# CHEMISTRY OF ACRONYCINE, XII. FURTHER OLIGOMERS OF NORACRONYCINE[1]

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ABSTRACT.—The polymerization of noracronycine (**2**) with methanolic HCl has yielded a second tetramer of **2**, designated as AB-4 and determined to have the structure **7** through spectroscopic analysis. Two further pentamers of **2**, designated as AB-6A and AB-6B, have also been obtained, and their structures are tentatively proposed as **9** and **5**, respectively.
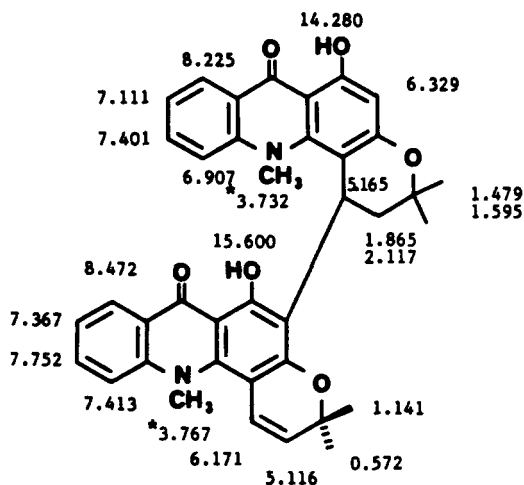
Acronycine (**1**), an alkaloid from the bark of *Baurella simplicifolia* (Endl.) Hartley (Rutaceae) (2-5), possesses a broad spectrum of in vivo antineoplastic activity (6-9), yet relatively little is known of its chemistry and mode of action (4,5). As reported previously, when noracronycine (**2**) was treated with 98% H_2SO_4 under N_2 at room temperature, AB-1 (**3**) was selectively synthesized in 4.0% yield (10). Yields could be improved by treating **2** with varying ratios of 98% H_2SO_4 and MeOH. The optimal yield (39%) of **3** was observed with 98% H_2SO_4-MeOH (1:1) (10). However, treatment of **2** with 98% H_2SO_4-MeOH (1:9) afforded AB-3 (**4**) in 28% yield (10), together with other minor products. On this basis, it was thought that if a mixture of AB-1 (**3**) and **2** were used instead of **2** alone, the yields of the trimer and the tetramer would be increased.

	R
1	CH_3
2	H
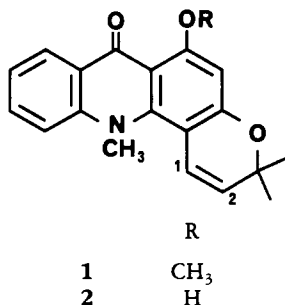
A 3:1 mixture of **2** and **3** was prepared by treating **2** with 98% H_2SO_4-MeOH (9:1) (10), and the resulting orange-yellow powder was redissolved in a mixture of 98% H_2SO_4-MeOH (1:9) and stirred for 24 h under N_2 at room temperature. The final reaction mixture was rich not only in AB-3 (**4**) (20% yield), but also in AB-4 (9% yield). Previously, AB-4 had been detected as one of the very minor products when **2** was treated with 98% H_2SO_4-MeOH (1:9), and was isolated in only 0.16% yield when **2** was allowed to react with methanolic HCl. At that time, no further studies were conducted because of limited availability. The structure elucidation of AB-4, which is presented here, was conducted principally through a ^1H-nmr comparison of AB-4 with **2**, **3**, **4**, and the pentamer AB-5A (**5**) available from previous work (11-14).

