CHEMISTRY OF ACRONYCINE I. CARBON-13 NMR STUDIES OF ACRONYCINE AND RELATED COMPOUNDS

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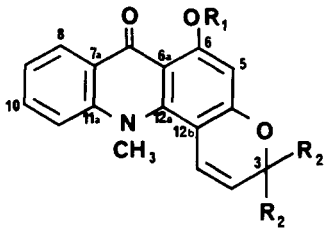
ABSTRACT.—Complete and unambiguous ^{13}C-nmr assignments have been made for acronycine (**1**) through examination of both fully coupled and INEPT spectra. By analogy, chemical shift assignments were also made for dihydroacronycine (**2**), noracronycine (**3**), and dihydronoracronycine (**4**). A characteristic deshielding effect on an *N*-methyl group in this system was disclosed.

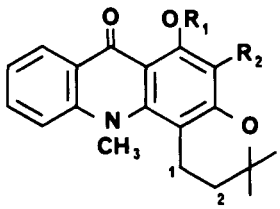
Cytotoxicity testing using the KB system demonstrated that the *O*-methyl group is essential for activity.

Acronycine (**1**), an alkaloid from the scrub ash *Acronychia baueri* Schott (Rutaceae) (1-3), possesses the broadest spectrum of *in vivo* antineoplastic activity of any plant-derived natural product (4,5). Acronycine (**1**) is an acridone alkaloid with an additional hemiterpene unit attached at C-4 of the parent nucleus and cyclized to form a pyran ring. Initially, there was a question as to whether acronycine had a linear or angular structure, and the presently accepted structure was deduced from chemical (6) and spectroscopic (7) evidence. An X-ray crystallographic analysis of 5-bromo-1,2-dihydroacronycine confirmed that the parent compound had the 3*H*-pyrano [2,3-c] acrid-7-one nucleus (8).

As a prelude to biological studies to be reported elsewhere (9), a study was undertaken of the ^{13}C-nmr spectrum of acronycine (**1**) and some simple derivatives (2-4). A number of papers have appeared on the ^{13}C-nmr spectra of quinoline (10-12) and acridone alkaloids (13-16), including some possessing a five-carbon unit attached at C-4 (14,15). However, no studies on the acronycine series of derivatives have been published.



	R_1	R_2
1	CH_3	CH_3
3	H	CH_3
12	H	H



	R_1	R_2
2	CH_3	H
4	H	H
11	CH_3	Br

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined using a Kofler hot plate and are uncorrected. The uv spectra were obtained with a Beckman model DB-G spectrophotometer. The ir spectra were obtained with a Beckman model 18-A spectrophotometer with polystyrene calibration at 1601 cm^{-1}; absorption bands are reported in wave numbers (cm^{-1}). Proton-nmr spectra were recorded in $CDCl_3$ with a Varian T-60A instrument, operating at 60 MHz with a Nicolet Model TT-7 Fourier

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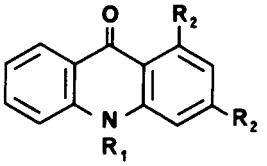
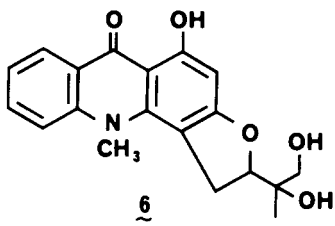


	R_1	R_2
5	CH_3	OCH_3
7	H	H
10	CH_3	H



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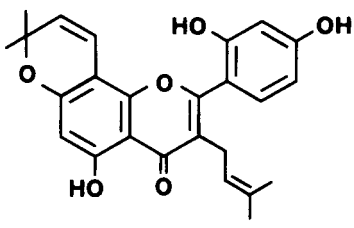

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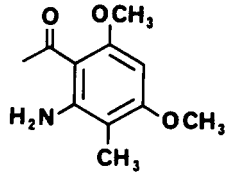

