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Acridone Alkaloids. X.[1] ^{13}C-Nuclear Magnetic Resonance Spectra of Acridone Alkaloids

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The ^{13}C-nuclear magnetic resonance spectra of twenty-seven acridone alkaloids including angular pyrano[2,3-*c*]acridones and linear pyrano[3,2-*b*]acridones have been analyzed and assigned. The information should be useful for the structure elucidation of new acridone alkaloids.

Keywords——^{13}C-NMR spectra; acridone; prenylacridone; pyrano[2,3-*c*]acridone; pyrano[2,3-*b*]acridone; acronycine

Acronycine (acronine) is an antitumor-active pyranoacridone alkaloid isolated from *Acronychia bauerii.*[2] Many other pyranoacridone alkaloids have also been isolated from the plants of Rutaceae;[3] we have reported the isolation and structural elucidation of some new acridone alkaloids from Rutaceaous plants.[1,4] The present investigation was aimed at establishing ^{13}C-nuclear magnetic resonance (NMR) spectroscopy as a convenient tool in the structural elucidation of new acridone alkaloids. There have already been some reports of ^{13}C-NMR spectra of acridones[5] and some acridone alkaloids.[6] However, no reports on the ^{13}C-NMR spectra of pyranoacridone alkaloids have been published.

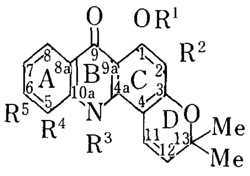
In this study, we have undertaken careful analyses of the spectra of twenty-seven acridone alkaloids including pyrano[2,3-*c*]acridones (angular type), pyrano[3,2-*b*]acridones (linear type), and prenylacridones as well as some of derivatives of the pyrano[2,3-*c*]acridone alkaloids. The information should be useful for the structural elucidation of new acridone alkaloids.

The assignments of all resonances except for singlets were confirmed by off-resonance decoupling and single-frequency selective proton-decoupling[7] experiments. The assignment of singlets other than carbonyl and the quaternary carbon (C-13) signals was facilitated by comparisons with the spectra of acridones reported previously[6] and with those of simpler model compounds, and by consideration of the known substituent effects in the aromatic ring.[8] In some cases, weak-decoupling experiments were also carried out to distinguish singlets among signals. The chemical shifts of acridone alkaloids measured in this work are presented in Tables I, II, and III. The system numberings cited in this paper are shown in Charts 1 and 2.

Singlets

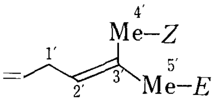
The carbonyl carbon signals of the acridones and the pyranoacridones bearing an intramolecularly hydrogen-bonded 1-hydroxyl group are observed in the region of 179.7—182.5 ppm. On the other hand, the signals of the 1-methoxy compounds appear at 3.6—4.3 ppm higher field relative to the corresponding 1-hydroxy compounds.

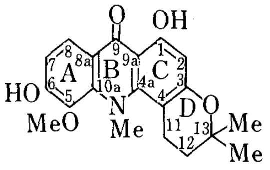
The resonances of the C-13 carbon (carrying dimethyl) in the pyranoacridones occur within a very narrow range. In the spectra of the angular pyrano[2,3-*c*]acridones bearing no *N*-methyl group, the resonances appear in the region of 76.6—77.0 ppm, whereas the presence of the *N*-methyl group moves the C-13 signal slightly upfield (0.3—0.6 ppm) relative to the



	R^1	R^2	R^3	R^4	R^5		R^1	R^2	R^3	R^4	R^5
1 :	H	H	H	H	H	**9** :	H	pnl	H	H	H
2 :	H	H	Me	H	H	**10** :	H	pnl	Me	H	H
3 :	Me	H	H	H	H	**11** :	Me	pnl	Me	H	H
4 :	Me	H	Me	H	H	**12** :	H	pnl	H	OH	H
5 :	H	H	H	OH	H	**13** :	H	pnl	Me	OH	H
6 :	H	H	Me	OH	H	**14** :	H	pnl	H	OMe	H
7 :	H	H	Me	OMe	OH	**15** :	H	pnl	Me	OMe	H
8 :	H	H	Me	OMe	OMe	**16** :	Me	pnl	Me	OMe	H

pnl =





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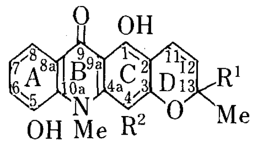
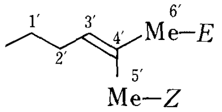


