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CHEMISTRY OF ACRONYCINE IX. FORMATION OF DIMERS OF NORACRONYCINE-MECHANISTIC STUDIES[1]

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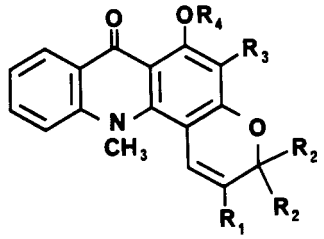
ABSTRACT.—The mechanisms of two acid-mediated coupling reactions of noracronycine (**2**) have been studied using deuterium-labeled acids. Dimerization of noracronycine (**2**) using D_2SO_4 afforded AB-1-d_4 (**8**), whereas coupling **2** and dihydronoracronycine (**3**) in 10N DCl/MeOD (1:2.5) afforded dihydro AB-2-d_8 (**15**). In addition, in the dimerization reaction of **2** using D_2SO_4-CH_3OD (1:1) followed by dilution with D_2O, AB-1-d_{16} (**19**) was obtained instead of **8**. Initial protonation at the C_2 position of noracronycine (**2**) was verified during these studies.

Acronycine (**1**), an alkaloid from the Australian scrub ash *Baurella simplicifolia* (Endl.) Hartley (Rutaceae) (2,3), possesses a broad spectrum of in vivo antineoplastic activity (4,5). Because of our interest in the development of acronycine (**1**) and/or related compounds as antineoplastic agents, we have been investigating the chemical and spectroscopic properties of acronycine (**1**) and its derivatives. Thus far, we have reported on ^{1}H- and ^{13}C-nmr studies of acronycine (**1**) and its simple derivatives (6,7), on the dimerization (8) and trimerization (9) of noracronycine (**2**), on the unexpected reactivity of dihydronoracronycine (**3**) (10), on the selective synthesis of dimers and trimers of noracronycine (**2**) and related compounds (1), and on the facile conversion of dihydronoracronycine (**3**) to dihydroisonoracronycine (**4**) (11).



	R_1	R_2	R_3	R_4
1	H	CH_3	H	CH_3
2	H	CH_3	H	H
9	D	CH_3	D	H
10	D	CH_3	D	CH_3
18	D	CD_3	D	H

In the course of these experiments, it was found that AB-1 (**5**), a dimer composed of two noracronycine (**2**) molecules, could be selectively synthesized by treating noracronycine (**2**) with 98% H_2SO_4, (4% yield) or a mixture (1:1) of MeOH and 98% H_2SO_4 (40% yield), at room temperature under N_2. On the other hand, when a 1:10 mixture of noracronycine (**2**) and dihydronoracronycine (**3**) was refluxed on a steam bath with a mixture of MeOH-10N aqueous HCl (5:2), dihydro AB-2 (**6**), a dimer composed of isonoracronycine (**7**) and dihydronoracronycine (**3**) was obtained in 86% yield (8). In order to clarify the mechanisms involved in these two dimerization reactions, they were performed using 98% D_2SO_4, a mixture of MeOD and 98% aqueous (D_2O) D_2SO_4 and a mixture of MeOD-10N aqueous (D_2O) DCl, respectively.

[1]For the previous paper in this series see reference 1.

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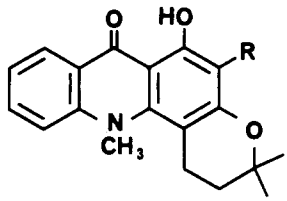
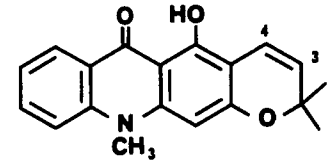