In the ^1H-nmr spectrum of AB-4, four sets of geminal methyl signals (δ 0.465, 0.484, 0.543, 0.873, 0.940, 1.005, 1.487, and 1.647), four hydrogen-bonded phenolic OH signals (δ 14.291, 14.979, 15.087, and 15.458), four N-CH₃ signals (δ 3.290, 3.296, 3.643, and 3.681) and seventeen aromatic protons were observed. Nine resonances, three triplets at δ 1.358 ($J=12.8$ Hz), 1.712 ($J=11.8$ Hz) and 2.080
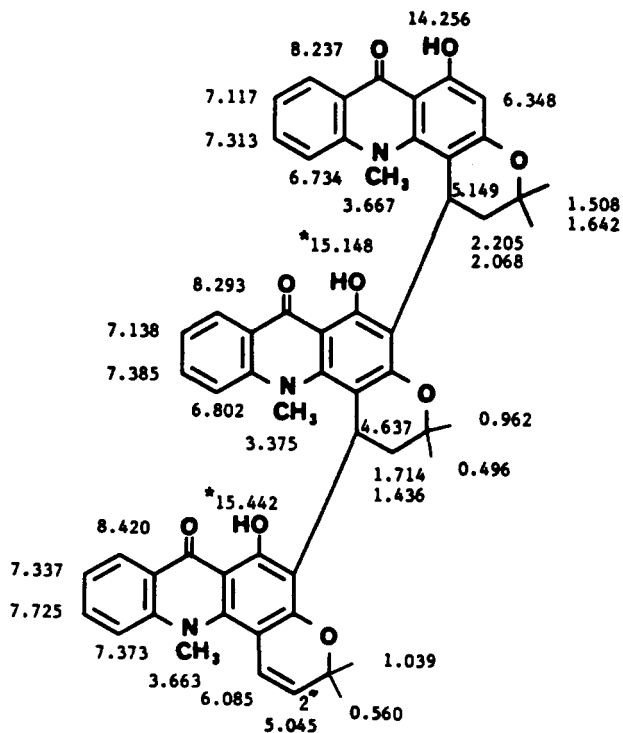

14.280
8.225 O   HO
7.111   6.329
7.401
6.907 CH₃   5.165   1.479
*3.732   1.595
15.600   1.865
8.472 O   HO   2.117
7.367
7.752
7.413 CH₃   1.141
*3.767
6.171   0.572
5.116

3   AB-1

(J=12.4 Hz), and six doublets of doublets at δ 1.441 (J=11.4, 8.0 Hz), 1.809 (J= 12.7, 6.6 Hz), 2.214 (J=13.4, 6.7 Hz), 4.563 (J=12.1, 6.8 Hz), 4.623 (J=11.9, 6.7 Hz), and 5.168 (J=11.6, 7.1 Hz) were attributed to the protons of three pyran rings (12). However, only one aromatic singlet (δ 6.362) and only one pair of doublets (J=9.6 Hz) for the chromene ring (δ 4.994 and 6.041) were observed. These data suggested that AB-4 was a tetramer of noracronycine (2) where the three carbon-carbon bonds had been formed between C-1 of one unit and C-5 of another unit (12-14).

Unambiguous ¹H-nmr assignments for noracronycine (2), AB-1 (3), AB-2 (6), and AB-3 (4) had previously been achieved through the use of selective proton decoupling

14.256
8.237 O   HO
7.117   6.348
7.313
6.734 CH₃   5.149   1.508
3.667   1.642
*15.148   2.205
2.068
8.293 O   HO
7.138
7.385
6.802 CH₃   4.637   0.962
3.375
1.714   0.496
1.436
*15.442
8.420 O   HO
7.337
7.725
7.373 CH₃   1.039
3.663
6.085   2*   0.560
5.045

