[Chem. Pharm. Bull. 25(11)3018—3022(1977)]

UDC 547.856.1.02 : 543.422.25.06

^{13}C Nuclear Magnetic Resonance Studies of Anti-inflammatory 2(1H)-Quinazolinones

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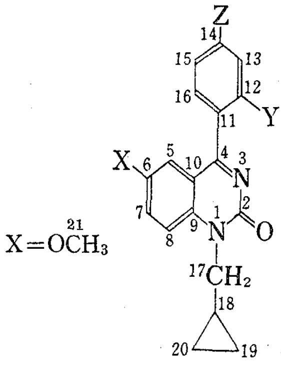
(Received March 26, 1977)

The ^{13}C NMR spectra of twelve 1-cyclopropylmethyl-4-phenyl-2(1H)-quinazolinones including a potent anti-inflammatory agent SL-573 were investigated, and the all carbon resonances were assigned mainly by the off-resonance technique, substituent effects on the 4-phenyl groups and ^{13}C–^{19}F couplings. It is noteworthy that the good correlations were found between Hammett parameters σ_p and the ^{13}C chemical shifts of the *para*-substituted quinazolinone (**1** and **7**—**12**)-frame carbons in spite of the large dihedral angles between the quinazolinone and phenyl ring planes (42.8° for SL-573).[1]

Keywords——^{13}C NMR study; anti-inflammatory agent; anti-inflammatory 2(1H)-quinazolinone; ^{13}C–^{19}F coupling; ^{13}C substituent effect; Hammett parameter; spectral analyses; spectral assignment; off-resonance and gated decoupling

Recently, various quinazolinones have been investigated as the potent anti-inflammatory and analgesic agents, and several reports have been published.[2–5] Of these, the crystal and molecular structure of 1-cyclopropylmethyl-4-phenyl-6-methoxy-2(1H)-quinazolinone (SL–573) **1** with marked biological activities was studied by the X-ray diffraction method[2] in which the dihedral angle between the quinazolinone and phenyl ring planes was found to be 42.8°. Then it has been thought that SL–573 and its related compounds with biological activities possessed also stereochemical interests as the aromatic systems with "half-conjugated" phenyl groups. Therefore, the ^{13}C nuclear magnetic resonance spectra which have been currently potent and popular for structural and electronical investigations of organic compounds were studied in this paper about various 1-cyclopropylmethyl-4-phenyl-2(1H)-quinazolinones in order to examine the problems between the biological activities and the stereochemical and electronical matters.



1: $X=OCH_3$, $Y=Z=H$, (SL–573)
2: $X=Y=Z=H$,
3: $X=OCH_3$, $Y=Cl$, $Z=H$,
4: $X=OCH_3$, $Y=Br$, $Z=H$,
5: $X=OCH_3$, $Y=NO_2$, $Z=H$,
6: $X=OCH_3$, $Y=OCH_3$, $Z=H$,
7: $X=OCH_3$, $Y=H$, $Z=CH_3$,
8: $X=OCH_3$, $Y=H$, $Z=F$,
9: $X=OCH_3$, $Y=H$, $Z=Cl$,
10: $X=OCH_3$, $Y=H$, $Z=Br$,
11: $X=OCH_3$, $Y=H$ $Z=NO_2$,
12: $X=OCH_3$, $Y=H$, $Z=OCH_3$,

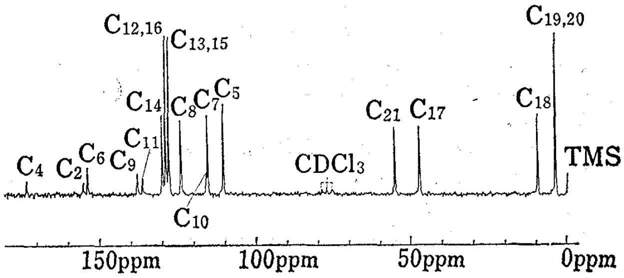


Fig. 1. ^{13}C NMR Spectrum of SL–573

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[1] Location: *Takatsukasa, Takarazuka, Hyogo, 665, Japan.*
[2] M. Kimura, T. Hirohashi, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **49**, 2696 (1976).
[3] T. Komatsu, H. Awata, Y. Sakai, T. Inukai, M. Yamamoto, S. Inaba, and H. Yamamoto, *Arzneim-Forsch.*, **22**, 1958 (1972).
[4] H. Yamamoto, C. Saito, H. Awata, M. Yamamoto, Y. Sakai, and T. Komatsu, *Arzneim-Forsch.*, **23**, 1266 (1973).
[5] K. Sozo, *Kagaku to Kogyo* (Tokyo), **27**, 307 (1975).