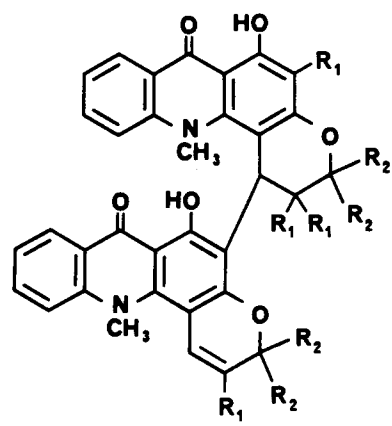
	R
3	H
11	D



4 3,4-H_2
7

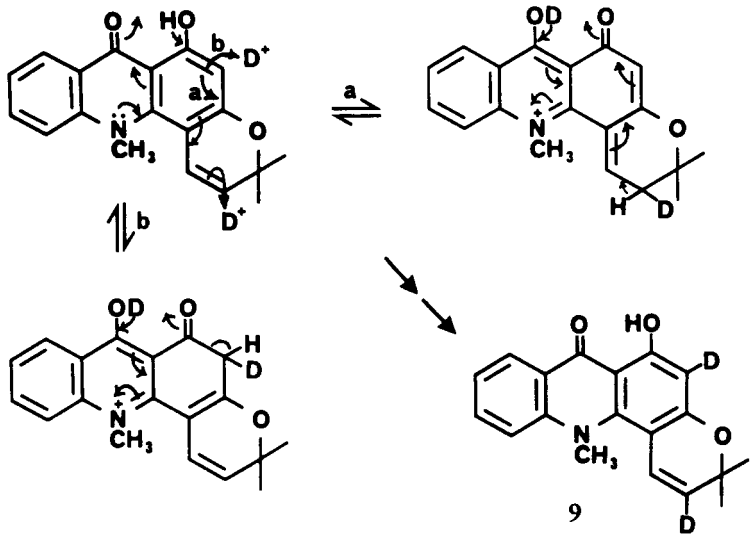
Noracronycine (**2**) was dissolved in 98% D_2SO_4, and the solution was stirred under N_2 at room temperature. After two days, the two products were shown by tlc comparison with authentic samples to have the same chromatographic mobility as AB-1 (**5**) and noracronycine (**2**).

The mass spectrum of deutero AB-1 indicated a M^+ at *m/z* 618, 4 mass units higher than the AB-1 (**5**, *m/z* 614) obtained by using 98% H_2SO_4 (12). Location of the deuterium label was determined through nmr spectroscopy. In the ^{1}H-nmr spectrum, the 2-H_2 and the 2′-methine signal were not observed, and the 5-H was substantially (ca. 80%) reduced in intensity. As expected from these changes, the dibenzylic proton (1-H), originally observed as a doublet of doublets (J=7.3 and 11.7 Hz) and the 1′-methine originally observed as a doublet (J=9.6 Hz) (1,8), were reduced in complexity to singlets at δ 5.153 and 6.170, respectively. Hence, the structure of AB-1-d_4 was established to be **8**, in which the increase of four mass units is readily explained.