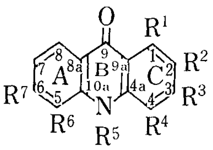
18 : R^1=



, R^2=H

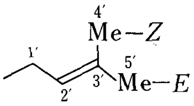
19 : R^1=Me, R^2=OMe

Chart 1



	R^1	R^2	R^3	R^4	R^5	R^6	R^7
20 :	OH	H	OH	pnl′	Me	H	H
21 :	OH	H	OMe	pnl′	Me	H	H
22 :	OH	H	OMe	pnl′	Me	OH	H
23 :	OH	pnl	OH	pnl′	Me	OH	H
24 :	OH	H	OH	pnl′	Me	OMe	OH
25 :	OH	H	OMe	H	Me	OMe	OH
26 :	OH	H	OMe	H	Me	OMe	OMe
27 :	OH	H	OMe	OMe	Me	OH	H

pnl=



pnl′=

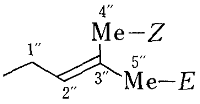


Chart 2

Table I. ^{13}C-NMR Assignments for Pyrano[2,3-*c*]acridones

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-4a	C-8a	C-9a	C-10a	C-11	C-12	C-13	13-Me
1[a]	159.5	96.5	164.2	104.4	117.4	133.3	121.4	125.0	180.9	141.0	119.3	98.1	138.0	116.5	125.0	76.8	27.7
2[a]	161.4	97.4	164.9	106.6	116.2	133.9	121.9	125.7	180.7	144.6	121.4	100.9	144.1	121.4	122.7	76.3	26.8
3[a]	157.5	93.4	162.5	107.0	116.9	132.2	121.0	126.1	176.6	140.2[c]	122.6	99.9	139.9[c]	116.7	125.6	76.6	27.6
4[b]	159.2	94.2	162.9	110.5	115.9	132.5	121.7	127.0	177.1	146.7	125.3	103.0	144.4	121.7	122.9	76.3	26.8
5[a]	159.2	96.6	164.0	104.1	145.1	116.6	121.5	115.1	180.9	136.6	120.1	97.8	130.7	115.1	125.9	76.9	27.6
6[a]	161.1	97.5	164.3	106.9	147.7	120.1	123.3	116.0	181.8	148.5	124.7	102.1	137.0	121.0	123.6	76.6	27.1
7[a]	160.6	97.8	164.3	106.4	142.5	156.2	113.4	122.2	181.1	147.4	117.4	102.3	136.7	120.6	124.1	76.5	27.0
8[b]	161.1	98.2	164.5	106.7	142.3	157.5	108.2	122.4	181.4	147.7	118.7	102.5	138.4	120.8	124.1	76.6	27.1
9[a]	157.6	108.9	161.4	104.3	117.2	133.1	121.2	125.3	181.1	140.9	119.4	97.9	136.2	116.8	125.0	76.7	27.7
10[a]	159.0	109.3	161.7	106.2	116.1	133.6	121.5	125.5	180.5	144.4	121.2	100.5	142.2	121.7	122.4	76.1	26.7
11[b]	157.4	118.9	159.8	113.6	115.9	132.7	121.6	127.2	176.7	144.8[c]	124.7	106.5	144.7[c]	122.0	124.1	76.1	26.9
12[a]	157.4	108.9	161.2	104.0	144.9	116.3	121.2	115.4	181.1	134.7	120.0	97.4	130.7	115.1	126.0	76.8	27.6
13[a]	158.8	109.5	161.2	106.5	145.8	119.8	122.9	116.0	181.8	148.4	124.7	101.9	137.0	121.3	123.3	76.3	27.0
14[b]	157.6	109.4	161.4	104.3	146.3	111.2	120.6	116.7	180.9	134.3	119.7	97.4	130.8	114.8	126.2	77.0	27.7
15[b]	159.1	110.3	161.5	107.1	146.0	115.2	122.7	117.8	181.9	150.5	125.0	102.2	138.2	121.5	123.6	76.4	27.1
16[b]	157.2	119.4	159.2	114.4	147.9	114.3	122.9	118.4	177.9	150.8	128.6	108.1	137.7	121.4	125.4	76.2	27.1
17[a]	161.1	98.6	161.8	106.5	143.5	155.9	113.1	122.0	181.4	150.4	117.6	101.0	136.6	21.8	32.8	75.1	26.6