Results and Discussion

I. ^{13}C NMR Chemical Shifts

Natural-abundance 20 MHz ^{13}C FT nuclear magnetic resonance (NMR) spectra were obtained using the ^{1}H noise decoupling technique, and the ^{13}C chemical shifts (ppm from internal tetramethyl silane (TMS)) of twelve quinazolinones **1**—**12** recorded in CDCl$_3$ solu-

Table I. ^{13}C NMR Chemical Shifts and the Melting Points of **1**—**12**

	1	**2**	**3**	**4**	**5**	**6**
	(SL–573)	(6–H)	(o-Cl)	(o-Br)	(o-NO$_2$)	(o-OCH$_3$)
mp (°C)	116	152	116	95	103	86
C_2	155.52	155.73	155.43	155.46	155.25	155.76
C_4	173.53	174.59	172.54	173.55	172.22	173.38
C_5	110.88	130.06[a]	110.28	110.48	109.00	111.13[c]
C_6	154.25	114.48[b]	154.50	154.48	154.68	154.25
C_7	115.98	135.16	116.00	115.93	116.25	115.55
C_8	124.49	121.92[b]	125.01	124.95	124.79[c]	124.36
C_9	138.43	143.76	138.00	138.13[a]	137.99	137.64
C_{10}	116.38	116.03	116.88	116.79	116.97	117.59
C_{11}	136.73	136.69	131.89[a]	137.88[a]	132.45	126.22
C_{12}	129.39	129.65	135.84[a]	121.03	147.61	156.63
C_{13}	128.38	128.35	129.71	132.91	124.79[c]	111.13[c]
C_{14}	130.40	130.44[a]	130.90[b]	130.93[b]	130.81[d]	131.32
C_{15}	128.38	128.35	127.09	127.59	134.12	120.91
C_{16}	129.39	129.65	130.19[b]	130.16[b]	130.81[d]	130.28
C_{17}	47.65	47.68	47.90	47.93	47.99	47.77
C_{18}	9.80	9.68	9.80	9.80	9.82	9.83
$C_{19,20}$	4.02	4.06	4.05	4.07	4.07	4.04
C_{21}	55.68		55.68	55.72	55.70	55.60[d]
12-OCH$_3$						55.60[d]

	7	**8**	**9**	**10**	**11**	**12**
	(p-CH$_3$)	(p-F)	(p-Cl)	(p-Br)	(p-NO$_2$)	(p-OCH$_3$)
mp (°C)	138	154	144	150	149	149
C_2	155.63	155.44	155.35	155.39	155.19	155.63
C_4	173.54	172.39	172.25	172.39	171.53	172.78
C_5	111.08	110.69	110.46	110.54	109.93	111.02
C_6	154.25	154.41	154.37	154.41	154.64	154.19
C_7	115.87	116.13	116.13[e]	116.09[e]	116.43	115.89
C_8	124.33	124.65	124.73	124.73	125.39	124.16
C_9	138.49	138.57	138.53	138.64	138.78	138.42
C_{10}	116.54	116.28	116.13[e]	116.09[e]	116.03	116.42
C_{11}	134.01	132.94	135.18	135.69	142.81	129.11
C_{12}	129.56	131.71	130.88	131.07	130.51	131.38
C_{13}	129.07	115.58	128.68	131.67	123.66	113.79
C_{14}	140.72	164.09	136.64	125.08	148.86	161.62
C_{15}	129.07	115.58	128.68	131.67	123.66	113.79
C_{16}	129.56	131.71	130.88	131.07	130.51	131.38
C_{17}	47.62	47.73	47.71	47.75	47.96	47.52
C_{18}	9.80	9.83	9.79	9.79	9.79	9.79
$C_{19,20}$	4.01	4.05	4.02	4.03	4.06	4.00
C_{21}	55.72	55.75	55.73	55.79	55.87	55.71
14-OCH$_3$						55.40
14-CH$_3$	21.43					

a, b) Assignment of these resonances may be reversed.
c, d) These resonances were observed as two overlapped signals.
e These resonances also overlapped, but split off in the off-resonance decouplings.

tions are summarized in Table I. The ^{13}C resonances were generally assigned by the following methods: (1) chemical shift values expected for specific types of carbons; (2) the use of the ^{1}H off-resonance decoupling technique; (3) the use of the gated decoupling technique without nuclear overhauser (NOE) effect; (4) the effect of substituted groups on phenyl rings of the C_4 positions and the effect of methoxy groups of the C_6 positions; (5) ^{13}C—^{19}F couplings in the fluoro-substituted **8**.