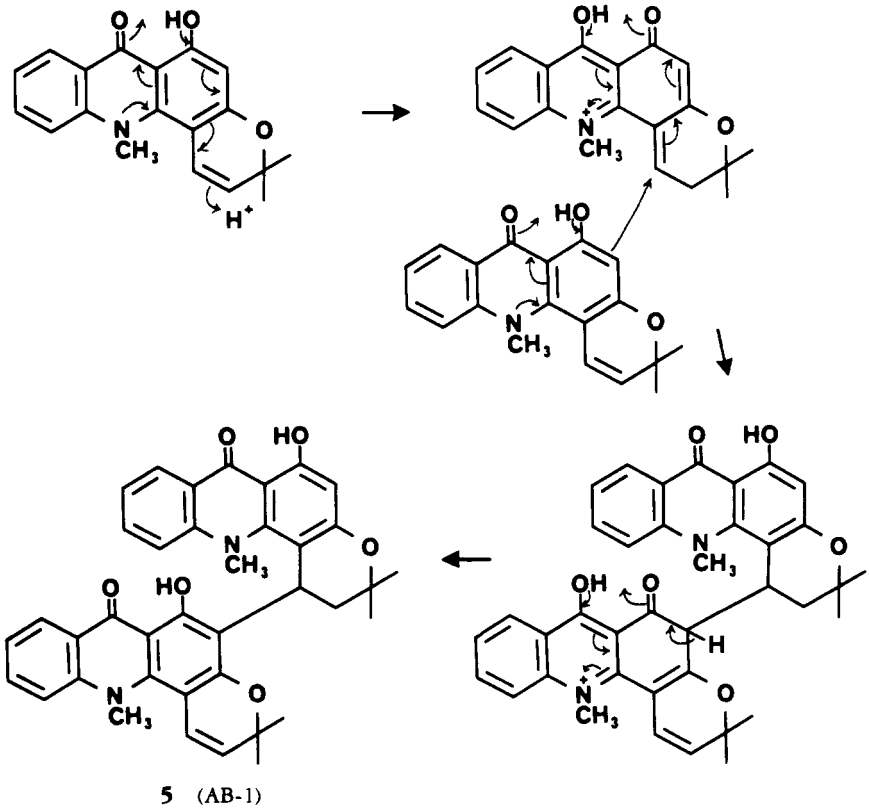
	R_1	R_2
5	H	CH_3
8	D	CH_3
19	D	CD_3

The unreacted noracronycine was also evaluated by ms and ^{1}H nmr. The M^+ at *m/z* 309 was 2 mass units higher than that of noracronycine (**2**, M^+ 307) (7). In the ^{1}H-nmr spectrum, no 2-methine signal was observed, and the H-5 singlet was reduced to about a quarter of its usual intensity (7). In agreement with these changes, the H-1 doublet (δ 6.565, J=9.6 Hz) (7) was simplified to a singlet. From the accumulated data, noracronycine-d_2 was demonstrated to have the structure **9**. Because the deuterium incorporation at C-2 of noracronycine (**2**) was essentially 100%, it was estimated that equilibrium reaction a (Scheme 1) developed rapidly. At the same time, exchange at C-5 was also occurring (reaction b). If the second noracronycine unit is trapped instead of D^+, dimerization occurs to afford AB-1.



SCHEME 1. Formation of Noracronycine-d_2 (**9**)

Previously (8), a reaction mechanism was presented for the formation of AB-1 (**5**) under acidic conditions, which was initiated by protonation at C_2 followed by nucleophilic attack of a second unit of **2**. In the presently described studies, initial protonation at C-2 or noracronycine (**2**) and the nucleophilic attack of C-5 of the second noracronycine unit have been verified (Scheme 2).



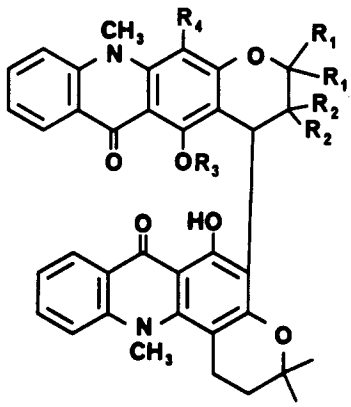
5 (AB-1)

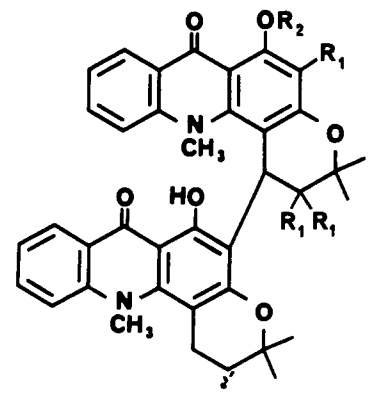
SCHEME 2. Mechanism of Formation of AB-1

When the same reaction was conducted using acronycine (**1**) instead of noracronycine (**2**), no dimerization reaction was observed. In the deutero acronycine (**10**) isolated 100% D-exchange at C-2 was also observed.

When a 1:10 mixture of noracronycine (**2**) and dihydronoracronycine (**3**) was refluxed with methanolic HCl, the linear-angular type dimer, dihydro AB-2 (**6**), was obtained in 86% yield (1, 8). To clarify this reaction mechanism, the same reaction was conducted using a 2:5 mixture of 10N DCl and CH_3OD. Two compounds, chromatographically identical with dihydro AB-2 (**6**) and dihydronoracronycine (**3**), were isolated by preparative tlc. As expected, the M^+ of the dihydronoracronycine obtained appeared at *m/z* 310, one mass unit higher than **3**. In its ^{1}H-nmr spectrum, the aromatic singlet at δ 6.17 was reduced in intensity by about 80%. No other changes were observed. Consequently, the structure of dihydronoracronycine-d_1 was defined as **11**.

On the other hand, dihydro AB-2 (**6**) was regarded as being formed by the rearrangement of dihydro AB-1 (**12**) as shown in Scheme 3 (8). As a result, during the formation of deuterodihydro AB-1 (**13**), it was anticipated that three deuteriums would be introduced, at the C_2-methylene and at C-5. In the process of the rearrangement, **13** would lose the C_5-D and gain a deuterium at C-12 to afford a dihydro AB-2-d_3 (14).