4   AB-3

and nOe techniques (12,13). Tentative ^{1}H-nmr assignments for the all-angular pen-
tamer AB-5A were accomplished through a comparison of the ^{1}H-nmr data with those
of noracronycine (**2**), AB-1 (**3**), and AB-3 (**4**) (11-14).
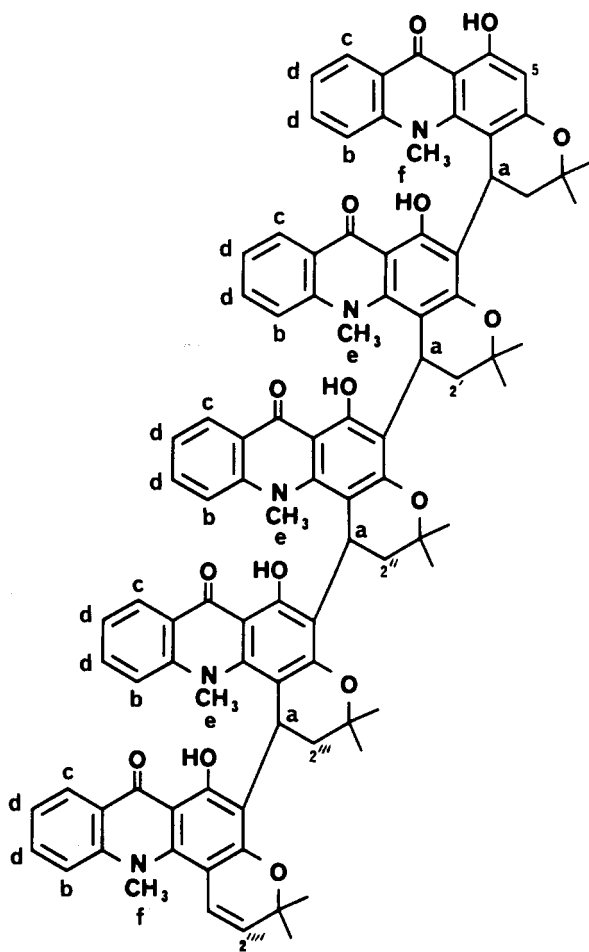
5   AB-5A, AB-6B

In the ^{1}H-nmr spectrum of AB-4, there were three doublets that could be assigned
to the four aromatic protons *peri* to the N-CH$_3$ groups, namely the signals at δ 6.651
(d, 1H, J=8.5 Hz), 6.760 (d, 2H, J=8.5 Hz), and 7.362 (d, 1H, J=8.2 Hz). In the
^{1}H-nmr spectrum of noracronycine (**2**), this signal appeared at δ 7.447 and in AB-2 (**7**)
at δ7.420 and 7.459 (13). But in the ^{1}H-nmr spectrum of AB-1 (**3**), AB-3 (**4**), and AB-
5A (**5**), these signals appeared at δ 6.907 and 7.413, δ 6.734, 6.802 and 7.373 and δ
6.606, 6.670, 6.743, 6.758 and 7.356, respectively (11-14). That is, the signal(s)
from the upper unit(s) appeared about 0.51-0.75 ppm higher than those from the lower
unit, and also 0.54-0.84 ppm higher than that in noracronycine (**2**) (10,13). Three
higher-field signals were observed in the spectrum of AB-4 [(δ 6.651 and 6.760 (2H)],
suggesting the presence of three angular units each attached to an angular unit (12-14).
Therefore, it was envisaged that AB-4 possessed the angular-angular-angular-angular
structure represented by **7**.

Most of the features of the ^{1}H-nmr spectrum of AB-4 (**7**) could now be assigned
with certainty. A singlet aromatic proton (δ 6.362, C-5H), a pair of doublets (δ 4.994,
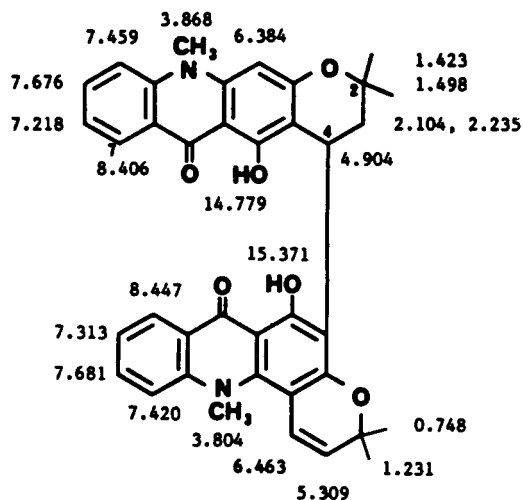
6   AB-2
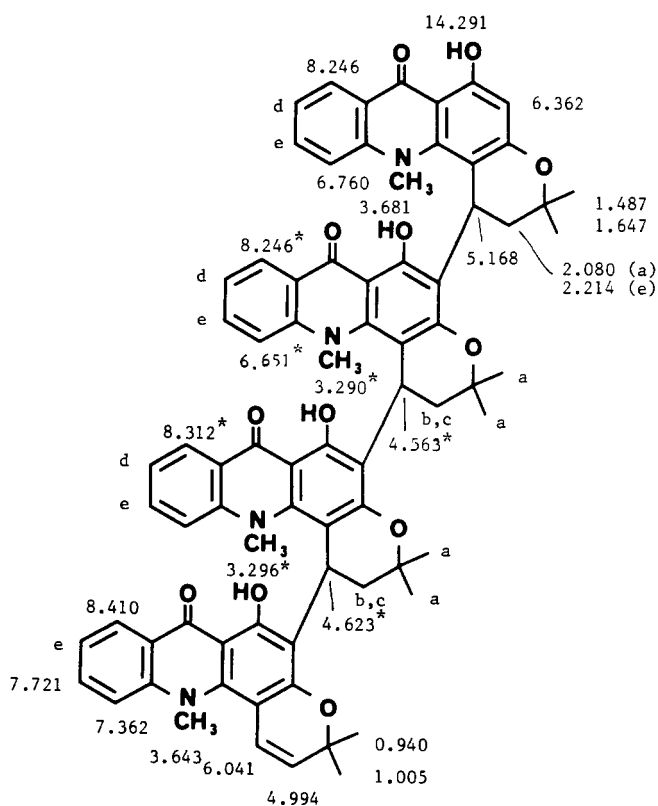
7   AB-4

