# CHEMISTRY OF ACRONYCINE VIII.   SELECTIVE SYNTHESIS OF DIMERS AND TRIMERS OF NORACRONYCINE AND RELATED COMPOUNDS[1]

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ABSTRACT.—Improved synthetic procedures for the formation of a number of dimeric de-
rivatives of noracronycine (**2**) are described based on acid-catalyzed reactions in methanolic HCl
or methanolic $H_2SO_4$. A detailed analysis of their high-field proton nmr spectral characteristics
is presented. The synthesis and structure determination of a new trimer of noracronycine (**2**)
possessing the linear-angular-angular structure (**15**) is described.

Acronycine (**1**), a hemiterpene acridone alkaloid (2-4) isolated from the Australian
scrub ash *Baurella simplicifolia* (Endl.) Hartley (Rutaceae) (5), is reported to have the
broadest spectrum of in vivo antineoplastic activity of any plant-derived alkaloid (6-8).
In spite of this, very little is known of its chemistry or mechanism of action.

Because of our interest in the development of acronycine (**1**) and/or its derivatives as
antineoplastic agents, we have been investigating their chemical and spectroscopic
properties (1, 9-15). An area of particular interest has been the nature of the complex
mixture formed when noracronycine (**2**) is treated with hot methanolic HCl (11).

Through extensive chromatographic analysis, we ascertained that the mixture con-
tained the dimers of noracronycine, AB-1 (**3**) and AB-2 (**4**) (11), a trimer, AB-3 (**5**)
(12), a tetramer, AB-5B, and at least one pentamer, AB-5A (13). Additionally, we
demonstrated that when noracronycine (**2**) and dihydronoracronycine (**6**) in the ratio of
1:10 were refluxed in methanolic HCl, a clean reaction occurred from which a dimer,
dihydro AB-2 (**7**) (11), could be isolated in 86% yield based on **2**, together with excess,
unreacted dihydronoracronycine (**6**). Like AB-2 (**4**), this product contains a rearranged
isonoracronycine (**8**) unit. Through an interesting condensation-disproprotionation
reaction,[3] dihydro AB-2 (**7**) was also obtained when a 1:10 mixture of AB-1 (**3**) or AB-2
(**4**) and dihydronoracronycine (**6**) were refluxed with methanolic HCl for 6 h (14).
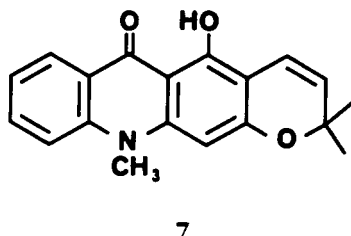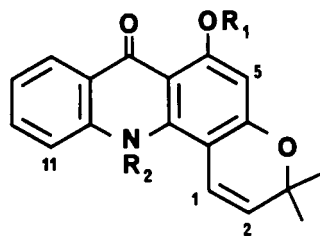


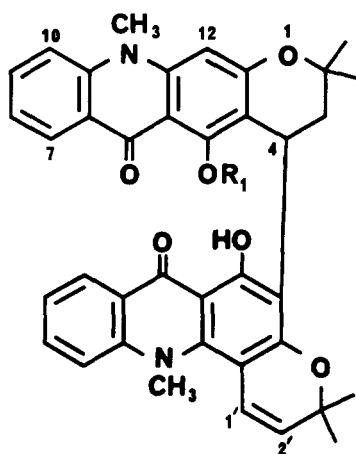| | $R_1$ | $R_2$ |
|---|---|---|
| **1** | $CH_3$ | $CH_3$ |
| **2** | H | $CH_3$ |
| **6** | H | $CH_3$, 1,2-$H_2$ |
| **10** | $CH_3$ | H |

[3]A referee has pointed out that a decoupling-recombination mechanism would also explain the ob-
served results.

With these results in hand, we began to examine further the selective synthesis of other dimers of noracronycine (2) and related compounds. When the coupling of 2 and 6 was performed at room temperature, a 1:1 mixture of dihydro AB-1 (9) and dihydro AB-2 (7) was obtained, as well as unreacted 6 (11). However, if des-$N$-methyl acronycine (10) was used instead of 2, and a 1:10 mixture of 10 and 6 was refluxed in methanolic HCl on a steam bath for 6 h, des-$N$-methyl-$O$-methyl dihydro AB-1 (11) was obtained. Significantly, no rearrangement of the upper unit was observed in this coupling reaction. The angular-angular skeleton of this compound was demonstrated through $^1$H-nmr analysis as described subsequently. When acronycine (1) was used in place of des-$N$-methyl acronycine (10) in the coupling reaction with 6, $O$-methyl dihydro AB-1 (12) was obtained. A 6-hydroxy group and a chromene unit are therefore essential for the rearrangement reaction to be observed. An improved yield of 12 was obtained when a 1:2 mixture of 1 and 6 was treated in the same way. The angular-angular array of this compound was demonstrated when the identical compound was obtained through coupling acronycine (1) and dihydronoracronycine (6) in methanolic HCl at room temperature, and through the observation of an upfield shift of a doublet assigned to the proton *peri*- to the $N$-methyl group (11).

When noracronycine (2) was treated with methanolic HCl at room temperature, AB-1 (3), AB-3 (5), AB-5A, etc, were obtained as well as a substantial amount of unreacted noracronycine (2) (11). Under these conditions, no compounds with the rearranged unit, namely, AB-2 (4) and AB-5B, were observed.
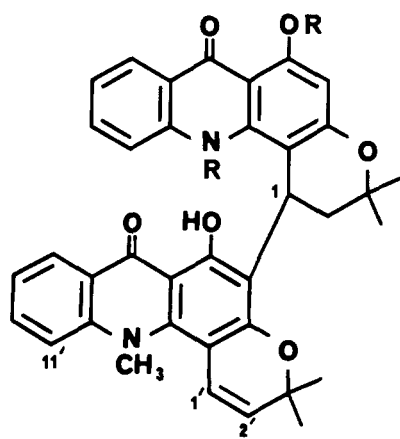