	N-Me	1-OMe	5-OMe	6-OMe	C-1′	C-2′	C-3′	C-4′	C-5′
1									
2	43.5								
3		55.8							
4	44.2	56.2							
5									
6	48.6								
7	48.6		59.8						
8	49.0		60.3	56.3					
9					21.2	122.8	130.5	17.8	25.7
10	43.4				21.4	122.5	130.6	17.8	25.7
11	44.2	62.1			22.5	123.1	130.9	18.0	25.8
12					21.1	122.7	130.3	17.8	25.7
13	48.4				21.3	122.5	130.6	17.8	25.7
14			55.9		21.4	122.9	130.5	18.0	25.9
15	49.0		56.0		21.5	122.6	131.0	18.0	25.9
16	48.2	61.9	55.9		22.5	123.3	130.8	18.0	25.8
17	47.4		59.6						

a) In $CDCl_3+(CD_3)_2SO$. *b)* In $CDCl_3$. *c)* May be interchanged.

Table II. ^{13}C-NMR Assignments for Pyrano[3,2-*b*]acridones

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
18[b]	158.5	102.5	160.8	92.0	146.4[c]	120.6	122.6	117.4	180.1
19[a]	153.2	103.4	154.4	129.5	148.1	119.9	122.7	116.1	182.1

	C-4a	C-8a	C-9a	C-10a	C-11	C-12	C-13	13-Me
18	146.7[c]	123.3	105.2	133.7	116.3	125.9	80.5	27.2
19	142.3	124.4	106.1	137.0	116.0	126.8	77.9	28.3

	N-Me	4-OMe	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
18	41.0		22.7	41.8	123.9	131.8	17.7	25.7
19	46.4	60.6						

a) In $CDCl_3+(CD_3)_2SO$. *b*) In $CDCl_3$. *c*) May be interchanged.

corresponding imino compounds, and the signals appear at 76.1—76.6 ppm. On the other hand, in the case of the linear pyrano[3,2-*b*]acridones, no shielding effect on the C-13 carbon resonance is observed in the presence of the *N*-methyl group, and the C-13 signals are seen at 77.9 and 80.5 ppm.

Doublets

The C-11 resonance of the angular pyranoacridones is affected by the *N*-methyl group. In the *N*-unsubstituted pyrano[2,3-*c*]acridone derivatives, the C-11 signals appear at 114.8—116.8 ppm, whereas in the *N*-methyl compounds, they appear at lower field, at 120.6—122.0 ppm. In contrast, the C-12 signals in the *N*-methyl compounds are moved upfield by 2.3—2.7 ppm relative to the corresponding imino compounds. In the case of the linear pyrano[3,2-*b*]acridones, the C-11 resonance is not affected by the *N*-methyl group and appears at 116.0 and 116.3 ppm, as in the case of the *N*-unsubstituted pyrano[2,3-*c*]acridones.

Triplets

The methylene signals (C-1′) of the prenyl groups at C-2 when two oxygenated substituents are present at the *ortho*-positions appear in the region of 21.1—22.5 ppm. On the other hand, the methylene signals (C-1″) of the prenyl group at C-4 in the *N*-methyl compounds move downfield to 26.0—27.1 ppm.

Quartets

(a) Methoxyl Groups——The chemical shifts of the methoxyl groups with adjacent substituents at both *ortho*-positions are between 59.6—62.1 ppm. In other cases, lacking the substituents at both or either *ortho*-position, the methoxyl signals appear at 55.3—56.3 ppm.