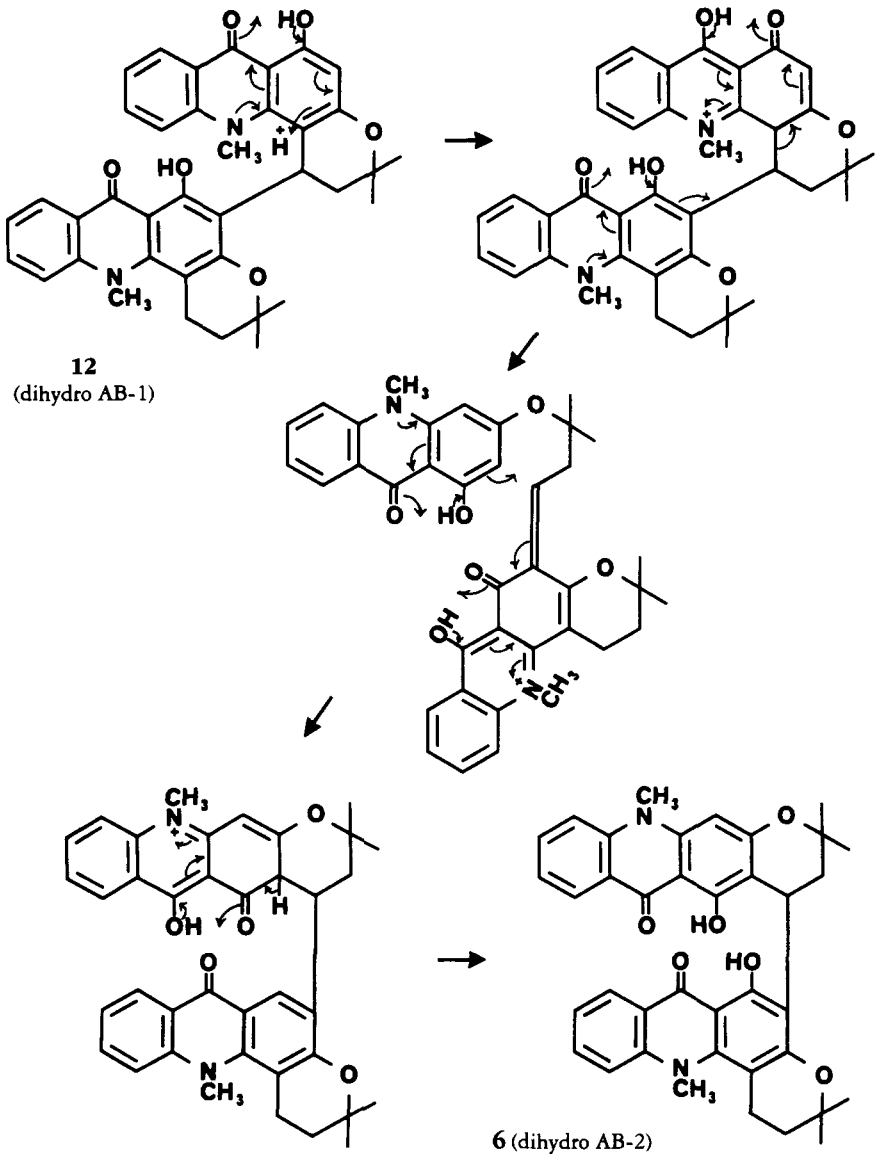


	R_1	R_2	R_3	R_4
6	CH_3	H	H	H
14	CH_3	D	H	D
15	CD_3	D	H	H
17	CH_3	H	CH_3	H

	R	R_2
12	H	H
13	D	H
16	H	CH_3

Such a compound would have an estimated M^+ at *m/z* 619. However, the observed M^+ of deuterodihydro AB-2 was at *m/z* 625, an increase of 9 mass units. Examination of the ^{1}H-nmr spectrum of this compound showed that the C_3-methylene was fully deuterated, and surprisingly, a set of geminal methyl signals had also disappeared. In the ^{1}H-nmr spectrum of dihydro AB-2 (**6**), four methyl signals assigned to the two geminal signals are observed, namely, δ 0.700 (3H, s), 1.157 (3H, s), 1.435 (3H, s), and 1.495 (3H, s) (1, 8). But in the ^{1}H-nmr spectrum of the d_8 derivative, only two such signals were observed, at δ 0.703 and δ 1.161. These two higher field signals had previously been assigned to the lower, angular unit of dihydro AB-2 (**6**). No deuterium incorporation at the C-5 position was observed, and the structure of deuterodihydro AB-2 was therefore defined as **15**. Consequently, in addition to the rearrangement mechanism shown in Scheme 3 (8), a ring-opening mechanism (Scheme 4) may also be occurring during the formation of dihydro AB-2-d_8 (**15**).

When acronycine (**1**) was used instead of noracronycine (**2**) in the coupling reaction described above, no rearrangement of the upper unit occurred (**1**), and dihydromethyl