| | $R_1$ | $R_2$ |
|---|---|---|
| 3 | H | $CH_3$ |
| 9 | H | $CH_3, 1',2'$-$H_2$ |
| 11 | $CH_3$ | H, $1',2'$-$H_2$ |
| 12 | $CH_3$ | $CH_3, 1',2'$-$H_2$ |
| 13 | $CH_3$ | $CH_3$ |

| | $R_1$ | $R_2$ |
|---|---|---|
| 4 | H | $CH_3$ |
| 8 | H | $CH_3, 1',2'$-$H_2$ |
| 15 | $CH_3$ | H, $1',2'$-$H_2$ |

For the purpose of improving the yields of the unrearranged compounds, 98% $H_2SO_4$ was used on 2 instead of methanolic HCl. Surprisingly, only AB-1 (3) was formed under these conditions, albeit in very low (4%) yield. No reaction was observed and only unreacted acronycine (1) was recovered when 1 was treated with 98% $H_2SO_4$ at room temperature.

An improved yield of AB-1 (3) was obtained when noracronycine (2) was treated with methanolic $H_2SO_4$ (98% $H_2SO_4$-MeOH, 2:5, v/v) instead of 98% $H_2SO_4$ at room temperature under a $N_2$ atmosphere. This prompted us to study the reaction of noracronycine (2) in methanolic $H_2SO_4$ using ten different solvent ratios. Yields were op-

timized when MeOH-98% $H_2SO_4$ in the ratio 1:1 or 3:2 was used. When noracronycine (2) was treated with a mixture of 98% $H_2SO_4$ and MeOH in the ratio 1:1, the yield of AB-1 (3) was about 40%, a tenfold increase compared with 98% $H_2SO_4$. Catalytic hydrogenation of 3 afforded dihydro AB-1 (9) in almost quantitative yield (11). As reported previously (14), dihydro AB-1 (9) could also be produced, in about 40% yield, through a condensation-disproportionation reaction together with dihydro AB-3 (13), by treating a 1:10 mixture of AB-1 (3) and dihydronoracronycine (6) with methanolic HCl under a $N_2$ atmosphere at room temperature for 24 h.

Acronycine (1) and noracronycine (2) were mixed in the ratio 10:1 and stirred in 98% $H_2SO_4$ at room temperature for 24 h. It was anticipated that using this ratio of starting materials 2 would preferentially react with 1, and that 1 would not self-condense. In any event, a dimer displaying a $M^+$ 628 was obtained in 29% yield, whose structure was established to be O-methyl AB-1 (13) inasmuch as catalytic hydrogenation afforded 12. On the other hand, when noracronycine (2) was treated with p-toluene sulfonic acid in $CH_2Cl_2$ under reflux, AB-2 (4) was synthesized in good (45%) yield together with some (16%) AB-1 (3). Catalytic hydrogenation of 4 afforded dihydro AB-2 (8) almost quantitatively (11).

The proposed mechanisms of formation of O-methyl AB-1 (13), O-methyl dihydro AB-1 (12), and des-N-methyl-O-methyl dihydro AB-1 (11) involve an initial protonation at C-2 of acronycine (1) or des-N-methyl acronycine (10), followed by nucleophilic attack at C-5 of the second unit and deprotonation. Because no 6-OH group exists in 1 or 10, the site of protonation was regarded as different from the protonation of noracronycine (2) (11). The absence of a 6-OH also accounts for the lack of rearrangement even if the reactions are carried out in refluxing methanolic HCl.

During the study of the selective synthesis of AB-1 (3), it was found that AB-3 (5) the angular-angular-angular trimer of noracronycine (2), was formed in fairly good yield by successively treating 2 with a 9:1 and a 1:9 mixture of 98% $H_2SO_4$ and MeOH. AB-3 (5) had first been isolated from the complex reaction mixture obtained by



5
14   1″,2″-$H_2$
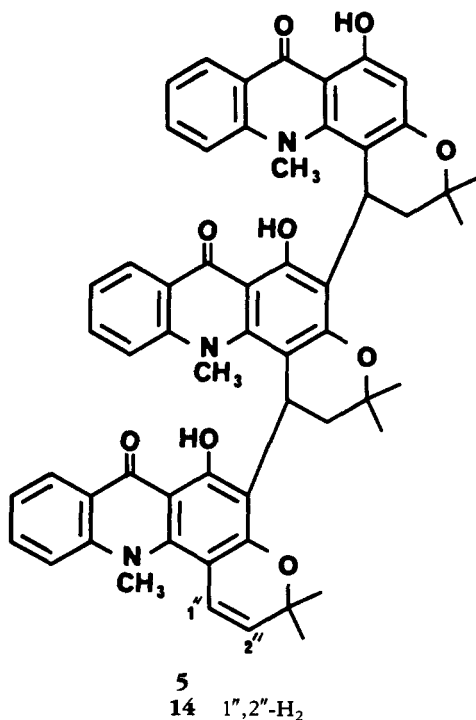
treating noracronycine (**2**) with methanolic HCl. However, the yield of **5** in this in-stance was very low (1.8%) (12). Catalytic hydrogenation of **5** afforded the dihydro de-rivative **14** (12).

This latter compound, dihydro AB-3 (**14**), could also be obtained, together with dihydro AB-1 (**9**) (14), by coupling AB-1 (**3**) and dihydronoracronycine (**6**) in methanolic HCl at room temperature. Consequently, it was anticipated that the linear-angular-angular trimer **15** would be obtained if the reaction described above was con-ducted between AB-2 (**4**) and dihydronoracronycine (**6**). As it transpired, a previously unknown trimer was isolated in addition to dihydro AB-1 (**9**) and dihydro AB-2 (**8**), and its structure elucidation will be described subsequently.