(b) *N*-Methyl Groups——As Mester *et al.*[6b] reported, the *N*-methyl signals of acridone derivatives having no substituents at both *peri*-positions appear at 33—35 ppm, and those of the 4-methoxy derivatives are observed at 41—42 ppm. Further, the following features also became apparent in this study: in the pyrano[2,3-*c*]acridones or the 4-prenylacridones having no substituent at C-5, the *N*-methyl signals appear in the region of 43.4—44.2 ppm, and in those having a substituent such as hydroxyl or methoxyl group at C-5, they are observed considerably downfield at 47.4—49.0 ppm. However, the acridones bearing oxygenated substituents at C-5 and C-6, and lacking the substituent at C-4 show the *N*-methyl signals slightly upfield at 39.9—40.0 ppm. On the other hand, the *N*-methyl signal of the linear

TABLE III. ^{13}C-NMR Assignments for Acridones

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-4a	C-8a	C-9a	C-10a
20[a]	162.7	97.1	164.3	106.4	116.4	133.6	121.0	125.4	180.8	147.1	121.0	105.2	145.6
21[b]	163.7	93.3	165.3	106.9[c]	116.3	133.8	121.2	125.9	181.7	146.7[c]	121.2	106.5[c]	146.1[c]
22[a]	163.0	93.4	165.0	108.9	148.6[c]	119.9	122.7	116.1	182.9	150.3[c]	124.8	107.2	138.4
23[a]	159.5	109.0	161.4	107.2[c]	148.6[c]	119.6	122.4	116.0	182.5	148.9[c]	124.7	106.9[c]	138.1
24[b]	162.7[c]	98.6	162.9[c]	107.2[c]	142.6	154.6	112.0	122.5	182.0	150.5	118.2	106.9[c]	136.0
25[a]	164.6[c]	94.2	165.4[c]	90.2	138.8	156.4	112.7	122.4	179.7	147.0	116.1	104.4	135.3
26[b]	165.2[c]	94.1	165.9[c]	90.7	138.7	157.7	107.4	122.9	180.3	147.5	117.6	104.8	137.0
27[a]	159.4[c]	93.5	160.0[c]	129.8	148.2	119.9	122.5	115.7	181.9	141.9	124.1	105.8	137.2

	N-Me	3-OMe	4-OMe	5-OMe	6-OMe	C-1′	C-2′	C-3′	C-4′	C-5′	C-1′′	C-2′′	C-3′′	C-4′′	C-5′′
20	43.4										26.9	124.6	131.1	18.0	25.5
21	43.8	55.9									27.1	124.5	131.6	18.1	25.6
22	48.1	55.9									26.3	123.8	131.3	18.0	25.7
23	48.1					21.6	122.6	132.5[c]	17.9	25.7	26.7	123.3	133.4[c]	18.1	25.7
24	47.7			59.9							26.6	123.3	135.2	18.1	25.8
25	39.9	55.3		60.9											
26	40.4	55.5		61.3	56.3										
27	46.0	56.0	60.0												

a) In $CDCl_3+(CD_3)_2SO$. *b*) In $CDCl_3$. *c*) May be interchanged.

pyrano[3,2-*b*]acridone (**18**) is observed at 41.0 ppm though a hydroxyl group is present at C-5. In the pyrano[3,2-*b*]acridone (**19**) and the acridone (**27**) carrying both a methoxyl group at C-4 and a hydroxyl group at C-5, the *N*-methyl signals appear further downfield at 46.0 and 46.4 ppm, respectively.

(c) **Methyl Signals of Prenyl Groups**——The *E*-methyl groups appear at 25.5—25.9 ppm and the *Z*-methyl groups are observed at higher field, at 17.7—18.1 ppm. Such upfield shifts of carbon resonances due to steric interactions are well known.[9)]

Substituent Effect of C-5 and C-6 Substituents

Previously, Mester *et al.*[6b)] showed that introduction of substituents such as methoxyl and hydroxyl groups onto ring A or ring C does not affect the ^{13}C chemical shifts of ring C or ring A carbons, respectively. In our present study, the C-4a signal was found to be affected by the introduction of a methoxyl or hydroxyl group at C-5. In the case of the *N*-methyl compounds bearing a methoxyl or hydroxyl group at C-5 and no substituent at C-6, the C-4a signals are moved downfield by 3.6—6.1 ppm, whereas the C-4a signal is moved upfield by 4.4—6.6 ppm in the case of the corresponding imino compounds. When a methoxyl or hydroxyl group is introduced at C-6 simultaneously with a methoxyl group at C-5, the upfield shifts (0.9 to 3.6 ppm) of the C-4a signals are smaller than those in the case of the *N*-methyl compounds only bearing an oxygenated substituent at C-5. Furthermore, the chemical shifts of the *N*-methyl groups move downfield by 4.0—6.4 ppm when a methoxyl or hydroxyl group is introduced at C-5.