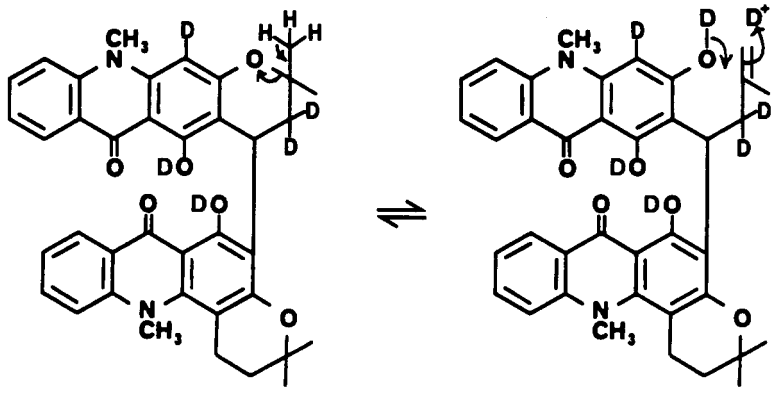


SCHEME 3. Rearrangement of dihydro AB-1 (**12**) to dihydro AB-2 (**6**)

AB-1 (**16**) was obtained instead of dihydromethyl AB-2 (**17**) (1). This fact indicated that the C_6-OH must perform an important role in the rearrangement from dihydro AB-1 (**12**) to dihydro AB-2 (**6**).

The observation that C-5 position of deutero AB-2 was not labeled, even though it should be replaced by D during the rearrangement reaction, suggested that some of the D exchanged at this position might be replaced by H during the work-up process. Consequently, the following experiment was conducted using D_2O for the initial dilution during the work-up process.

Previously, it was shown that when noracronycine (**2**) was treated with 98% H_2SO_4-MeOH (1:1)), AB-1 (**5**) was obtained in 39% yield (1). Therefore, noracronycine (**2**) was treated with 98% D_2SO_4-MeOD (1:1) and, at the conclusion, the reaction mixture was diluted with D_2O (instead of H_2O) and extracted with $CHCl_3$. The combined $CHCl_3$ layers were washed successively with D_2O, 5% $NaHCO_3/H_2O$



SCHEME 4. Formation of dihydro AB-2-d_9

solution and H_2O. Deuteronoracronycine and deutero AB-1 were purified by preparative tlc and the mass and ^{1}H-nmr spectra of these compounds were examined.

The M^+ of the deuteronoracronycine obtained was not at *m/z* 309 as expected, but rather at *m/z* 315. In accordance with this mass increase, the ^{1}H-nmr spectrum indicated the signals corresponding to the geminal methyl group to be absent, and the C_5-H to be completely exchanged (in the ^{1}H-nmr spectrum of **9**, 20% C_5-H was observed). Only nine protons were observed in the ^{1}H-nmr spectrum of this compound, namely, the N-CH_3 (δ 3.902), a singlet for C_1-H (δ 6.546), four coupled aromatic protons (δ 7.295, 7.423, 7.711 and 8.360), and a hydrogen bonded OH (δ 14.713). Consequently, the structure of the deuteronoracronycine obtained herein was defined as **18**.

Examination of the ^{1}H-nmr spectrum of the deutero AB-1 obtained in this experiment indicated the absence of the geminal methyl signals, the C_5-H, the C_2 methylene protons, and the $C_{2'}$-H. These changes were in accordance with the ms data, in which a M^+ was observed at *m/z* 630, indicating the presence of 16 deuteriums. Consequently, the structure of the deutero AB-1 obtained through this experiment was concluded to be **19**.

Because exchange was observed not only at the C-2 and C-2′ positions, but also of the C_5-H and the geminal methyl groups, it was thought that when the reaction was complete, all of these positions were exchanged by D, but through the dilution with H_2O, the geminal CD_3 and part of the C_5-D were re-exchanged to CH_3 and C_5-H, respectively.

Through these experiments, it was also found that the geminal methyls of the upper unit of deuterodihydro AB-2 (**15**) after workup are still CD_3. Therefore, it appears that even after the dilution with H_2O, no reexchange of these upper geminal CD_3 to CH_3 takes place in the case of deuterodihydro AB-2 (**15**). Opening of the lower chroman ring is therefore considerably more facile than cleavage of the chroman ring in he upper, linear unit. This ties in well with the observed rearrangement of dihydronoracronycine (**3**) to its linear isomer **4** (11), which is apparently not an equilibrium process.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mass spectra were obtained on a Varian MAT 112S double focusing spectrometer. The ^{1}H-nmr spectra were obtained in $CDCl_3$ with a Varian T-60A instrument, operating at 60 MHz with a Nicolet Model TT-7 Fourier Transform attachment or on a Nicolet NT-360 instrument, operating at 360 MHz, at the NSF Regional NMR Facility at the University of Illinois at Urbana, Urbana-Champaign, Illinois. Tetramethylsilane (TMS) was used as an internal standard and chemical shifts were recorded in δ ppm units. Silica gel GHLF plates (Analtech, Inc., 75 Blue Hen Drive, Newark, Delaware 19711) were used for preparative tlc and tlc analyses.