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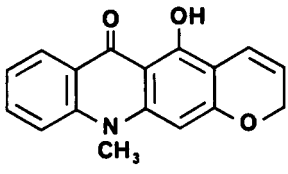

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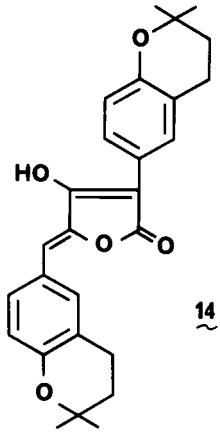

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Transform attachment. ^{13}C-nmr spectra were recorded in $CDCl_3$ on a Brüker CXP 180 instrument operating at 45.26 MHz, and the INEPT spectrum was obtained at the NSF Regional NMR Facility at the University of Illinois, Urbana-Champaign, on a Nicolet NT-360 instrument operating at 90.54 MHz. Mass spectra were measured using a Varian MAT 112S double focusing instrument operating at 70 eV.

ACRONYCINE (1).—A crude acronycine-containing mixture of alkaloids from *A. baueri* (100 g)[2] was dissolved in $CHCl_3$:C_6H_6 (1:1, 1 l) and eluted with the same solvent system after absorption on a column of neutral alumina[3] (1 kg). The resulting crude acronycine was chromatographed on a column of silica gel[4] (1.2 kg) using chloroform as the eluent. Acronycine (1) crystallized from C_2H_5OH as slightly yellow, fine needles possessing the following physical and spectral properties: mp 172.5-174.5°, Lit. (17) 176-177°; ir, ν max (KBr) 2965, 2910, 1637, 1621, 1601, 1589, 1574, 1565, 1493, 1392, 1346, 1205, 1130, 1090, 1039, and 1030 cm^{-1}; uv, λ max (EtOH) 224 (log ϵ 4.39), 260 (sh, 4.60), 281 (4.69), 293 (4.64), 308 (4.41), and 380 nm (4.01); ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.52 (6H, s, $-C(CH_3)_2$), 3.77 (3H, s, $-NCH_3$), 3.96 (3H, s, $-OCH_3$), 5.47 (1H, d, J=9.7 Hz, H-2), 6.30 (1H, s, H-5), 6.50 (1H, d, J=9.7 Hz, H-1), 7.06-7.69 (3H, m, H-9, H-10 and H-11) and 8.37 (1H, dd, J=1.5 and 7.5 Hz, H-8); ^{13}C-nmr, see table 1; ms, *m/z* 321 (M^+, 74.6%), 307 (21.7), 306 (100), 292 (21.7), 276 (8.3), 262 (26.9), 161 (8.6), 154 (6.0), 140 (9.1), 139 (10.1), 132 (7.3), 125 (6.8), 118 (13.2), 104 (7,1), and 79 (9.6).

[2]Obtained through the courtesy of Dr. M. Gorman, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN.

[3]Fisher Scientific Company, Fairlawn, NJ.

[4]E. Merck, Darmstadt, W. Germany.