The $^1$H-nmr assignments for AB-1 (**3**), AB-2 (**4**), and dihydro AB-2 (**8**), obtained through decoupling and nOe techniques, are presented in Tables 1 and 2 (11). This prior work greatly aided in the assignment of the $^1$H-nmr spectra of dihydro AB-1 (**9**), O-methyl AB-1 (**13**) and O-methyl dihydro AB-1 (**12**), and these data are summarized in Table 1. Assignments for the 6-OH and the 6'-OH protons of AB-1 (**3**) had been made previously solely by comparison with the $^1$H-nmr data of noracronycine (**2**) (11). That is, since the chemical shift of the 6-OH proton of **2** was δ 14.718, the peak in **3** observed at δ 14.280 was assigned to the 6-OH, and the signal at δ 15.600 was attrib-uted to the 6'-OH proton. These assignments were confirmed through comparison of the $^1$H-nmr data of O-methyl AB-1 (**13**) and O-methyl dihydro AB-1 (**12**). These com-pounds have only one H-bonded phenolic OH in the lower unit, and consequently the signals at δ 15.582 and 15.070 in **13** and **12**, respectively, could be assigned unam-biguously. The assignments of δ 14.280 and 14.254 to the 6-OH proton in the respec-tive upper units and of δ 15.600 and 15.118 to the 6'-OH proton in the lower units of **3** and **9**, respectively, were thus established. Irradiation of the signal at δ 5.051 in the $^1$H-nmr spectrum of O-methyl dihydro AB-1 (**12**) produced a 4.8% nOe effect in the methyl singlet at δ 3.540, which could therefore be assigned to the N-methyl group of the upper unit.

The $^1$H-nmr assignments for des-N-methyl-O-methyl dihydro AB-1 (**11**) were made through a similar procedure to that conducted for other AB-1 derivatives. At-tribution of the aromatic singlet (δ 6.215), a pair of methylene groups (δ 1.34 (2H), 2.678 (1H) and 2.847 (1H)), a doubly benzylic proton (δ 4.866), a pair of methylene protons (δ 2.144 and 2.502), two pairs of geminal methyl singlets (δ 0.868, 1.364, 1.377 and 1.526), and an NH (δ 8.780) were made principally through a comparison with the $^1$H-nmr data of **3**, **9**, and **13**.

Assignments for the two sets of four aromatic protons were made through homonuclear decoupling. Thus, irradiation of the proton *peri* to the carbonyl group at δ 8.312 reduced the triplet at δ 7.056 to a doublet, and irradiation in the region of δ 7.027 and 7.056 simplified the signals at δ 8.312 and 7.408 to singlets. A doublet at δ 8.423 could also be assigned to a proton *peri* to a carbonyl group and a doublet at δ 7.429 to the aromatic signal *peri* to nitrogen. When the δ 7.429 and 7.408 region was irradiated, the triplet at δ 7.725 was reduced to a doublet, and consequently, the sec-ond set of four aromatic protons could be assigned.

A three-proton singlet at δ 3.833 was assigned to an N-methyl group, and irradia-tion produced an 18% nOe enhancement at δ 7.429; consequently, this latter proton could be assigned to the $C_{11'}$-H and the set of aromatic protons shown in the A ring to the upper unit. When the three-proton singlet at δ 3.951 was irradiated, a 30% nOe enhancement was observed in the aromatic singlet at δ 6.215. This established that the compound had the angular-angular structure of **11**, rather than the linear-angular structure **15**.

A number of interesting features were noted through closer examination of the $^1$H-

TABLE 1. ¹H-NMR Spectral Assignments of AB-1 (3) and Its Derivatives[a,b]

| Proton(s) | AB-1 (3) | Dihydro AB-1 (9) | O-Methyl AB-1 (13) | O-Methyl dihydro AB-1 (12) | Des-N-Methyl-O-methyl dihydro AB-1 (11) |
|---|---|---|---|---|---|
| 1 | 5.165 (dd, 7.3, 11.3) | 5.098 (dd, 7.1, 11.7) | 5.126 (dd, 7.1, 11.7) | 5.051 (dd, 6.9, 11.6) | 4.866 (t, 9.5) |
| 2e | 2.117 (dd, 7.2, 13.2) | 2.115 (dd, 7.1, 13.1) | 2.128 (dd, 6.9, 13.2) | 2.136 (dd, 7.2, 13.4) | 2.114 (dd, 8.7, 13.3) |
| 2a | 1.865 (t, 12.4) | 1.852 (t, 12.4) | 1.893 (t, 12.5) | 1.866 (t, 12.4) | 2.502 (t, 11.7) |
| 5 | 6.329 | 6.331 | 6.359 | 6.356 | 6.215 |
| 8 | 8.225 (dd, 1.4, 8.0) | 8.231 (d, 7.2) | 8.179 (d, 7.8) | 8.187 (d, 8.3) | 8.312 (d, 7.8) |
| 9 | 7.111 (t, 7.4) | 7.108 (t, 7.5) | 7.002 (t, 7.4) | 7.005 (t, 7.4) | 7.056 (t, 7.7) |
| 10 | 7.401 (t, 8.7) | 7.362 (t, 7.7) | 7.224 (t, 7.8) | 7.187 (t, 7.3) | 7.408 (t, 8.2) |
| 11 | 6.907 (d, 8.5) | 6.800 (d, 8.5) | 6.671 (d, 8.3) | 6.545 (d, 8.5) | 7.027 (d, 8.0) |
| 6-OH | 14.280 | 14.254 | — | — | — |
| 6-OCH₃ | — | — | 3.997 | 4.009 | 3.951 |
| N₁₂-CH₃ | 3.732[c] | 3.668[c] | 3.650[c] | 3.543 | — |
| N₁₂-H | — | — | — | — | 8.780 |
| 13-CH₃, 14-CH₃ | 1.479, 1.595 | 1.472, 1.604 | 1.490, 1.599 | 1.488, 1.598 | 1.377,[c] 1.526 |
| 1' | 6.171 (d, 9.6) | 2.470 (m) | 6.145 (d, 9.5) | 2.443 (m) | 2.678, 2.847 (m) |
| 2' | 5.116 (d, 9.6) | 1.239, 1.409 (m) | 5.075 (d, 9.7) | 1.225, 1.361 (m) | 1.34 (m) |
| 8' | 8.472 (dd, 1.2, 8.0) | 8.419 (d, 8.4) | 8.484 (d, 7.8) | 8.432 (d, 8.4) | 8.423 (d, 8.1) |
| 9' | 7.369 (t, 8.9) | 7.321 (t, 7.2) | 7.371 (t, 7.6) | 7.329 (t, 7.6) | 7.337 (t, 7.4) |
| 10' | 7.752 (dt, 1.4, 7.9) | 7.714 (t, 7.9) | 7.756 (t, 7.8) | 7.720 (t, 7.4) | 7.725 (t, 7.7) |
| 11' | 7.413 (d, 8.7) | 7.386 (d, 8.5) | 7.421 (d, 8.6) | 7.397 (d, 8.5) | 7.429 (d, 8.7) |
| 6'-OH | 15.600 | 15.118 | 15.582 | 15.070 | 16.080 |
| N₁₂'-CH₃ | 3.767[c] | 3.591[c] | 3.713[c] | 3.578 | 3.833 |
| 13'-CH₃, 14'-CH₃ | 0.572, 1.141 | 0.445, 1.019 | 0.491, 1.067 | 0.368, 0.932 | 0.868, 1.364[c] |