PREPARATION OF ACRONYCINE (**1**), NORACRONYCINE (**2**), AND DIHYDRONORACRONYCINE

(**3**).—The preparation and physical and spectral properties of these compounds were described previously (6,7).

TREATMENT OF NORACRONYCINE (**2**) WITH 98% H_2SO_4 AT ROOM TEMPERATURE.—The reaction procedures and physical and spectral properties of AB-1 (**5**) were described previously (1).

TREATMENT OF NORACRONYCINE (**2**) WITH 98% D_2SO_4 AT ROOM TEMPERATURE.—Noracronycine (**2**, 25.4 mg) was dissolved in 98% D_2SO_4 (6.0 ml), and the orange-yellow solution was stirred under a N_2 atmosphere for 2 days. The reaction mixture was diluted with H_2O (50 ml) and extracted with $CHCl_3$ (2×50 ml). The combined $CHCl_3$ layers were successively washed with 5% $NaHCO_3$ solution (50 ml) and H_2O (50 ml) and dried (Na_2SO_4). Concentration of the filtered $CHCl_3$ layer in vacuo afforded a yellow powder which, through preparative tlc on silica gel eluting with $CHCl_3$, afforded deutero AB-1 (**8**) and deuteronoracronycine (**9**). Deutero AB-1 (**8**) was obtained as an orange-yellow powder: ^{1}H nmr ($CDCl_3$, 360 MHz) δ 0.572 (3H, s, 13′- or 14′-CH_3), 1.142 (3H, s, 14′- or 13′-CH_3), 1.476 (3H, s, 13- or 14-CH_3), 1.591 (3H, s, 14- or 13-CH_3), 3.732 (3H, s, N-CH_3), 3.770 (3H, s, N-CH_3), 5.153 (1H, s, H-1), 6.170 (1H, s, H-1′), 6.330 (0.2H, s, H-5), 6.909 (1H, d, J=8.5 Hz, H-11), 7.110 (1H, t, J=7.4 Hz, H-9), 7.369 (1H, t, J=8.0 Hz, H-9′), 7.401 (1H, t, J=8.8 Hz, H-10), 7.413 (1H, d, J=8.8 Hz, H-11′), 7.753 (1H, t, J=7.6 Hz, H-10′), 8.227 (1H, d, J=7.7 Hz, H-8 or H-8′), 8.475 (1H, d, J=7.6 Hz, H-8′ or H-8), 14.324 (1H, s, 6-OH), and 15.619 (1H, s, 6′-OH); ms, *m/z* 618 (M^+, 100%), 603 (54), 575 (53), 376 (15), 375 (24), 374 (23), 361 (11), 333 (32), 332 (40), 323 (26), 322 (71), 321 (95), 312 (29), 311 (79), 310 (86), 307 (40), 306 (25), 305 (28), 294 (28), 293 (28), 280 (30), 279 (41), 253 (30), 252 (32), 244 (25), and 243 (20).

Deuteronoracronycine (**9**) was obtained as a yellow powder: ^{1}H nmr ($CDCl_3$, 60 MHz) δ 1.50 (6H, s, 13- and 14-CH_3), 3.82 (3H, s, N-CH_3), 6.18 (0.25 H, s, H-5), 6.49 (1H, s, 1-H), 7.05-7.79 (3H, m, H-9, H-10 and H-11), 8.26 (1H, dd, J=1.5 and 7.8, Hz H-8), and 14.67 (1H, s, D_2O exchangeable, 6-OH); ms *m/z* 310 (13%), 309 (M^+, 32), 308 (M^+, 14), 295 (31), 294 (100), 293 (42), 280 (11), 279 (33), 278 (15), 147 (13), and 125.5 (11).

TREATMENT OF ACRONYCINE (**1**) WITH 98% D_2SO_4 AT ROOM TEMPERATURE.—Acronycine (**1**, 12.0 mg) was dissolved in 98% D_2SO_4 (3.0 ml) and the orange solution was stirred under a N_2 atmosphere for 2 days. The reaction mixture was diluted with H_2O (50 ml), neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (3×50 ml). The combined $CHCl_3$ layers were dried (Na_2SO_4) and concentrated in vacuo to afford a yellow powder (11.4 mg). Preparative tlc on silica gel eluting with $CHCl_3$-MeOH (99:1) afforded deuteroacronycine (**10**, 7.7 mg) and a mixture of minor products (2.9 mg).