1,2-DIHYDROACRONYCINE (**2**).—Acronycine (**1**, 300 mg) was dissolved in C_2H_5OH (12 ml) in the presence of 10% Pd/C (35 mg) and glacial HOAc (3 drops). Hydrogen gas was passed into this mixture, and stirring was continued overnight. Chromatography of the resulting product over silica gel (30 g), eluting with chloroform, afforded 1,2-dihydroacronycine (**2**, 280 mg, 93% yield), which crystallized from C_2H_5OH as pale yellow prisms possessing the following physical and spectral properties: mp 139.0-140.0° Lit. (18) 140-141.5°; ir, ν max (KBr) 3422, 2970, 2930, 2850, 1632, 1592, 1580, 1494, 1434, 1390, 1368, 1320, 1287, 1257, 1234,, 1202, 1183, 1155, 1128, 1117, 1087, 1027, 941, 872, 810, 753, and 747 cm^{-1}; uv, λ max (EtOH) 226 (log ϵ 4.17), 253 (sh, 4.34), 264 (sh, 4.53), 272 (4.60), 298 (4.51), 315 (4.01), and 380 nm (3.89); ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.43 (6H, s, -C $(CH_3)_2$), 1.72 (2H, t, J=6.4 Hz, 2-H_2), 2.83 (2H, t, J=6.4 Hz, 1-H_2), 3.72 (3H, s, -NCH_3), 3.93 (3H, s, -OCH_3), 6.24 (1H, s, H-5), 7.02-7.70 (3H, m, H-9, H-10 and H-11) and 8.31 (1H, dd, J= 1.5 and 7.7 Hz, H-8); ^{13}C-nmr, see table 1; ms, *m/z* 323 (M^+, 100%), 306 (19.0), 295 (9.9), 294 (46.7), 279 (5.5), 278 (5.5), 268 (13.7), 250 (17.9), 239 (25.8), 238 (67.4), 236 (18.0), 224 (8.2), 210 (26.7), 196 (8.1), 180 (7.2), and 167 (9.7).

NORACRONYCINE (**3**).—Noracronycine was prepared basically according to the method of Brown *et al.* (18). Thus, acronycine (**1**, 2.0 g) was dissolved with heating to 70° in 10% aqueous HCl (120 ml) to afford a deep red solution. After cooling to room temperature, acronycine HCl was obtained as red needles. Heating acronycine HCl (1.8 g) on an oil bath at 140° for 60 min afforded a yellow powder, which was chromatographed over silica gel (20 g) eluting with chloroform. The resulting noracronycine (**3**, 1.0 g, 65% yield) was crystallized from C_2H_5OH as bright yellow needles possessing the following physical and spectral properties: mp 200.5-201.0°, Lit. (18) 200.5-201°; ir, ν max (KBr) 3420, 2904, 2838, 1637, 1594, 1572, 1551, 1507, 1494, 1480, 1405, 1334, 1273, 1171, 1144, 1015, 892, and 751 cm^{-1}; uv, λ max (EtOH) 227 (log ϵ 4.22), 256 (4.41), 284 (4.68), 295 (sh, 4.63), 312 (4.37), 342 (sh, 3.68), and 410 nm (3.69); ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.50 (6H, s, -$C(CH_3)_2$), 3.82 (3H, s, -NCH_3), 5.45 (1H, d, J=9.7 Hz, H-2), 6.18 (1H, s, H-5), 6.49 (1H, d, J=9.7 Hz, H-1), 7.05-7.79 (3H, m, H-9, H-10 and H-11), 8.25 (1H, dd, J= 1.4 and 7.8 Hz, H-8), and 14.68 (1H, s, 6-OH, D_2O exchangeable); ^{13}C-nmr, see table 1; ms, *m/z* 307 (M^+, 32.0%), 293 (20.7), 292 (100), 278 (6.7), 277 (27.8), 210 (1.1), 191 (2.0), 178 (2.1), 154 (3.9), 146 (11.2), 140 (3.7), 132 (4.9), and 125 (9.3).

