162.0	^1J_d163.8	-
	^2J_t 7.6			^3J_d 7.9	^3J_d 8.1	^3J_d 8.0	^3J_d 8.1	^3J_t 7.6
11	^1J_d211.2	-	-	^1J_d164.4	^1J_d165.0	^1J_d160.5	^1J_d164.5	-
	^3J_q 3.8	m	^3J_t6.9a	^3J_d 7.0	^3J_d 7.5	^3J_d 9.0	^3J_d 7.2	$^3J_{dt}$10.2, 6.2
12	^1J_d212.7	-	c	^1J_d166.4	^1J_d165.4	^1J_d161.1	^1J_d165.1	-
		^3J_t4.4		^3J_d 6.9	^3J_d 8.0	^3J_d 8.8	^3J_d 7.1	$^3J_{dt}$10.2, 7.2

s: singlet; d: doublet; t: triplet: q: quartet; m: multiplet; a: apparent multiplicity; b: broad; c: overlapping multiplet

in compounds **1, 2, 4** and **5** from those given in Ref. [11] and for **1** and **2** from those in Ref. [12], measured in *DMSO*-d_6 solutions.

The large value of the one-bond C–H coupling constant of the ternary carbon C-2 adjacent to N-1 and N-3 ($^1J_{C\text{-}2,H\text{-}2} \approx 204$–$213$ Hz, see Table 3) also allowed this carbon to be distinguished from those of the homocyclic ring ($^1J_{C_{Ar},H} \approx 160$–$166$ Hz) in both series of compounds. The quaternary carbons C-4, C-4a, and C-8a were assigned based on the standard chemical shifts and characteristic splitting caused by long-range carbon–proton coupling constants, ($^3J_{C,H}$), obtained from the ^{13}C gated-decoupling mode spectra (Table 3). On the basis of chemical shifts, the most deshielded signal was expected to be due to the amide carbonyl (C-4), and the observed coupling constants over three bonds with H-5 and H-2 confirmed this assignment. As expected, the ring fusion carbon C-8a, directly attached to the heteroatom, resonates at much lower field than C-4a [19]. Thus, whereas C-4a is coupled over three bonds with H-6 and H-8 and appears as a triplet or as a double doublet, the C-8a signal is split by ^3J couplings with H-2, H-5, and H-7 and appears as a double triplet except when H-2 was replaced by a methyl (**2** and **8**), phenyl (**3** and **9**), or benzyl group (**4** and **10**). In these cases, the signal for C-8a is a clear triplet. The remaining signal, due to C-2 in compounds **2–4** and **8–10**, is coupled over two or three bonds with the substituent at position 2. This completes the assignment of the ^{13}C NMR spectra.

In the thione series **7–12**, the main differences in the chemical shift values with respect to those of the corresponding quinazolinone compounds were found for C-4 and C-4a which show a strong deshielding effect of *ca.* 26 ppm for C-4 and *ca.* 6.5 ppm for C-4a. Influenced to a lesser extent, C-5 is shifted to lower field by *ca.* 3.5 ppm, whereas the chemical shift of C-8a decreases by *ca.* 4.5 ppm. These results are consistent with previous investigations on structurally related compounds [20].

Experimental

The 4(3*H*)-quinazolinones **1–6** were obtained by dehydrative cyclization of the appropriate anthranilamides which in turn were synthesized from isatoic anhydride [21]. The thione analogues **7–12** were prepared from the corresponding quinazolinones by refluxing with phosphorous pentasulfide in pyridine [22].

All ^1H and ^{13}C NMR spectra were measured in 5 mm tubes with solutions prepared in 0.7 ml of *DMSO*-d_6. All chemical shifts given are relative to *TMS*. Spectra were recorded on a Varian XL 300 GS spectrometer. Routine proton spectra (300 MHz) were recorded with a pulse angle of 45° and an acquisition time of 3.75 s. The data size was 32 k at a spectral width of 4 kHz. Routine ^{13}C NMR spectra (75 MHz) were recorded with broad-band decoupling, a pulse angle of 40°, and an acquisition time of 0.91 s. The data size was 32 k at a spectral width of 16.5 kHz, a relaxation delay: 2 s.