Deuteroacronycine (**10**) was obtained as pale yellow fine needles: ^{1}H nmr ($CDCl_3$, 60 MHz) δ 1.52 (6H, s, 13- and 14-CH_3), 3.78 (3H, s, N-CH_3), 3.96 (3H, s, -OCH_3), 6.30 (0.9H, s, H-5), 6.50 (1H, s, H-1), 7.05-7.73 (3H, m, H-9, H-10 and H-11), and 8.37 (1H, dd, J=1.2 and 7.7 Hz, H-8); ms *m/z* 323 (M^+, 10%), 322 (M^+, 11), 321 (2), 309 (5), 308 (18), 307 (20), 294 (7), 293 (9), 292 (5), 264 (9), and 263 (12).

COUPLING OF NORACRONYCINE (**2**) AND DIHYDRONORACRONYCINE (**3**) IN 10N HCl-MeOH (1:25) UNDER REFLUX.—The reaction procedures and physical and spectral properties of dihydro AB-2 (**6**) were described previously (1,8).

COUPLING OF NORACRONYCINE (**2**) AND DIHYDRONORACRONYCINE (**3**) IN 10N DCl-MeOD (1:25) UNDER REFLUX.—Noracronycine (**2**, 2.2 mg) and dihydronoracronycine (**3**, 22.0 mg) were dissolved in MeOD (7.5 ml) and 10N aqueous DCl (3.0 ml), and the solution heated on a steam bath for 6 h. The reaction mixture was diluted with H_2O (50 ml), neutralized with $NaHCO_3$, and extracted with $CHCl_3$ (2×100 ml). The combined $CHCl_3$ layers were washed with H_2O (100 ml), dried (Na_2SO_4), and concentrated in vacuo to afford an orange-yellow powder (26.8 mg). Through repeated preparative tlc on silica gel eluting with $CHCl_3$ and C_6H_6-EtOAc (9:1), deuterodihydro AB-2 (**15**, 3.7 mg) and deuterodihydronoraronycine (**11**, 19.6 mg) were isolated.

Deuterodihydro AB-2 (**15**) was obtained as an orange-yellow powder: ^{1}H nmr ($CDCl_3$, 360 MHz) δ 0.703 (3H, s, 13′- or 14′-CH_3), 1.161 (3H, s, 14′- or 13′-CH_3), 1.572 (2H, m, 2′-CH_2), 2.798 (2H, m, 1′-CH_2), 3.799 (3H, s, N-CH_3), 3.837 (3H, s, N-CH_3), 4.892 (1H, s, H-4), 6.368 (1H, s, H-12), 7.220 (1H, t, J=7.7 Hz, H-8 or H-9′), 7.269 (1H, t, J=7.7 Hz, H-9′ or H-8), 7.403 (1H, d, J=8.5 Hz, H-10 or H-11′), 7.458 (1H, d, J=8.8 Hz, H-11′ or H-10), 7.678 (2H, t, J=7.7 Hz, H-9 and H-10′), 8.396 (1H, d, J=7.9 Hz, H-7 or H-8″), 8.418 (1H, d, J=7.7 Hz, H-8′ or H-7), 14.715 (1H, s, OH), and 14.926 (1H, s, OH); ms *m/z* 624 (M^+, 15%), 314 (13), 313 (12), 312 (12), 311 (12), 310 (17), 309 (31), 297 (20), 296 (37), 295 (30), 294 (23), 293 (14), 275 (13), 255 (11), 254 (20), 252 (11), 242 (18), 241 (51), 226 (11), 225 (17), 213 (11), 207 (10), 195 (11), 179 (11), 169 (12), 165 (11), 157 (11), 149 (13), 148 (11), 147 (12), 145 (12), 141 (11), 125 (14), 123 (16), 121 (11), 119 (18), and 115 (13).

Deuterodihydronoracronycine (**11**) was obtained as a yellow powder: ^{1}H nmr ($CDCl_3$, 60 MHz) δ

1.42 (6H, s, 13- and 14-CH_3), 1.72 (2H, t, J=6.4 Hz, 2-H_2), 2.87 (2H, t, J=6.4 Hz, 1-H_2), 3.87 (3H, s, N-CH_3), 6.17 (0.2H, s, H-5), 7.07-7.80 (3H, m, H-9, H-10 and H-11), 8.26 (1H, dd, J=1.0 and 7.7 Hz, H-8) and 14.25 (1H, s, D_2O exchangeable, 6-OH); ms *m/z* 311 (14%), 310 (M^+, 57), 309 (19), 256 (6), 255 (30), 254 (12), 253 (6), 243 (19), 242 (100), 241 (37), 227 (8), 226 (25), 225 (13), 214 (9), 213 (7), 212 (12), 199 (5), 197 (6), 184 (7), 183 (6), 155 (6) and 154 (5).