1,2-DIHYDRONORACRONYCONE (**4**).—Noracronycine (**3**, 410 mg) was dissolved in C_2H_5OAc (40 ml) in the presence of 10% Pd/C (40 mg) and glacial HOAc (8 drops). Hydrogen gas was passed into this mixture, and stirring was continued overnight. The resulting crude product was crystallized from $CHCl_3$:C_2H_5OH (1:2) to afford yellow cubes of dihydronoracronycine (**4**, 390 mg, 95% yield) possessing the following physical and spectral properties: mp 218.0-219.0°, Lit. (18) 215-216°; ir, ν max (KBr) 3420, 1616, 1580, 1550, 1464, 1389, 1317, 1268, 1157, 1138 and 1115 cm^{-1}; uv, λ max (EtOH) 228 (log ϵ 4.25), 252 (4.48), 266 (sh, 4.55), 276 (4.69), 300 (4.13), 332 (4.09), and 397 nm (3.87); ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.43 (6H, s, -$C(CH_3)_2$), 1.74 (2H, t, J=6.3 Hz, 2-H_2), 2.89 (2H, t, J=6.3 Hz, 1-H_2), 3.85 (3H, s, -NCH_3), 6.19 (1H, s, H-5), 7.09-7.82 (3H, m, H-9, H-10 and H-11), 8.31 (1H, dd, J= 1.3 and 7.6 Hz, H-8), and 14.24 (1H, s, 6-OH, D_2O exchangeable); ^{13}C-nmr, see table 1; ms, *m/z* 309 (M^+, 65.6%), 292 (1.4), 254 (33.7), 241 (100), 225 (25.4), 213 (8.5), 212 (8.5), 196 (6.4), 184 (5.8), 182 (5.3), 168 (3.7), 167 (3.5), 154 (5.6), 140 (2.7), and 127 (4.5).

BIOLOGICAL ACTIVITY OF THE COMPOUNDS **1-4**.—Each of the synthesized compounds **2-4** as well as acronycine (**1**) itself was evaluated in the KB test system *in vitro* (19). Acronycine (**1**) and 1,2-dihydroacronycine (**2**) were weakly active, but neither of the *O*-nor derivatives **3** and **4** was cytotoxic.

ASSIGNMENT OF THE ^{13}C-NMR SPECTRA.—Broad band and single-frequency off-resonance decoupled ^{13}C-nmr spectra of acronycine (**1**), dihydroacronycine (**2**), noracronycine (**3**), and dihydronoracronycine (**4**) were obtained at 45.26 MHz. An INEPT experiment (20-23) of acronycine (**1**) was carried out at 90.54 MHz. Chemical shift assignments (table 1) were made as follows:

Acronycine (**1**). Assignments for the carbonyl, the methoxy carbon, the *N*-methyl and the aliphatic methyl groups were readily achieved (24), and C-3 was assigned by comparison with dimethylchromene (25), morusin (26), and neorautenane (27). Comparison with published data, particularly those relating to the compounds 1,3-dimethoxy-10-methylacridone (**5**) (14), gravacridondiol (**6**) (14), acridone (**7**) (14), morusin (**8**) (26), and calculated (24) shifts for the compound **9** permitted the assignment of C-5, C-6a, C-7a, C-8, C-10, C-11, and C-12b.

Three sets of signals remained to be assigned: (a) at 144.30 and 146.51 ppm (C-11a and C-12a), (b) at 121.49, 121.53, and 122.72 ppm (C-1, C-2 and C-9), and (c) at 159.02 and 162.75 ppm (C-4a and C-6). Although in 1,2-dihydroacronycine (2) the signal at 121.64 ppm could be assigned to C-9, this did not serve to assign all the signals in the region of 122 ppm in acronycine itself.

A fully-coupled ^{13}C-nmr spectrum of acronycine served to make this distinction and also permitted unambiguous assignment of all the remaining resonances. Thus, distinction between C-11a and C-12a could be made on the basis that C-11a should be a more complex signal because it couples ($^3J_{CH}$) to both

TABLE 1. ^{13}C-nmr assignments of acronycine (**1**) and derivatives.[a]