A typical HETCOR spectrum was acquired with a spectral width of 2350 Hz at 75 MHz in the f_2 domain and 435 Hz in the f_1 domain. The spectra were acquired with 1 k data points in f_2 and 128 increments in f_1 (128 transients each). Before processing, zero filling in f_1 was applied (512 data points). The delay between pulses was 1.0 s. The values of polarization transfer and the refocussing delay were 4 and 2 ms, respectively.

Acknowledgements

Two of the authors (*M.C.* and *A.B.*) express their sincere thanks to the *C.S.I.R., Govt. of India*, for the award of a Research Grant (No. 2/293/89-EMR-II); one of us (*A.B.*) expresses her gratitude to the

authorities of *Bose Institute* for providing her with a Senior Institute Fellowship during the course of this work. Partial financial support from *CoNaCyT-México* is acknowledged.

References

[1] Pachter I. J., Raffauf R. F., Ullyot G. E., Ribeiro O. (1960) J. Am. Chem. Soc. **82**: 5187
[2] O'Donovan D. G., Horan H. (1970) J. Chem. Soc. (C): 2466
[3] Barringer D. F. Jr., Berkelhammer G., Wayne R. S. (1973) J. Org. Chem. **38**: 1937
[4] Fiedler E., Fiedler H.-P., Gerhard A., Keller-Schierlein W., König W. A., Zähner H. (1976) Arch. Microbiol. **107**: 349
[5] Numata A., Takahashi C., Matsushita T., Miyamoto T., Kawai K., Usami Y., Matsumura E., Inoue M., Ohishi H., Shingu T. (1992) Tetrahedron Lett. **33**: 1621
[6] Metha D. R., Naravane J. S., Dessai R. M. (1963) J. Org. Chem. **28**: 445
[7] Arndt R. R., Eggers S. H., Jordaan A. (1967) Tetrahedron **23**: 3521
[8] Glasser A. C., Diamond L., Combs G. (1971) J. Pharm. Sci. **60**: 127
[9] Mukherjee D. D., Nautiyal S. R., Prasad C. R., Dhawan B. N. (1980) Indian J. Chem. **71**: 480
[10] Reif E., Ericson R. J.: Ger. Pat. No. 2 118 683, November 11, 1971; cit. (1972) C. A. **76**: 725462
[11] Bhattacharyya J., Pakrashi S. C. (1980) Heterocycles **14**: 1469
[12] Spassov S. L., Atanassova I. A., Haimova M. A. (1985) Magn. Reson. Chem. **23**: 795
[13] Akazome M., Kondo T., Watanabe Y. (1993) J. Org. Chem. **58**: 310
[14] (a) Hikino H., Nabetani S., Takemoto T. (1973) Yakugaku Zasshi **93**: 619; (b) Chadwick D. J., Easton I. W. (1983) Acta Crystallogr., Sect. C **39**: 454
[15] Bergman J., Brynolf A. (1990) Tetrahedron **46**: 1295
[16] Tsantrizos Y. S., Xu X.-J., Sauriol F., Hynes R. C. (1993) Can. J. Chem. **71**: 1362
[17] Nishio T., Fujisawa M., Omote Y. (1987) J. Chem. Soc. Perkin Trans I: 2523.
[18] Black P. J., Heffernan M. L. (1965) Aust. J. Chem. **18**: 707; also see references cited therein
[19] (a) Pugmire R. J., Grant D. M., Robins M. J., Robins R. K. (1969) J. Am. Chem. Soc. **91**: 6381; (b) Khan N., Ansari M. S., Robien W. (1993) Monatsh. Chem. **124**: 783. In this work, the ^{13}C chemical shifts for the related molecule 1,2-dimethyl-4(1*H*)-quinazolinone were misquoted from Ref. [11]. Our assignments in *DMSO*-d_6 are in accordance with the original values
[20] (a) Faure R., Galy J. P., N'Gadi L., Barbe J. (1989) Magn. Reson. Chem. **27**: 92. (b) Chauhan M. S., Still I. W. J. (1975) Can. J. Chem. **53**: 2880
[21] Patel V. S., Patel S. R. (1965) J. Indian Chem. Soc. **42**: 531
[22] Fry D. J., Kendall J. D., Morgan A. J. (1960) J. Chem. Soc. 5062

Received November 8, 1994. Accepted November 17, 1994