a	(3H,s): 0.465, 0.484, 0.543, 0.873
b	(1H, t): 1.358, 1.712
c	(1H, dd): 1.441, 1.809
d	(1H, t): 7.115, 7.136, 7.157
e	(1H, t): 7.311, 7.331 (2H), 7.363
OH:	14.979, 15.087, 15.458

C-2‴H and δ 6.041, C-1‴H), four sets of geminal methyl signals [0.465, 0.484, 0.543, and 0.873 (13′-CH₃, 14′-CH₃, 13″-CH₃, and 14″-CH₃), δ 0.940 and 1.005 (13‴- CH₃ and 14‴-CH₃) and δ 1.487 and 1.647 (13-CH₃ and 14-CH₃)], a set of methine and methylene protons [δ 5.168 (C-1H), δ 2.080 and 2.214 (C-2Ha and C-2He, respectively)], and one of the four hydrogen-bonded phenolic protons [δ 14.291 (C-6 OH)] were assigned by comparison with the ¹H-nmr spectra of noracronycine (**2**), AB-1 (**3**), AB-3 (**4**), and AB-5A (**5**) (11-14). Assignment of the sixteen aromatic protons was achieved mainly through comparison with the ¹H-nmr spectra of **2, 3, 4,** and **5** (11-14). In addition, a number of nOe experiments were also conducted on AB-4.

By irradiating δ 3.681 (N-CH₃), a 12% nOe at δ 6.760 (d, 1H) and 16% nOe at δ 5.168 (dd, 1H, C-1H) were observed, and when δ 3.643 (N-CH₃) was irradiated, an 11% nOe was observed at δ 6.041 (d, 1H, C-1‴ H). In addition, when δ 3.29 (N-CH₃×2) was irradiated, a 7% nOe at δ 6.760 (d, 1H), a 10% nOe at δ 6.651 (d, 1H) and a 20% nOe at δ 4.6 (dd, 1H×2) were observed.

Because the signals at δ 5.168 (C-1H) and δ 6.041 (C-1‴H) had been previously assigned, δ 3.681 (N-CH₃) and δ 6.760 (d, 1H) were attributed to N₁₂-CH₃ and C-11H, respectively, and δ 3.643 (N-CH₃) was assigned to N₁₂‴-CH₃. Two sets of methine and methylene protons [δ 1.358 and 1.712 (each t), δ 1.441, 1.809, 4.563 and 4.623 (each dd)] and two three-proton singlets (δ 3.290 and 3.296) were assigned to the chromane and N-methyl protons of the second and third units.