[a]Recorded at 360 MHz in CDCl₃, δ TMS (CDCl₃)=0 ppm.
[b]Multiplicities (d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet) and coupling constants (Hz) are given in parentheses. Other signals are singlets.
[c]Assignments in a vertical column may be reversed.

TABLE 2.    $^1$H-nmr Spectral Assignments of AB-2 (**4**) and Dihydro AB-2 (**7**)[a, b]

| Proton(s) | Compound | |
|---|---|---|
| | AB-2 (**4**) | Dihydro AB-2 (**7**) |
| 3e | 2.104 (dd, 7.7, 13.4) | 2.103 (dd, 7.8, 13.2) |
| 3a | 2.235 (t, 12.0) | 2.163 (t, 11.1) |
| 4 | 4.904 (dd, 7.7, 11.5) | 4.906 (dd, 7.9, 11.2) |
| 7 | 8.406 (dd, 1.4, 8.0) | 8.389[d] (dd, 1.4, 7.9) |
| 8 | 7.218 (t, 7.5) | 7.215[e] (t, 7.5) |
| 9 | 7.676 (dd, 6.9, 8.6) | 7.674 (ddd, 0.9, 7.2, 8.2) |
| 10 | 7.459 (d, 8.7) | 7.454 (d, 8.7) |
| 12 | 6.384 | 6.366 |
| 5-OH | 15.371[c] | 14.931[f] |
| $N_{11}$-CH$_3$ | 3.868 | 3.795 |
| 13-CH$_3$, 14-CH$_3$ | 1.423, 1.498 | 1.435, 1.495 |
| 1' | 6.463 (d, 9.6) | 2.799 (m) |
| 2' | 5.309 (d, 9.6) | 1.568 (m) |
| 8' | 8.447 (dd, 1.4, 8.1) | 8.411[d] (dd, 1.5, 7.9) |
| 9' | 7.313 (t, 7.5) | 7.264[e] (t, 7.5) |
| 10' | 7.681 (dd, 6.9, 8.6) | 7.674 (ddd, 0.9, 7.2, 8.2) |
| 11' | 7.420 (d, 8.4) | 7.398 (d, 8.4) |
| 6'-OH | 14.779[c] | 14.721[f] |
| $N_{12'}$-CH$_3$ | 3.804 | 3.831 |
| 13'-CH$_3$, 14'-CH$_3$ | 0.748, 1.231 | 0.700, 1.157 |

[a]Recorded at 360 MHz in CDCl$_3$, δ TMS (CDCl$_3$)=0 ppm.
[b]Multiplicities (d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet) and coupling (Hz) are given in parentheses. Other signals are singlets.
[c-f]Assignments in a vertical column may be reversed.

nmr spectra of the dimers **3, 4, 8, 9, 11, 12,** and **13**. In the angular-angular dimers, higher field shifts of the C$_{11}$ protons (*peri* to nitrogen) were observed in **3, 9, 11, 12,** and **13** (Table 3). Since **11** shows this effect, the *N*-CH$_3$ group is not required; rather, the effect appears to be caused by shielding of the A ring by the A'-ring on the lower unit. The most marked effect was noted in **12** where the difference in chemical shift between the C$_{11}$-H and the C$_{11'}$-H was 0.852 ppm. On the other hand, the smallest difference was observed in compound **11** which lacks the *N*-methyl group in the upper unit.

As seen in Table 3, among compounds **3, 9, 12,** and **13**, it appears that the effect is

TABLE 3.    Summary of Chemical Shift Differences between H-11 and H-11' in AB-1 (**3**) and AB-2 (**4**) and Their Derivatives[a]

| Compound | Chemical Shift (δ ppm) | | Δδ |
|---|---|---|---|
| | H-11 | H-11' | (H-11-H-11') |
| Noracronycine (**2**) | 7.447 | — | — |
| AB-1 (**3**) | 6.907 | 7.413 | 0.506 |
| Dihydro AB-1 (**9**) | 6.800 | 7.386 | 0.586 |
| Des-*N*-methyl-*O*-methyl dihydro AB-1 (**11**) | 7.027 | 7.429 | 0.402 |
| *O*-Methyl dihydro AB-1 (**12**) | 6.545 | 7.397 | 0.852 |
| *O*-Methyl AB-1 (**13**) | 6.671 | 7.421 | 0.750 |
| AB-2 (**4**) | 7.459[b] | 7.420 | −0.039 |
| Dihydro AB-2 (**8**) | 7.454[b] | 7.398 | −0.056 |

[a]Recorded at 360 MHz in CDCl$_3$, δ TMS (CDCl$_3$)=0 ppm
[b]H-10

greatest in the methylated derivatives (**12** and **13**). As anticipated, the $C_{11}$-H resonances of **3, 9, 11, 12,** and **13** were shifted to higher field (0.402 ppm in **11** to 0.852 ppm in **12**) on comparison with noracronycine (**2**). The data, in part, reflect the difference between the three-dimensional structures of these compounds. The effect was not observed in the $^1$H-nmr spectra of AB-2 (**4**) and dihydro AB-2 (**7**) (Table 2). These higher field shifts were suspected to be caused by the shielding effect of the A′-ring. Through this same effect, the $C_8$, $C_9$, and $C_{10}$ protons also appeared at higher field compared with those for $C_{8'}$, $C_{9'}$, and $C_{10'}$, although the effects were less marked.