For example, the ^{13}C NMR of **1** (SL–573) were assigned as follows (Fig. 1 and Table I): ^{13}C signals of C_{17}, C_{18}, $C_{19,20}$ and C_{21} were smoothly assigned by the ^{1}H off-resonance decoupled spectrum and the chemical shifts of the complete proton decoupled spectrum. The $C_{13,15}$, $C_{12,16}$ and C_{14} resonances were determined by considering the number of carbon nuclei from the relative peak intensity of the gated decoupling spectrum without NOE effect and by assuming that the *ortho*-carbon ($C_{12,16}$) resonance shifted to the same magnetic field as the *para*-carbon (C_{14}) resonance relative to the *meta*-carbon ($C_{13,15}$) resonance, which is like the ^{13}C resonances of the biphenyl and the benzophenone.[6,7] The C_5, C_7 and C_8 resonances were assigned by considering the ^{13}C NMR chemical shift values of unsubstituted quinazoline[8] and the effect of a methoxy group on the C_6 position in comparison with the ^{13}C NMR of **2**. A signal of 154.25 ppm was assigned to the C_6 position by considering the effect of the methoxy group in comparison with the C_6 resonance of **2**. Two signals of the lowest magnetic field were assigned to the C_2 (155.52 ppm) and C_4 (173.53 ppm) positions, respectively, by the following reasons[9]: (1) the C_4 resonances in a series of quinazolinones (**1** and **3**—**12**) must show larger ^{13}C substituent effects than those of the C_2 resonances by introducing the functional groups into 4-phenyl rings (Table I and II); (2) the carbonyl C_2 resonances of various uracils were observed in the same magnetic field ($\delta_{TMS}=150.9$—152.8 ppm[10]) as the C_2 resonance of **1**. The C_{11} resonance was assigned as follows: (1) the C_{11} resonances of **1** and **2** should be observed in the practically same magnetic field: (2) the C_{11} resonances of **1** and **7**—**12** should shift in the same way as the *para*-carbon resonances of the mono-substituted benzenes. In the remaining two signals (116.38 and 138.43 ppm), the C_9 carbon which is adjacent to the nitrogen atom was assigned to the lower magnetic resonance and the C_{10} carbon to the higher. Furthermore, this assignment was thought to be supported by the result that the chemival shifts' degrees of the C_{10} resonances due to the substituent effects were generally larger than those of the C_9 resonances in the ^{13}C NMR of **1** and **3**—**12** (Table I and II).

Now all the carbon resonances of **1** were assigned to the individual positions, respectively. Also in **2**—**12** the ^{13}C resonances were assigned, similarly. Especially ^{13}C—^{19}F coupling constants of fluorobenzene[11] were considered in assignments of ^{13}C resonances of the fluoro-substituted **8** (Table I and III).

II. Substituent Effects and ^{13}C—^{19}F Couplings

Recently the dihedral angle of **1** between the quinazolinone and phenyl ring planes was found to be 42.8° by the X-ray diffraction method.[2] Since it is probable that the para-substituted quinazolinones **7**—**12** keep the same dihedral angles as **1**, the chemical shift values from **1** were investigated and summarized in Table II. As expected, the ^{13}C resonances of 1-cyclopropylmethyl and 6-methoxy carbons were constant. However it seemed noteworthy

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6) G.C. Levy, G.L. Nelson, and J.D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972).
7) G.C. Levy and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," John Wiley and Sons, Inc., New York·London·Sydney·Toronto, 1972, p. 81.
8) R.J. Pugmire, D.M. Grant, M.J. Robins, and R.K. Robins, *J. Am. Chem. Soc.*, **91**, 6381 (1969).
9) Furthermore, in our unpublished data the C_2 resonance of 1-cyclopropylmethyl-4-phenyl-6-methoxy-3,4-dihydro-2(1H)-quinazolinone, which is the 3,4-dihydro-type of **1**, was observed in the same magnetic field ($\delta_{TMS}=154.67$ ppm) as the C_2 resonance of **1**, but the C_4 resonance shifted into a high magnetic field ($\delta_{TMS}=57.84$ ppm).
10) A.R. Tarpley, Jr., and J.H. Goldstein, *J. Am. Chem. Soc.*, **93**, 3573 (1971).
11) F.J. Weigert and J.D. Roberts, *J. Am. Chem. Soc.*, **91**, 4940 (1969).

that the ^{13}C chemical shifts of individual quinazolinone-frame carbons (C_2 and C_{4-10}) exhibited more or less fairly good correlations with Hammett parameters σ_p in spite of the large dihedral angles between the quinazolinone and phenyl ring planes. (*e.g.* a plot of the C_2 chemical shift values of Table II and σ_p values is shown in Fig. 2). Furthermore the degrees of these correlations were available to the ^{13}C assignments, as previously discussed in I. However the ^{13}C chemical shifts of the *ortho*-substituted quinazolinones (**1** and **3**—**6**) did not correlate to the σ_p values any more than those of the para-substituted quinazolinones. It is probably because the individual dihedral angles between the quinazolinone and phenyl ring planes are different due to the steric and electronic factors of *ortho*-groups. Therefore, the ^{13}C NMR of the *ortho*-substituted quinazolinones were not investigated more than those of the *para*-substituted in this paper.