It was confirmed that higher-field-shifted N-methyl signal(s), and the methine and methylene signals of the chromane unit(s) could be assigned to the unit(s) inserted between two angular type noracronycine moieties as previously observed in the ¹H-nmr spectra of AB-3 (**4**), dihydro AB-3 (**8**), AB-5A (**5**), and the linear-angular-angular-angular tetramer AB-5B (13,14). Thus, AB-4 (**7**) represents the second tetrameric acridone derivative obtained.

Two further oligomers of noracronycine (**2**) were obtained from the chromatography of the mixture obtained from the treatment of **2** with acid. Originally obtained as a mixture, AB-6, which showed ten N-CH₃ signals and ten hydrogen-bonded phenolic protons, gave separated products AB-6A and AB-6B that were identified as pentamers of **2**.

AB-6A was obtained as a yellow powder displaying a typical acridone uv spectrum. The ¹H-nmr spectrum displayed geminal methyl signals (δ 0.537, 0.669, 0.733, 0.978, 1.162, 1.343, 1.465, and 1.662), five hydrogen-bonded phenolic OH signals (δ 12.896, 14.303, 15.148, 15.436, and 15.597), five N-CH₃ signals (δ 3.342, 3.588, 3.,635, 3.664, and 3.693) and twenty-one aromatic protons. The pyran ring methylene protons were not clearly delineated, but four benzylic protons on the pyran ring were observed as doublets of doublets at δ 4.606, 4.799, and 5.154 (2H), and a pair of doublets (*J*=9.6 Hz) at δ 5.043 and 6.106 was attributed to the chromene ring protons on the terminal unit. The structure was deduced based on the previous assignments of the monomers, dimers, trimers, and oligomers in this series (11-14).

Three higher-field protons *peri-* to the N-CH₃ were observed in the spectrum of AB-6A [δ 6.539 and 6.729 (2H)], suggesting the presence of three angular units each attached to an angular unit. The fifth unit should, therefore, be a linear unit, i.e., derived

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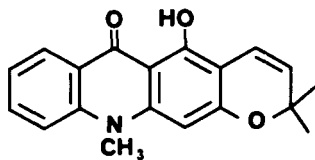
from isonoracronycine (**8**). Confirmation of this came from the presence of two doublets at δ 7.395 (J=8.4 Hz) and 7.412 (J=8.6 Hz) for aromatic protons *peri-* to the N-CH$_3$ group and their adjacent protons at δ 7.76 (2H). On this basis, AB-6A is proposed to have the linear-angular-angular-angular-angular-linear structure shown in **9**, together with the tentative proton assignments.
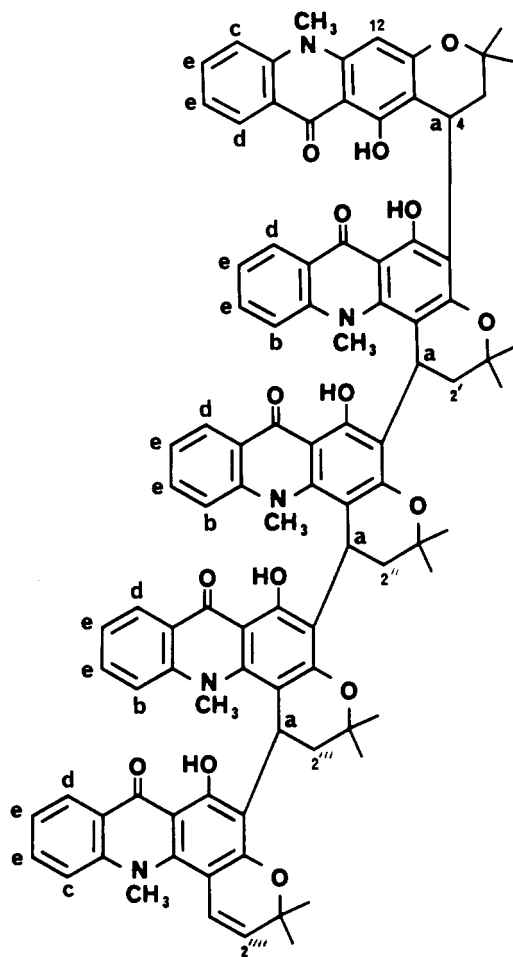
9   AB-6A