A facile method to distinguish whether the dimer has the linear-angular system or the angular-angular system is to count the number of triplet resonances that appear in the region of δ 7.7. If the dimer exhibits two such signals in this region, the dimer has the linear-angular system. The method is useful because this signal or signals can be distinguished easily from other aromatic resonances.

Higher field shifts of the geminal methyl units of the lower units of dimers **3, 4, 7, 9, 11, 12,** and **13** were also observed (Tables 1 and 2). Larger effects were observed in the $^1$H-nmr spectra of the dimers **3, 9, 12,** and **13**, which have the angular-angular system than those of **4** and **7**, which have the linear-angular system. In **11**, this effect was not as large as those observed for **3, 9, 12,** and **13**. These effects are postulated to be caused by the shielding of ring C in the upper unit (11).

A linear-angular system and an angular-angular system can also be distinguished by the use of nOe experiments. For example, when the $N$-methyl resonance (δ 3.795) of dihydro AB-2 (**7**) was irradiated, a 15% nOe enhancement was observed in the doublet at δ 7.454, as well as a 20% nOe enhancement in the singlet at δ 6.366.

These inferences obtained through the application of decoupling and nOe experiments permitted the assignment of the $^1$H-nmr spectrum and structure elucidation of AB-3 (**5**) as described previously (12). In the $^1$H-nmr spectrum of AB-3 (**5**), one of the three $N$-methyl singlets was shifted to higher-field by 0.3 ppm. Through nOe experiments, this signal was assigned to the $N_{12'}$-$CH_3$ (in the middle unit). No such signal was observed in the $^1$H-nmr spectra of dimers **3, 4, 8, 9, 11, 12,** and **13**. In addition, one of the two dibenzylic proton signals appeared at 0.5 ppm higher field. This signal was shifted to higher field on comparison with the corresponding dibenzylic proton signals of the dimers **3, 4, 8, 9, 11, 12,** and **13**. A higher-field shift of one of the three $N$-methyl signals was also observed in the $^1$H spectrum of dihydro AB-3 (**14**). These data were useful in deducing the structure of the new trimer described previously.

In the $^1$H-nmr spectrum of the new trimer, three $N$-methyl signals were observed with only one aromatic singlet. These data substantiated that the compound was a trimer of noracronycine. Only one doublet shifted to higher field was noted, which could be attributed to protons *peri* to the $N$-$CH_3$ groups, instead of two as has been observed in the $^1$H-nmr spectra of AB-3 (**5**) and dihydro AB-3 (**14**). On the other hand, two signals were observed in the region of δ 7.7 as had previously been observed in the $^1$H-nmr spectra of AB-2 (**4**) and dihydro AB-2 (**7**). These data indicated that the trimer had the linear-angular-angular system indicated in **16**.

No higher field shifted $N$-$CH_3$ signal or dibenzylic proton was observed in the spectrum of **16**, as had been noted in the $^1$H-nmr spectra of AB-3 (**5**) and dihydro AB-3 (**13**), suggesting that these shifts were observed only when an angular unit was inserted between two angular units. These inferences have proved to be extremely valuable in examining the structures of higher order oligomers of noracronycine (**2**) (13).

The mechanism of formation and biological activity of these compounds will be described subsequently.

## EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined using a Kofler hotstage
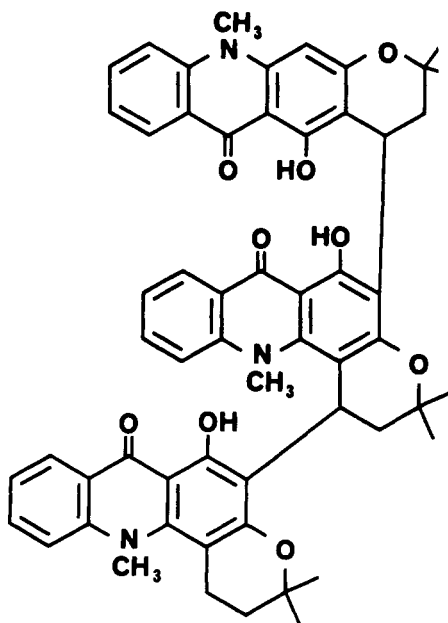
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microscope and are uncorrected. Uv spectra were recorded on a Beckman model DB-G spectrophotometer and ir spectra on a Beckman model IR 18-A spectrophotometer with polystyrene calibration at 1601 cm$^{-1}$ or a Nicolet model MX-1 FT-IR interferometer. Mass spectra were obtained with Varian MAT 112S double focussing spectrometer. $^1$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), Newark, Delaware, was used for preparative tlc.

PREPARATION OF ACRONYCINE (**1**), NORACRONYCINE (**2**), DIHYDRONORACRONYCINE (**6**), AND DES-N-METHYL ACRONYCINE (**10**).—The preparation and the physical and spectroscopic properties of these compounds have been described previously (10,15).

TREATMENT OF NORACRONYCINE (**2**) WITH METHANOLIC HCl.—Reaction procedures and the physical and spectroscopic properties of three of the products, AB-1 (**3**), AB-2 (**4**), and AB-3 (**5**), formed under reflux and at room temperature have been described previously (11,12).

SYNTHESIS OF DIHYDRO AB-2 (**7**).—(a) By coupling noracronycine (**2**) and dihydronoracronycine (**6**)—Reaction procedures and the physical and spectroscopic properties of dihydro AB-2 (**7**) were described previously (11). The $^1$H-nmr data are given in Table 2. (b) by refluxing a 1:10 mixture of AB-1 (**3**) or AB-2 (**4**) with dihydronoracronycine (**6**) in methanolic HCl. The reaction procedures and physical and spectral properties of dihydro AB-2 (**7**) were described previously (11,14). (c) through hydrogenation of AB-2 (**4**). Reaction procedures and the physical and spectroscopic properties of dihydro AB-2 (**7**) were described previously (11).