Carbon	Chemical Shifts (ppm)			
	1	**2**	**3**	**4**
1	121.53	22.90	122.12	22.98
2	122.72	33.39	123.09	34.34
3	76.01	75.01	75.57	75.03
4a	162.75	160.80	165.55	162.69
5	94.19	95.88	98.06	99.04
6	159.02	159.67	161.77	162.04
6a	110.37	111.20	107.12	107.45
7	176.77	177.87	181.30	181.46
7a	125.26	126.12	121.66	122.50
8	126.77	127.09	126.44	126.22
9	121.49	121.64	121.58	121.80
10	132.21	132.35	133.88	133.56
11	115.65	116.33	116.19	116.51
11a	144.30	146.16	144.61	145.45
12a	146.51	150.34	145.21	148.02
12b	102.82	101.71	101.06	100.12
3-(-CH_3)$_2$	26.54	26.84	27.02	26.92
12-CH_3	43.86	44.23	43.69	43.75
6-OCH_3	55.99	56.18	—	—

[a]Recorded in $CDCl_3$ at 45.26 MHz; chemical shifts are recorded in δ (ppm) using the TMS as standard, $\delta_{CDCl_3} = +76.9$ ppm.

10-CH and 8-CH, whereas C-12a should couple only to 1-CH. The widths at half-peak height (C-11a, 21 Hz; C-12a, 6.5 Hz) substantiated this analysis. Similarly, C-6 should have no $^3J_{CH}$, merely some weaker coupling through oxygen with the attached methyl, whereas C-4a is coupled to 1-CH and should, therefore, be a somewhat broader signal. Again, visual inspection permitted this distinction.

Carbon-2 is expected to be the most complex doublet in the fully coupled spectrum because it should couple markedly to the six protons of the geminal dimethyl group. Inspection of an expanded spectrum permitted a broadened doublet at 122.72 ppm to be attributed to C-2. A signal at 121.53 ppm had orig-

TABLE 2. Coupling constants ($^1J_{CH}$ and $^3J_{CH}$) in acronycine (**1**).

Carbon	$^1J_{CH}$ (Hz)	$^3J_{CH}$ (Hz)
1	163.6(163.8)[a]	—
2	164.8(162.6)	(~3.0)
3	—	—
4a	—	—
5	162.4(161.6)	—
6	—	4.9
6a	—	4.9
7	—	—
7a	—	8.6(5.6)
8	163.0(163.9)	7.3(7.7)
9	163.6(163.5)	8.6
10	161.1(157.9)	8.6(9.0)
11	161.1(158.9)	7.3(6.0)
11a	—	—
12a	—	2.4
12b	—	—
3-(-CH_3)$_2$	127.4(128.1)	—
12-CH_3	140.0(140.0)	—
6-OCH_3	144.9(144.7)	—

[a]Data in parentheses are from the INEPT experiment.

nally been assigned to C-1 and C-9. However, examination of the scale-expanded, fully coupled spectrum permitted calculation and assignment of two distinct chemical shifts for these carbons, since a slightly broadened doublet was observed for the signal at 121.53 ppm, whereas a clear doublet of doublets (J=8.6, 163.6 Hz) was disclosed for the signal at 121.49 ppm. These signals can, therefore, be unambiguously attributed to C-1 (no $^3J_{CH}$ coupling) and C-9 ($^3J_{CH}$ coupling to 11-CH), respectively.