TABLE II. ^{13}C Substituent Effects[a] of *para*-Substituted Quinazolinones (**7**—**12**)

	7 (p-CH_3)	**8** (p-F)	**9** (p-Cl)	**10** (p-Br)	**11** (p-NO_2)	**12** (p-OCH_3)
C_2	+0.11	−0.08	−0.17	−0.13	−0.33	+0.11
C_4	+0.01	−1.14	−1.28	−1.14	−2.00	−0.75
C_5	+0.20	−0.19	−0.42	−0.34	−0.95	+0.14
C_6	0.00	+0.16	+0.12	+0.16	+0.39	−0.06
C_7	−0.11	+0.15	+0.15	+0.11	+0.45	−0.09
C_8	−0.16	+0.16	+0.24	+0.24	+0.90	−0.33
C_9	+0.06	+0.14	+0.10	+0.21	+0.35	−0.01
C_{10}	+0.16	−0.10	−0.25	−0.29	−0.35	+0.04

a) ppm relative to SL-573 (p-H type) standard; positive shifts downfield.

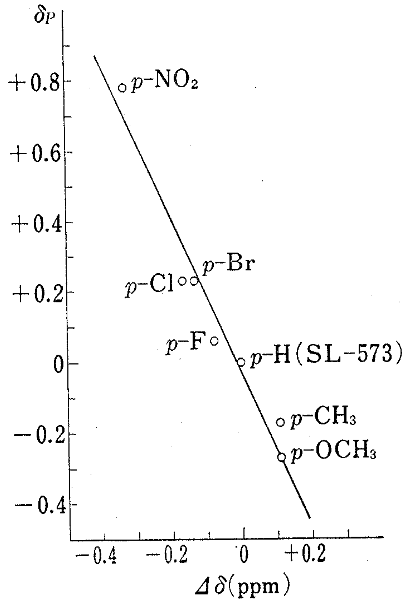

Fig. 2. A Plot of ^{13}C Substituent Effects (of C_2 Resonances) *vs.* Hammett Parameters δ_p

TABLE III. ^{13}C—^{19}F Coupling Constants of **8**

	J_{C-F} (Hz)
C_{11}	3.2
$C_{12,16}$	8.3
$C_{13,15}$	22.1
C_{14}	251.0

^{13}C—^{19}F couplings were observed only in the ^{13}C resonances of 4-phenyl group of **8**. Coupling constants (J_{C-F}) of the individual phenyl carbon resonances are summarized in Table III. and were similar to those of the fluorobenzene.[11]

Further studies of the substituent effects of the aromatic systems with "half-conjugated" phenyl groups and ^{13}C—^{19}F couplings in these and related compounds are in progress and will be reported.

Experimental

Compounds **1**—**12** was prepared according to the method previously reported.[3] All compounds were confirmed by ^{13}C NMR, ^{1}H NMR, IR spectra and elemental analyses, and the melting points from ethyl acetate, which are not corrected, are included in Table I.

Pulse FT NMR spectra were measured with a Varian CFT-20 spectrometer at operating 20 MHz in 8 mm tubes at ordinary probe temperature. All spectra were obtained for $CDCl_3$ solutions (whose concentrations were *ca.* 0.5 mol/liter) and spectrometer was locked to the ^2D signal of $CDCl_3$. Spectra were recorded with a spectral width of 4500 Hz and 8 K data points at an acquisition time of 0.9 sec, a number of transient of 1 K—3 K and an pulse delay of 0—6 sec. In addition to the ordinary pulse FT modes of the ^1H complete and ^1H off-resonance decouplings, the gated decoupling methods without NOE effect, if necessary, were available. Peak positions were determined by computer examination of the final fourier transformed spectrum and the ^{13}C chemical shifts (in ppm) were read relative to the resonance of internal TMS. All chemical shifts were given relative to within ± 0.8 Hz.

Acknowledgement The authors wish to express their sincere thanks to Mr. K. Aoki of NEVA Co. Ltd. for the measurement of ^{13}C NMR spectra, and also to Mr. T. Inoue of this laboratory for the experimental assistance.