HYDROGENATION OF AB-1 (**3**).—AB-1 (**3**, 12.8 mg) was dissolved in EtOAc (10.0 ml), 10% Pd/C (2.0 mg) was added, H$_2$ gas was introduced after flushing successively with N$_2$ and H$_2$ and the mixture stirred at room temperature for 24 h. The reaction mixture was filtered and concentrated to afford a yellow powder which was purified by preparative tlc on silica gel eluting with C$_6$H$_6$-EtOAc (9:1) to afford dihydro AB-1 (**9**, 12.6 mg) as pale yellow fine rhomboids, mp 310-314°; ir $\nu$ max (KBr) 1627, 1587, 1554, 1501, 1408, 1330, 1269, 1171, 1149, and 1119 cm$^{-1}$. Other spectral properties are reported separately (11) and the $^1$H-nmr data are presented in Table 1.

SYNTHESES OF DIHYDRO AB-1 (**9**) AND DIHYDRO AB-2 (**7**) BY COUPLING OF NORACRONYCINE (**2**) AND DIHYDRONORACRONYCINE (**6**).—The reaction procedures were reported previously (11), and the physical and spectral properties of **7** and **9** were described above and elsewhere (11).

SYNTHESIS OF DES-N-METHYL-O-METHYL DIHYDRO AB-1 (**11**).—Des-N-methyl acronycine (**10**, 1.0 mg) and dihydronoracronycine (**6**, 10.8 mg) were dissolved in MeOH (3.5 ml) and 10N aqueous HCl (1.4 ml), and the orange-yellow solution refluxed on a steam bath for 6 h. The reaction mixture was diluted

with $H_2O$ (50 ml) and neutralized with $NaHCO_3$. After extraction with $CHCl_3$ ($2 \times 50$ ml), the combined $CHCl_3$ layers were dried over $Na_2SO_4$. Concentration of the $CHCl_3$ layer afforded a yellow powder (7.7 mg). Preparative tlc using $C_6H_6$-EtOAc (1:1) as solvent afforded des-N-methyl-O-methyl dihydro AB-1 (11, 1.5 mg, 72% yield) as well as unreacted dihydronoracronycine (6, 3.9 mg), des-N-methyl acronycine (10, 0.2 mg), and other minor products (0.4 mg). Des-N-methyl-O-methyl dihydro AB-1 (11) was obtained as yellow fine rhomboids, mp 318-320°; ir $\nu$ max (KBr) 1629, 1603, 1589, 1561, 1557, 1451, 1332, 1143, 1130, and 1121 cm$^{-1}$; uv $\lambda$ max (CHCl$_3$) 368 (sh), and 387 nm; $^1$H nmr, see Table 1; ms $m/z$ (rel. int.) 616 (M$^+$, 46), 601 (16), 598 (15), 587 (12), 318 (10), 311 (15), 310 (68), 309 (26), 308 (48), 307 (100), 306 (10), 292 (31), 280 (22), 278 (26), 264 (12), 263 (13), 262 (18), 254 (19), and 236 (9).

SYNTHESIS OF O-METHYL DIHYDRO AB-1 (12).—(a) Acronycine (1, 5.5 mg) and dihydronoracornycine (6, 50.0 mg) were dissolved in MeOH (20 ml) and 10N aqueous HCl (8 ml). The solution was heated on a steam bath for 6 h. The orange reaction solution was poured into cold $H_2O$ (300 ml) and extracted with $CHCl_3$ ($2 \times 300$ ml). Combined $CHCl_3$ layers were washed successively with 5% $NaHCO_3$ solution (300 ml) and $H_2O$ (300 ml), dried over $Na_2SO_4$, and concentrated in vacuo to afford an orange-yellow powder (49.4 mg). Preparative tlc on silica gel afforded O-methyl dihydro AB-1 (12, 5.1 mg) as well as unreacted acronycine (1, 3.1 mg) and dihydronoracronycine (6, 34.4 mg). A small amount of dihydro AB-2 (7) and other minor products were detected by tlc. The O-Methyl dihydro AB-1 (12) was obtained as fine yellow rhomboids, mp 286-289°; ir $\nu$ max (KBr) 1630, 1592, 1580, 1561, 1557, 1452, 1331, 1148, 1135, and 1119 cm$^{-1}$; uv $\lambda$ max (CHCl$_3$) 255 (log $\epsilon$ 3.62), 279 (3.75), 305 (3.31), 388 (3.10), and 393 nm (3.07); $^1$H nmr, see Table 1; ms $m/z$ (rel. int.) 630 (M$^+$, 41), 615 (42), 374 (9), 323 (35), 322 (100), 321 (14), 318 (24), 315 (12), 309 (12), 308 (46), 306 (17), 287 (9), and 250 (12). (b) Acronycine (1, 10.5 mg) and dihydronoracronycine (6, 20.8 mg) were dissolved in MeOH (12.5 ml) and 10N aqueous HCl (5.0 ml), and the mixture heated on a steam bath for 6 h. After cooling, the reaction mixture was diluted with $H_2O$ (50 ml) and extracted with $CHCl_3$ ($2 \times 50$ ml). The combined $CHCl_3$ layers were successively washed with 5% $NaHCO_3$ solution (50 ml) and $H_2O$ (50 ml) and dried over $Na_2SO_4$. Preparative tlc of this fraction afforded O-methyl dihydro AB-1 (12, 8.5 mg, 41% yield), unreacted acronycine (1, 7.0 mg) and dihydronoracronycine (6, 17.4 mg). (c) Acronycine (1, 4.5 mg) and dihydronoracronycine (6, 4.4 mg) were dissolved in MeOH (3.5 ml) and 10N aqueous HCl (1.4 ml), and the orange-yellow solution stirred at room temperature under a $N_2$ atmosphere for 24 h. The reaction mixture was diluted with $H_2O$ (50 ml) and neutralized with $Na_2SO_4$. Concentration of the $CHCl_3$ layer afforded a yellow powder (10.8 mg). Preparative tlc using $C_6H_6$-EtOAc (9:1) as solvent afforded O-methyl dihydro AB-1 (12, 0.9 mg), unreacted acronycine (1, 4.0 mg) and dihydronoracronycine (6, 3.8 mg).