Substituent Effect of the *N*-Methyl Group

In the case of the 5-substituted pyrano[2,3-*c*]acridones, the presence of an *N*-methyl group causes downfield shifts of the resonances of C-6, C-4a, C-8a, C-9a, and C-10a by 3.0—3.5, 11.9—16.2, 4.6—5.3, 4.4—4.8, and 6.3—7.4 ppm, respectively. In the case of the 5-unsubstituted derivatives, however, the shifts are smaller than those in the case of the 5-substituted compounds, and the downfield shifts of C-6, C-4a, C-8a, C-9a, and C-10a are 0.3—0.6, 3.5—6.5, 1.8—2.7, 2.6—3.1, and 4.5—6.1 ppm, respectively. On the other hand, the C-11 resonances are moved downfield by 4.9—6.7 ppm and those of C-12 are moved upfield by 2.3—2.7 ppm regardless of the presence of the 5-substituent.

Conclusion

The following points emerge: (i) The chemical shifts of *N*-methyl carbons in acridone alkaloids are especially sensitive to the presence of substituents at the *peri*-positions (at C-4 and C-5). In the case of the presence of substituents at both *peri*-positions (C-4 and C-5), the *N*-methyl carbon resonances appear at 46—49 ppm. On the other hand, when a substituent at either C-4 or C-5 is lacking, the chemical shifts are *ca.* 40 ppm or 43—44 ppm, respectively. The *N*-methyl signals of the 4,5-unsubstituted acridone derivatives appear at 33—35 ppm.[6b)] (ii) In the case of the *N*-methyl derivatives bearing oxygenated substituents at both C-1 and C-3, the chemical shifts of C-1′ and/or C-1″ of the prenyl groups have diagnostic value in distinguishing the locations of the prenyl group at C-2 or C-4. (iii) Crombie and his co-workers[10)] have reported that the reactions of 1,3-dihydroxyacridone with 3-hydroxyisovaleraldehyde dimethylacetal, citral, and furnesal gave the corresponding angular pyrano[2,3-*c*]acridones along with the linear pyrano[3,2-*b*]acridones, and these two types of pyranoacridones were distinguished from each other by the photomeric Gibbs' test and/or by the nuclear Overhauser effects in the corresponding *N*-methylated compounds. In this study, it was found that the ^{13}C-NMR is a convenient tool for distinguishing the angular pyrano[2,3-*c*]acridones from the linear pyrano[3,2-*b*]acridones. In the case of the *N*-methyl derivatives, the angular pyrano[2,3-*c*]acridones and the linear pyrano[3,2-*b*]acridones show the C-11 signal at *ca.* 121 ppm, and *ca.* 116 ppm, respectively. The chemical shifts of the *N*-methyl group may also be effective for distinction between the linear and the angular derivatives, though not always. For example, pyrano[3,2-*b*]acridones bearing a carbon substituent at C-4 would show the *N*-methyl signal at the same region as the pyrano[2,3-*c*]acridone derivatives.

Experimental

Natural-abundance, proton decoupled, Fourier-transform ^{13}C-NMR spectra were recorded at the operating frequency of 25.00 MHz on a JEOL JNM-FX-100 Fourier-transform spectrometer equipped with a JEOL JEC-980B computer. For the measurements of chemical shifts, the spectra were taken at a 6002 Hz spectral width using a pulse repetition time of 2.0 s with 8 K data points and a 6.7 μs pulse width (flip angle 30°). Me_4Si was used as an internal reference. The samples were run in 5 mm o.d. tubes at ambient temperature in either $CDCl_3$ or a mixture of $(CD_3)_2SO$-$CDCl_3$ to provide a deuterium lock, according to solubility.(11) Shifts are reported in ppm downfield from Me_4Si. The isolation of the new compounds reported here has already been described.(1,4)

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