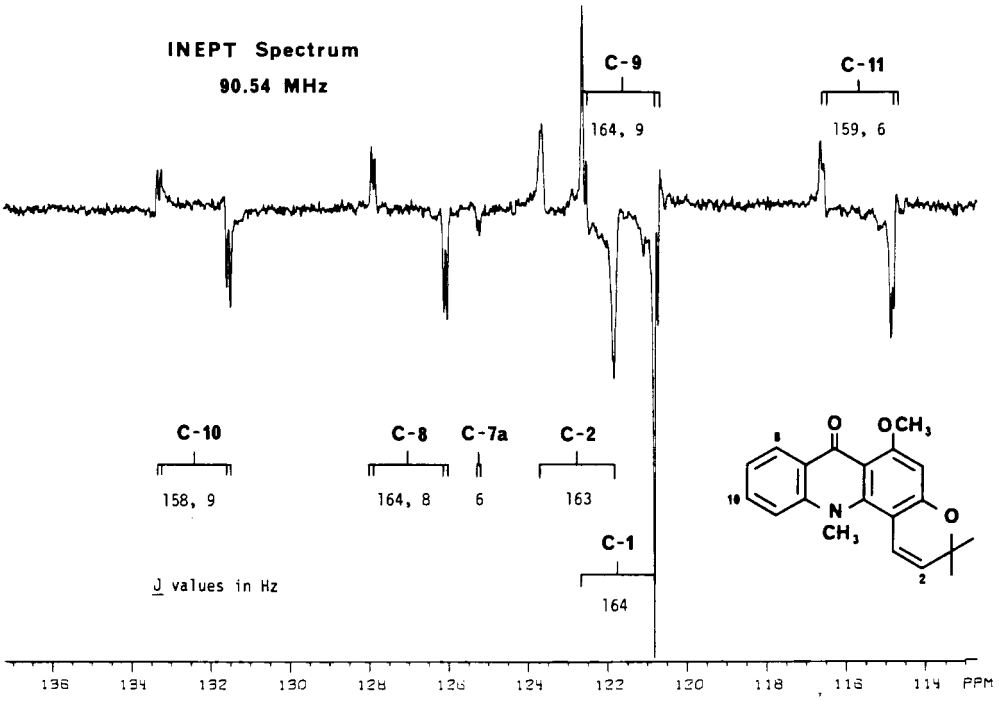

FIGURE 1. INEPT spectrum of acronycine at 90.54 MHz in $CDCl_3$, $\delta_{CDCl_3}=+76.9$ ppm. J values have been rounded out to nearest whole number.

A distinction between 121.53 and 122.72 ppm for C-1 and C-2 was confirmed from an INEPT spectrum (20-23), obtained at 90.54 Hz, in which the signal at 122.72 ppm was observed to exhibit long-range coupling ($^3J_{CH}\sim3$ Hz) with the gem-dimethyl protons. The INEPT spectrum (figure 1) also substantiated the assignment of many of the other carbons based on the long-range coupling constants summarized in table 2 in comparison with the data obtained from the fully coupled spectrum.

The fully coupled spectrum also allowed a number of other assignments to be verified (table 2) and coupling constants established. For example, literature data on the 2,2-dimethyl-chromene system (25,26,28) would suggest that C-1 should be in the region of 114-116 ppm and C-2 in the region of 127-131 ppm.[5] Thus, in the former instance confusion might arise with C-11 and in the latter case with C-10. In acronycine, therefore, C-1 is *deshielded* by approximately 7 ppm, and C-2 is *shielded* by approximately 6 ppm of their expected values. There is also one other carbon that has an unexpected shift, namely N-CH_3. Literature data (13,14) for the N-CH_3 in substituted acridone derivatives (table 3) suggest that this carbon should appear in the region of 31-34 ppm in acronycine. The observed shift, however, is 43.86 ppm, and a similar shift is observed for the other acronycine derivatives. Closest correspondence is seen with an acridone bearing a 4-methoxy group and suggests that there is considerable steric interaction between the N-CH_3 and C-1, possibly causing a perturbation in the chromene ring system.

Two observations are relevant at this point. Similar downfield shifts have been observed (11,29) for sterically crowded arylmethoxyl groups. For example, the 4-methoxyl group in a 3,4,5-trisubstituted phenethylamine is 5-6 ppm downfield of 3- and 5-methoxyl groups and is in an out-of-plane conformation (29). It is well established (30) that in *N*-methyl acridone (**10**) the methyl group is *in* the plane of the nucleus, whereas in 5-bromodihydroacronycine (**11**) (8), and in an acronycine dimer (31), the methyl group is 18° out of the plane. This effect is clearly related to the presence of a substituent at C-4, as the recent work on the pyrano-acridones **12** and **13**, which display N-CH_3 resonances at 43.07 and 33.88 ppm, respectively (16), shows. A somewhat smaller effect (~3.5 ppm) is observed in the rutacridone series (15).