SYNTHESIS OF AB-1 (3) BY TREATING NORACRONYCINE (2) WITH 98% $H_2SO_4$ AT ROOM TEMPERATURE.—Noracronycine (2, 305.8 mg) was dissolved in 98% $H_2SO_4$ (74 ml) and the yellow solution stirred at room temperature under $N_2$ atmosphere. After 24 h, the brown reaction mixture was poured into cold $H_2O$ (500 ml), extracted with $CHCl_3$ ($2 \times 1$ liter), and the combined $CHCl_3$ layers washed successively with 5% $NaHCO_3$ (1 liter) and $H_2O$ (1 liter), dried over $Na_2SO_4$, and concentrated in vacuo to afford an orange-yellow solid (282.4 mg). Column chromatography and repeated preparative tlc using $CHCl_3$ as solvent afforded AB-1 (3, 13.6 mg, 4% yield) as well as unreacted noracronycine (2, 184.8 mg). Identification of these compounds was accomplished by direct comparison with authentic samples. The physical and spectral properties of these compounds have been described previously (11).

SYNTHESIS OF O-METHYL AB-1 (13) BY COUPLING OF ACRONYCINE (1) AND NORACRONYCINE (2) IN 98% $H_2SO_4$ AT ROOM TEMPERATURE.—Acronycine (1, 50.0 mg) and noracronycine (2, 5.0 mg) were dissolved in 98% $H_2SO_4$, and the mixture stirred under a $N_2$ atmosphere at room temperature. After 2 days, the deep brown solution was poured into cold $H_2O$ and the diluted orange solution was extracted with $CHCl_3$ ($2 \times 100$ ml), dried over $Na_2SO_4$, and concentrated in vacuo to yield an orange-yellow powder (64.2 mg). Preparative tlc using $C_6H_6$-EtOAc (1:1) as solvent afforded O-methyl AB-1 (13, 3.0 mg, 29% yield), unreacted acronycine (1, 42.3 mg), noracronycine (2, 2.5 mg), and a mixture of minor products (1.9 mg). O-Methyl AB-1 (13) crystallized from $CHCl_3$ as fine yellow rhomboids, mp 273° (decomp.); ir $\nu$ max (KBr) 1630, 1599, 1591, 1580, 1561, 1557, 1495, 1485, 1267, and 1135 cm$^{-1}$; uv $\lambda$ max (CHCl$_3$) 258 (sh), 279, 306, 322 (sh), and 393 nm; $^1$H nmr, see Table 1; ms $m/z$ 628 (M$^+$, 16%), 613 (14), 372 (9), 322 (10), 321 (22), 320 (50), 309 (11), 308 (23), 306 (20), and 256 (10).

REACTION OF ACRONYCINE (1) WITH 98% $H_2SO_4$ AT ROOM TEMPERATURE.—Acronycine (1, 60.2 mg) was dissolved in 98% $H_2SO_4$ (15 ml) and the deep red solution stirred at room temperature under a $N_2$ atmosphere. After 4 days, the reaction mixture was poured into cold $H_2O$ (200 ml), extracted with 5% $NaHCO_3$ (300 ml) and $H_2O$ (300 ml), dried over $Na_2SO_4$ and concentrated in vacuo to afford unreacted acronycine (1, 52.0 mg).

HYDROGENATION OF O-METHYL AB-1 (14).—O-Methyl AB-1 (13, 1.0 mg) was dissolved in

EtOAc (1.0 mg), 5% Pd/C (0.5 mg) was added, $H_2$ gas was introduced after flushing successively with $N_2$ and $H_2$, and the mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and concentrated to afford a yellow powder (0.6 mg). By tlc analysis, the reaction product was found to be approximately 1:1 mixture of O-methyl dihydro AB-1 (**12**) and unreacted O-methyl AB-1 (**13**).

SYNTHESIS OF AB-2 (**4**) AND AB-1 (**3**) BY TREATING NORACRONYCINE (**2**) WITH *p*-TOLUENE SULFONIC ACID.—Noracronycine (**2**, 30.7 mg) and *p*-toluene sulfonic acid (65.5 mg) were dissolved in $CH_2Cl_2$ (10.0 ml) and refluxed on a steam bath for 6 h. The reaction mixture was poured into cold $H_2O$ (100 ml) and extracted with $CHCl_3$ (2×150 ml). The combined $CHCl_3$ layers were successively washed with 5% $NaHCO_3$ solution (100 ml) and $H_2O$ (100 ml), dried over $Na_2SO_4$, and concentrated in vacuo to afford an orange powder (37.5 mg). Preparative tlc afforded AB-1 (**3**, 4.9 mg, 16%) and AB-2 (**4**, 13.7 mg, 45%) as well as unreacted noracronycine (**2**, 7.3 mg) and other minor products (5.0 mg).

SYNTHESIS OF AB-1 (**3**) BY TREATING NORACRONYCINE (**2**) WITH METHANOLIC 98% $H_2SO_4$ IN VARIOUS CONCENTRATIONS.—Separate samples of noracronycine (**2**, 5 mg each) were dissolved in MeOH-98% $H_2SO_4$ (5.0 ml) in the following proportions 0:1, 1:9, 1:4, 3:7, 2:3, 1:1, 3:2, 7:3, 4:1, and 9:1. Each solution was stirred at room temperature under $N_2$ atmosphere, and after 24 h, each reaction mixture was poured into cold $H_2O$ (50 ml) and extracted with $CHCl_3$ (2×50 ml). The combined $CHCl_3$ layers were washed successively with 5% $NaHCO_3$ (50 ml) and $H_2O$ (50 ml), dried over $Na_2SO_4$, and concentrated in vacuo. Each sample was redissolved in $CHCl_3$ (0.2 ml) and applied to silica gel plates (20×20 cm, 0.25 mm thickness) and each plate was eluted with $CHCl_3$-MeOH (99:1). Band I (Rf 0.61), corresponding to unreacted noracronycine (**2**) and band II (Rf 0.40), corresponding to AB-1 (**3**) were removed and extracted with $CHCl_3$ (20 ml) and concentrated in vacuo. The yield of AB-1 (**3**) was optimized (40%) with the proportions 1:1 and 3:2 at this length of time.