AB-6B was also obtained as a yellow powder displaying a typical acridone uv spectrum. The ^{1}H-nmr spectrum displayed five sets of geminal methyl signals (δ 0.280, 0.516, 0.546, 0.741, 0.857, 0.878, 0.981, 1.000, 1.51, and 1.66), five hydrogen-bonded phenolic OH signals (δ 13.519, 14.327, 15.077, 15.247, and 15.429), five N-CH$_3$ signals (δ 3.283, 3.290, 3.493, 3.647, and 3.730) and twenty-one aromatic protons. These data established the pentameric nature of the compound. Once again, the pyran ring methylene protons were not clearly delineated, but four benzylic protons were observed as doublets of doublets at δ 4.513 (2H), 5.151 and 5.154. Characteristic doublets (J=9.6 Hz) were observed for the chromene ring protons of the terminal unit at δ 5.021 and 6.062. The structure of AB-6B was deduced to be the angular-angular-angular-angular-angular structure shown in **5** on the basis of the following interpretations.

There are four higher-field protons *peri-* to the N-CH$_3$ group at δ 6.531, 6.686, 6.775, and 6.827, suggesting the presence of four angular units each attached to an an-

gular unit, and only one lowfield signal at δ 7.317 (d, J=7.6 Hz) with its adjacent triplet at δ 7.712. Based on previous spectroscopic interpretations, these data would indicate the structure **5** for AB-6B.

The planar structures for AB-6B and AB-5A are therefore the same (14). They differ in their chromatographic properties and also in several aspects of their ^{1}H-nmr spectra. Among these differences is the fact that AB-5A has only one lower-field shifted doublet of doublets at δ 5.175 (14), whereas AB-6B has two such signals (δ 5.151 and δ 5.154), and in AB-6B one of the signals *peri*- to the carbonyl is shifted upfield by 0.254 ppm compared with the most upfield signal *peri*- to the carbonyl in AB-5A. It is therefore suggested that AB-5A and AB-6B differ in stereochemistry at one (or more) of the points of attachment of the angular nuclei.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined using a Kofler hot-stage microscope and are uncorrected. Uv spectra were recorded on a Beckman model DB-G spectrophotometer and ir spectra on a Nicolet model MX-1 FT-IR interferometer. ^{1}H-nmr spectra were recorded 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. Silica gel GHLF (Analtech) was used for preparative tlc.

PREPARATION OF NORACRONYCINE (**2**).—The formation and chemical and spectroscopic properties of **2** were described previously (11,15).

FORMATION OF AB-1 (**3**), AB-3 (**4**) AND AB-4 (**7**).—Noracronycine (**2**, 100 mg) was dissolved in a mixture of 98% H_2SO_4-MeOH (9:1) (100 ml), and the yellow solution was stirred at room temperature under N_2. After 24 h, the reaction mixture was diluted with H_2O (500 ml), and extracted with $CHCl_3$ (2×500 ml). The combined $CHCl_3$ layers were successively washed with 5% $NaHCO_3$ solution (500 ml) and H_2O (500 ml), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford an orange-yellow powder. The approximate ratio of AB-1 (**3**) and noracronycine (**2**) (1:3) of this reaction mixture was confirmed by tlc analysis (no other spots were detected). The reaction mixture was then redissolved in a mixture of 98% H_2SO_4-MeOH (1:9) (100 ml), and the yellow solution was stirred for 24 h under N_2 at room temperature to give an orange solution. The reaction mixture was worked up in the same manner as described above to afford an orange powder (126.2 mg).