[5]It should be noted that the assignments for the C-3 and C-4 chromene carbons in neorautenane (27) should be reversed.

TABLE 3. Chemical shift of the 10-methyl group in the 10-methyl-acrid-9-one series (14).

Compound	Mean Chemical Shift δ (ppm)	Number of examples
10-Methylacridone	33.5	1
No 4-substituent, 3-O-substituent 1-O-substituent	34.1±0.2	3
4-Substituent, 3-O-substituent 1-O-substituent	32.0±0.8	6
4-OCH_3 substituent	41.3±0.3	3
Acronycine and derivatives	43.88±0.21	4

1,2-Dihydroacronycine (2). With the completion of an unambiguous set of assignments for acronycine (**1**), assignments for the dihydroderivative **2** were relatively straightforward. As expected, two new methylene carbons appeared in the aliphatic region (δ 22.90 and 33.39). Comparison with the corresponding carbons (δ 26.7 and 32.2) in aspulvinone A (**14**) (32) indicates that these carbons can be assigned to C-1 and C-2, respectively. Some minor shifts were observed in ring C and for C-11a, but very little change was observed for either the resonance of the carbonyl (C-7) or the chromene ether carbon (C-3), and the N-CH_3 remains deshielded at 44.23 ppm.

Noracronycine (**3**) *and 1,2-dihydronoracronycine* (**4**). The spectra of **3** and **4** were assigned by analogy with those of **1** and **2**. Prior data (24,33) for the aromatic shifts induced on changing from -OCH_3 to -OH were somewhat misleading in assigning the ring C resonances, because of the possibility for hydrogen bonding with the acridone carbonyl group. Thus, in both **3** and **4**, C-4a and C-6 were shifted downfield, whereas C-6a, C-12a, and C-12b were each shifted upfield. The frequencies of C-6a and C-7a were each shifted upfield by about 3.6 ppm, whereas the carbonyl (C-7) and C-5 frequencies were shifted downfield by 3.6 ppm and 3.16-3.87 ppm, respectively. These results are in agreement with those obtained previously for compounds in the acridone series (14). Chemical shift differences between the resonances for C-1 and C-2 in **1** and **2**, and **3** and **4** were essentially identical (C-1: 98.63, 99.14; C-2: 89.33, 88.75).

DISCUSSION

Assignment of the ^{13}C-nmr spectrum of acronycine (**1**) has been completed through examination of the fully coupled, broad-band decoupled, and INEPT spectra. Some difficulty was experienced assigning signals in the region of 121-123 ppm, but observation of $^3J_{CH}$ in the fully coupled spectrum permitted these signals to be attributed unambiguously. A substantial (~11 ppm) deshielding of the *N*-methyl resonance was observed reflecting the out-of-plane nature of this group compared with the aromatic nucleus. Assignments were also made for the dihydro-, nor- and dihydronor- derivatives **2-4**. Characteristic shifts were observed for carbons 6a, 7, and 7a on removal of the methyl ether carbon and the formation of an intra-molecular hydrogen bond between the carbonyl at C-7 and the phenolic group at C-6.

This is the first unambiguous assignment of the ^{13}C-nmr spectrum of a compound in this important series of alkaloids.