COUPLING OF ACRONYCINE (**1**) AND DIHYDRONORACRONYCINE (**3**) IN HCl-MeOH (2:5) UNDER REFLUX.—The reaction procedures and the physical and spectral properties of dihydromethyl AB-1 (**16**) were described previously (1).

TREATMENT OF NORACRONYCINE (**2**) WITH 98% D_2SO_4-MeOD (1:1) AT ROOM TEMPERATURE FOLLOWED BY DILUTION WITH D_2O.—Noracronycine (**2**, 11.8 mg) was dissolved in a mixture of 98% D_2SO_4-MeOD (1:1, 10 ml), and the orange solution was stirred under a N_2 atmosphere for 24 h. The reaction mixture was diluted with D_2O (50 ml) and extracted with $CHCl_3$ (2×50 ml). The combined $CHCl_3$ layers were successively washed with D_2O (50 ml), 5% $NaHCO_3/H_2O$ solution (50 ml) and H_2O (50 ml), and dried (Na_2SO_4). Concentration of the $CHCl_3$ layer in vacuo afforded a yellow powder which, through preparative tlc on silica gel eluting with $CHCl_3$ afforded deutero AB-1 (**19**) and deuteronoracronycine (**18**).

Deutero AB-1 (**19**) was obtained as an orange-yellow powder: ^1H nmr ($CDCl_3$, 360 MHz) δ 3.733 (3H, s, N-CH_3), 3.771 (3H, s, N-CH_3), 5.149 (1H, s, H-1), 6.170 (1H, s, H-1′), 6.910 (1H, d, J=8.6 Hz, H-11), 7.112 (1H, t, J=7.5 Hz, H-9), 7.312 (1H, t, J=8.1 Hz, H-9′), 7.370 (1H, t, J=7.7 Hz, H-10), 7.415 (1H, d, J=8.8 Hz, H-11′), 7.754 (1H, t, J=7.9 Hz, H-10′), 8.227 (1H, d, J=7.8 Hz, H-8 or H-8′), 8.473 (1H, d, J=7.7 Hz, H-8′ or H-8), 14.332 (1H, s, 6-OH), and 15.620 (1H, s, 6′-OH); ms *m/z* 630 (M^+, 38%), 615 (18), 581 (31), 337 (30), 328 (30), 327 (58), 326 (29), 317 (30), 315 (39), 312 (26), 311 (35), 310 (37), 309 (20), 297 (33), 296 (20), 280 (21), 279 (30), 254 (20), 253 (25), and 252 (23).

Deuteronoracronycine (**18**) was obtained as a yellow powder: ^1H nmr ($CDCl_3$, 360 MHz) δ 3.902 (3H, s, N-CH_3), 6.546 (1H, s, H-1), 7.295 (1H, t, J=7.6 Hz, H-9), 7.423 (1H, d, J=8.0 Hz, H-11), 7.711 (1H, t, J=8.2 Hz, H-10), 8.360 (1H, d, J=8.0 Hz, H-8), and 14.713 (1H, s, 6-OH); ms *m/z* 315 (M^+ 315 (M^+, 70%), 314 (16), 298 (58), 297 (100), 296 (37), 283 (21), 282 (92), 281 (16), 254 (11), 157.5 (11), 148.5 (34), 148 (13), 141.5 (12), 134.5 (19), 134 (18), 133.5 (11), and 127 (41).

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LITERATURE CITED

1. S. Funayama and G.A. Cordell, *J. Nat. Prod.*, **48**, 536 (1985).
2. G.K. Hughes, F.N. Lahey, J.R. Price and L.J. Webb, *Nature*, **162**, 223 (1948).
3. F.N. Lahey and W.C. Thomas, *Aust. J. Sci. Res.*, **2A**, 423 (1949).
4. G.H. Svoboda, G.A. Poore, P.J. Simpson, and G.B. Boder, *J. Pharm. Sci.*, **55**, 758 (1966).
5. G.H. Svoboda, *Lloydia*, **29**, 206 (1966).
6. S. Funayama and G.A. Cordell, *Planta Med.*, **50**, 121 (1984).
7. S. Funayama, R.P. Borris, and G.A. Cordell, *J. Nat. Prod.*, **46**, 391 (1983).
8. S. Funayama, G.A. Cordell, H. Wagner, and H.L. Lotter, *J. Nat. Prod.*, **47**, 143 (1984).
9. S. Funayama and G.A. Cordell, *Planta Med.*, **48**, 263 (1983).
10. S. Funayama and G.A. Cordell, *Heterocycles*, **20**, 2379 (1983).
11. S. Funayama and G.A. Cordell, *J. Nat. Prod.*, **48**, 114 (1985).

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