The orange powder was dissolved in a small amount of $CHCl_3$ and subjected to preparative tlc on silica gel eluting with C_6H_6-EtOAc (9:1) to afford noracronycine (**2**, 25.8 mg), AB-1 (**3**, 19.2 mg), AB-3 (**4**, 20.4 mg), AB-4 (**7**, 8.6 mg), and a mixture of minor products (24.6 mg). AB-4 was obtained as a yellow powder; mp>300°; ir ν max (KBr) 3420, 1587, 1558, 1447, 1328, 1264, 1186, 1166, 1145, 1122, and 1099 cm^{-1}; uv ν max (CHCl$_3$) 257, 282, 307, 348, and 417 nm; ^{1}H nmr (δ, CDCl$_3$) 0.465 (3H, s), 0.484 (3H, s), 0.543 (3H, s), 0.873 (3H, s), 0.940 (3H, s, 3'''-CH$_3$), 1.005 (3H, s, 3'''-CH$_3$), 1.358 (1H, t, J=12.8 Hz), 1.441 (1H, dd, J=11.4, 8.0 Hz), 1.487 (3H, s, 3-CH$_3$), 1.647 (3H, s, 3-CH$_3$), 1.712 (1H, t, J=11.8 Hz), 1.809 (1H, dd, J=12.7, 6.6 Hz), 2.080 (1H, t, J=12.4 Hz, H$_{2a}$), 2.214 (1H, dd, J=13.4, 6.7 Hz, H$_{2e}$), 3.290 (3H, s), 3296 (3H, s), 3.643 (3H, s, N$_{12}$''-CH$_3$), 3.681 (3H, s, N-CH$_3$), 4.563 (1H, dd, J=12.1, 6.8 Hz), 4.623 (1H, dd, J=11.9, 6.7 Hz), 4.994 (1H, d, J=9.6 Hz, H$_{2'''}$), 5.168 (1H, dd, J=11.6, 7.1 Hz, H$_1$), 6.041 (1H, d, J=9.6 Hz, H$_{1'''}$), 6.362 (1H, s, H$_5$), 6.651 (1H, d, J=8.5 Hz), 6.760 (2H, d, J=8.5 Hz, H$_{11}$), 7.115 (1H, t, J=7.4 Hz), 7.136 (1H, t, J=7.6 Hz), 7.157 (1H, t, J=7.6 Hz), 7.311 (1H, t, J=7.9 Hz), 7.331 (2H, t, J=7.3 Hz), 7.362 (1H, d, J=8.2 Hz, H$_{11'''}$), 7.363 (1H, t, J=7.9 Hz), 7.721 (1H, dt, J=7.7, 1.2 Hz, H$_{10'''}$), 8.246 (2H, dd, J=7.7, 1.7 Hz, H$_8$), 8.312 (1H, dd, J=7.5, 0.8 Hz), 8.410 (1H, dd, J=7.7, 0.9 Hz, H$_{8'''}$), 14.291 (1H, s, C$_6$-OH), 14.979 (1H, s), 15.087 (1H, s), and 15.458 (1H, s).

FORMATION OF AB-6 AND THE SEPARATION OF AB-6A (**9**) AND AB-6B (**5**).—Noracronycine (**2**, 500 mg) was dissolved in MeOH (167 ml) and 10 N aqueous HCl (67 ml), and the mixture refluxed over a steam bath for 6 h. After cooling, the reaction mixture was concentrated in vacuo to about 100 ml and diluted with H_2O (400 ml). The solution was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (2×500 ml). After drying (Na_2SO_4), the $CHCl_3$ layer was concentrated in vacuo to afford an orange powder (557.5 mg). Repeated column chromatography on silica gel followed by repeated preparative tlc using C_6H_6-EtOAc (9:1) or $CHCl_3$-MeOH (249:1) as solvent afforded AB-6A (**9**, 1.8 mg) and AB-6B (**5**, 1.5 mg) after AB-1 (**3**, 13 mg) (12), AB-2 (**6**, 18 mg) (12), AB-3 (**4**, 9 mg) (13), AB-4 (**7**, 0.8 mg), AB-5A (**5**, 3.0 mg) (14) and AB-5B (4.1 mg) (14) had been isolated.