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LITERATURE CITED

1. G. K. Hughes, F. N. Lahey, J. R. Price, and L. J. Webb, *Nature*, **162**, 223 (1948).
2. F. N. Lahey and W. C. Thomas, *Aust. J. Sci. Res.*, **2A**, 423 (1949).
3. L. J. Drummond and F. N. Lahey, *Aust. J. Sci. Res.*, **2A**, 630 (1949).
4. G. H. Svoboda, *Lloydia*, **29**, 206 (1966).
5. G. H. Svoboda, G. A. Poore, P. J. Simpson, and G. B. Bodor, *J. Pharm. Sci.*, **55**, 758 (1966).
6. P. L. MacDonald and A. V. Robertson, *Aust. J. Chem.*, **19**, 275 (1966).
7. T. R. Govindachari, B. R. Pai, and P. S. Subramaniam, *Tetrahedron*, **22**, 3245 (1966).
8. J. Z. Gougoutas and B. A. Kaski, *Acta Cryst.*, **26B**, 853 (1970).
9. G. A. Cordell, H. H. S. Fong, D. D. Soejarto, and D. P. Waller, unpublished results.
10. P. A. Claret and A. G. Osborne, *Spectroscopy Lett.*, **9**, 167 (1976).
11. A. Ahond, F. Picot, P. Potier, C. Poupat, and T. Sévenet, *Phytochemistry*, **17**, 166 (1978).
12. N. M. D. Brown, M. F. Grundon, D. M. Harrison, and S. A. Surgenor, *Tetrahedron*, **36**, 3579 (1980).
13. I. Mester, D. Bergenthal, Zs. Rózsa, and J. Reisch, *Z. Naturforsch.*, **34b**, 516 (1979).
14. D. Bergenthal, I. Mester, Zs. Rózsa, and J. Reisch, *Phytochemistry*, **18**, 161 (1979).
15. I. Mester, J. Reisch, Zs. Rózsa, and K. Szendrei, *Heterocycles*, **16**, 77 (1981).
16. J. Reisch, I. Mester, S. K. Kapoor, Zs. Rózsa, and K. Szendrei, *Liebigs Ann. Chem.*, 85 (1981).
17. J. R. Beck, R. Kwok, R. N. Booher, A. C. Brown, L. E. Patterson, P. Pranc, B. Rockey, and A. Pohland, *J. Am. Chem. Soc.*, **90**, 4706 (1968).
18. R. D. Brown, L. J. Drummond, F. N. Lahey, and W. C. Thomas, *Aust. J. Sci. Res.*, **2A**, 622 (1949).
19. R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, **3** (2), 1 (1972).
20. G. A. Morris and R. Freeman, *J. Am. Chem. Soc.*, **101**, 760 (1979).
21. G. A. Morris, *J. Am. Chem. Soc.*, **102**, 428 (1980).
22. D. M. Dodrell and D. T. Pegg, *J. Am. Chem. Soc.*, **102**, 6388 (1980).
23. D. M. Dodrell, D. T. Pegg, W. Brooks, and M. R. Bendall, *J. Am. Chem. Soc.*, **103**, 727 (1981).
24. G. C. Levy, R. L. Lichter, and G. L. Nelson, "Carbon-13 N.M.R. Spectroscopy, 2nd ed.," John Wiley and Sons, New York, NY, 1980, pp. 338f.
25. C. Konno, Y. Oshima, and H. Hikino, *Planta Med.*, **32**, 118 (1977).
26. T. Nomura and T. Fukai, *Heterocycles*, **12**, 1289 (1979).
27. J. C. Breytenbach and G. J. H. Rall, *J. Chem. Soc., Perkin Trans. I*, 1804 (1980).
28. E. Wenkert and H. E. Gottlieb, *Phytochemistry*, **16**, 1811 (1977).
29. J. J. Knittel and A. Makriyannis, *J. Med. Chem.*, **24**, 906 (1981).
30. A. V. Dzyabckenko, V. E. Zavodnik, and V. K. Belskii, *Kristallografia*, **25**, 72 (1980).
31. S. Funayama, G. A. Cordell, H. Wagner, and H. Lotter, *J. Nat. Prod.*, in press (1983).
32. H. Sugiyama, N. Ojima, M. Kobayashi, Y. Senda, J. Ishiyama, and S. Seto, *Agr. Biol. Chem.*, **43**, 403 (1979).