SYNTHESIS OF AB-1 (**3**) BY TREATING NORACRONYCINE (**2**) WITH 98% $H_2SO_4$-MeOH (1:1) AT ROOM TEMPERATURE.—Noracronycine (**2**, 201.6 mg) was dissolved in 98% $H_2SO_4$-MeOH (1:1, 200 ml) and the orange solution stirred at room temperature under a $N_2$ atmosphere. After 24 h, the orange reaction mixture was poured into cold $H_2O$ (1 liter) and extracted with $CHCl_3$ (2×500 ml). The combined $CHCl_3$ layers were successively washed with 5% $NaHCO_3$ solution (500 ml) and $H_2O$ dried over $Na_2SO_4$, and concentrated to give an orange-yellow solid (251.8 mg). Repeated preparative tlc using $CHCl_3$-MeOH (99:1) as solvent afforded AB-1 (**3**, 81.3 mg, 40% yield) as well as unreacted noracronycine (**2**, 94.8 mg) and a mixture of minor products (32.1 mg).

SYNTHESIS OF DIHYDRO AB-1 (**9**) THROUGH THE COUPLING OF AB-1 (**3**) AND DIHYDRONORACRONYCINE (**6**) IN METHANOLIC HCl AT ROOM TEMPERATURE.—The reaction procedures and physical and spectral properties of dihydro AB-1 (**9**) were described previously (11,14).

SYNTHESIS OF AB-3 (**5**).—(a) A procedure describing the formation of AB-3 (**5**) together with AB-1 (**3**) and a pentamer, AB-5A has been published previously (11,12). An improved procedure follows. (b) Noracronycine (**2**, 100 mg) was dissolved in 98% $H_2SO_4$-MeOH (9:1, v/v, 100 ml) and the mixture stirred under a $N_2$ atmosphere at room temperature for 24 h. The reaction mixture was poured into cold $H_2O$ (500 ml) and extracted with $CHCl_3$ (2×500 ml). The combined $CHCl_3$ layers were washed with 5% $NaHCO_3$ solution (500 ml) and $H_2O$ (500 ml) and the solution dried ($Na_2SO_4$). Through tlc analysis, it was estimated that the reaction mixture contained AB-1 (**3**) and noracronycine (**2**) in the approximate ratio (1:3).

The reaction mixture was again dissolved in a mixture of 98% $H_2SO_4$-MeOH (1:9, v/v, 100 ml) and stirred under a $N_2$ atmosphere at room temperature. After 24 h, the reaction mixture was worked-up as previously described to afford, by preparative tlc, AB-3 (**5**) in 20% yield together with AB-1 (**3**, 19% yield) and a mixture of minor components.

SYNTHESIS OF DIHYDRO AB-3 (**13**).—(a) Dihydro AB-3 (**13**) could be produced through the coupling of AB-1 (**3**) and dihydronoracronycine (**6**) in methanolic HCl at room temperature, as described previously (12). (b) Catalytic (5% Pd/C) hydrogenation of AB-3 (**5**) was accomplished at room temperature in EtOAc to afford dihydro AB-3 (**13**) in 66% yield.

SYNTHESIS OF THE LINEAR-ANGULAR-ANGULAR TRIMER **16**.—AB-2 (**4**, 2.0 mg) and dihydronoracronycine (**6**, 10.0 mg) were dissolved in a mixture of 10N aqueous HCl-MeOH (2:5, 16 ml) and the yellow solution stirred under a $N_2$ atmosphere at room temperature. After 24 h, the reaction mixture was diluted by $H_2O$ (50 ml) and neutralized with $NaHCO_3$. Extraction with $CHCl_3$ (2×50 ml) followed by drying ($Na_2SO_4$) and concentration in vacuo afforded an orange-yellow powder. Preparative tlc of this reaction mixture afforded the trimer **16** (0.9 mg), dihydro AB-1 (**9**, 0.4 mg), dihydro AB-2 (**8**, 0.4 mg), unreacted AB-2 (**4**, 0.4 mg), and dihydronoracronycine (**6**, 6.6 mg).

The trimer **16** displayed the following spectral properties: ir $\nu$ max (KBr) 3470, 2953, 1636, 1629,

1624, 1617, 1590, 1561, 1457, 1449, 1437, and 1329 cm$^{-1}$; uv λ max (CHCl$_3$) 253, 292, 343, and 410 nm; $^1$H nmr δ (360 MHz, CDCl$_3$) 0.880 (3H, s), 0.976 (3H, s), 1.088 (3H, s), 1.466 (3H, s), 1.510 (3H, s), 1.961 (1H, dd, $J$=7.2, 12.7 Hz), 2.203 (1H, dd, $J$=7.7, 12.8 Hz), 3.559 (6H, s), 3.831 (3H, s), 4.944 (H, dd, $J$=7.3, 12.1 Hz), 4.978 (1H, dd, $J$=7.6, 11.7 Hz), 6.395 (1H, s), 6.708 (1H, d, $J$=8.5 Hz), 7.083 (1H, t, $J$=7.5 Hz), 7.242 (1H, t, $J$=7.5 Hz), 7.283 (1H, t, $J$=8.1 Hz), 7.304 (1H, t, $J$=7.5 Hz), 7.375 (1H, d, $J$=8.6 Hz), 7.482 (1H, d, $J$=8.7 Hz), 7.700 (2H, t, $J$=7.8 Hz), 8.267 (1H, d, $J$=8.6 Hz), 8.405 (1H, d, $J$=7.3 Hz), 8.444 (1H, d, $J$=8.7 Hz), 14.733 (1H, s), 14.856 (1H, s), and 14.968 (1H, s).

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