AB-6A (**9**) was obtained as a pale yellow powder; uv λ max (CHCl$_3$) 255, 279, 305 (sh), 343, and 415

nm; ^{1}H nmr (δ, CDCl$_3$) 0.537 (3H, s), 0.669 (3H, s), 0.733 (3H, s), 0.978 (3H, s), 1.162 (3H, s), 1.343 (3H, s), 1.465 (3H, s), 1.662 (3H, s), 3.342 (3H, s), 3.588 (3H, s), 3.635 (3H, s), 3.664 (3H, s), 3.693 (3H, s), 4.606 (1H, dd, J=6.3, 12.8 Hz, H-a), 4.799 (1H, dd, J=6.5, 12.0 Hz, H-a), 5.043 (1H, d, J=9.6 Ha, C$_2''''$-H), 5.154 (2H, dd, J=6.1, 11.7 Hz, H-a), 6.106 (1H, d, J=9.5 Hz, C$_1''''$-H), 6.367 (1H, s, C$_{12}$-H), 6.539 (1H, d, J=8.5 Hz, H-b), 6.729 (2H, d, J=8.5 Hz, H-b), 6.964 (1H, t, J=7.6 Hz, H-e), 7.031 (1H, t, J=7.5 Hz, H-e), 7.149 (2H, t, J=7.3 Hz, H-e), 7.298 (1H, t, J=8.0 Hz, H-e), 7.321 (2H, t, J=8.3 Hz, H-e), 7.369 (1H, t, J=7.8 Hz, H-e), 7.395 (1H, d, J=8.4 Hz, H-c), 7.412 (1H, d, J=8.6 Hz, H-c), 7.760 (2H, m, C$_9$-H and C$_{10}''''$-H), 8.023 (1H, d, J=7.9 Hz, H-d), 8.182 (1H, d, J=7.9 Hz, H-d), 8.224 (1H, d, J=8.1 Hz, H-d), 8.260 (1H, d, J=8.0 Hz, H-d), 8.466 (1H, d, J=7.9 Hz; H-d), 12.896 (1H, s), 14.303 (1H, s), 15.148 (1H, s), 15.436 (1H, s), and 15.597 (1H, s).

AB-6B (**5**) was isolated as a yellow powder; uv λ max (CHCl$_3$) 256, 283, 304 (sh), 347, and 414 nm; ^{1}H nmr 0.280 (3H, s), 0.516 (3H, s), 0.546 (3H, s), 0.741 (3H, s), 0.857 (3H, s), 0.878 (3H, s), 0.981 (3H, s), 1.000 (3H, s), 1.510 (3H, s), 1.660 (3H, s), 2.090 (1H, t, C$_2$-H$_a$), 2.250 (1H, dd, C$_2$-H$_e$), 3.283 (3H, s, H-e), 3.290 (3H, s, H-e), 3.493 (3H, s, H-e), 3.647 (3H, s, H-f), 3.730 (3H, s, H-f), 4.513 (2H, dd, J=6.3, 11.0 Hz, H-a), 5.021 (1H, d, J=9.6 Hz, C$_2''''$-H), 5.151 (1H, dd, J=6.2, 10.8 Hz, H-a), 5.154 (1H, dd, J=6.6, 12.5 Hz, H-a), 6.062 (1H, d, J=9.6 Hz, C$_1''''$-H), 6.357 (1H, s, C$_5$-H), 6.531 (1H, d, J=8.6 Hz, H-b), 6.686 (1H, d, J=8.6 Hz, H-b), 6.775 (1H, d, J=8.5 Hz, H-b), 6.827 (1H, d, J=8.5 Hz, H-b), 6.981 (1H, t, J=7.4 H, H-d), 7.041 (1H, t, J=7.6 Hz, H-d), 7.136 (2H, t, J=7.2 Hz, H-d), 7.176 (1H, t, J=7.5 Hz, H-d), 7.317 (1H, d, J=7.6 Hz, C$_{11}''''$-H), 7.389 (3H, t, J=7.8 Hz, H-d), 7.712 (1H, t, J=7.2 Hz, C$_{10}''''$-H), 7.974 (1H, d, J=7.4 Hz, H-c), 8.256 (1H, d, J=7.1 Hz, H-c), 8.277 (2H, d, J=7.8 Hz, H-c), 8.398 (1H, d, J=7.2 Hz, H-c), 13.519 (1H, s), 14.327 (1H, s), 15.077 (1H, s), 15.247 (1H, s), and 15.429 (1H, s).

ACKNOWLEDGMENTS

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