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CHEMISTRY OF ACRONYCINE, II. DIMERIZATION OF NORACRONYCINE[1,2]

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ABSTRACT.—Heating acronycine (**1**) or noracronycine (**2**) in methanolic HCl afforded several products of which six have been obtained in pure form. The simplest two of these are dimers of noracronycine **3** and **8**, one of which contains an isoacronycine skeleton. The structures of the isolates were established by single-crystal X-ray crystallography and substantiated by proton and ^{13}C-nmr spectroscopy. A mechanism is proposed for the rearrangement of the bisnoracronycine (**8**) to the isonoracronycine-noracronycine (**3**).

Acronycine (**1**) is an acridone alkaloid with an additional hemiterpene unit attached to the parent nucleus. In the initial structure considerations, the question arose as to whether the hemiterpene unit had cyclized to C-2 or C-4, to form a linear or angular structure, respectively. It was eventually shown that the angular structure was correct through a combination of chemical (2), spectroscopic (3), and X-ray crystallographic analyses (4).

First isolated from the Australian scrub ash *Acronychia baueri* Schott (Rutaceae) (5-7), acronycine (**1**) possesses the broadest spectrum of *in vivo* antineoplastic activity of any plant-derived natural product (8,9). In spite of this, very little is known of its chemistry or mode of action. Recognizing the importance of nmr spectroscopy in any type of structure determination concerning alkaloids and their derivatives, we began our work in this area by reporting on the assignment of the ^{13}C-nmr spectrum of acronycine and some simple derivatives (1). In the course of this work, noracronycine (**2**) was produced semisynthetically from acronycine (**1**) through a reaction first described by Brown *et al.* (10). This group observed that in the demethylation reaction of **1** with hot alcoholic HCl, an amorphous solid was obtained instead of **2**. Because of our interest in the development of acronycine and/or its derivatives as antineoplastic agents, we elected to investigate this reaction further.

Acronycine was dissolved in a mixture of MeOH and 10N HCl, and, after refluxing for 6 h, the organic residue was obtained as an orange-yellow powder. By tlc analysis, it was apparent that several products other than noracronycine and unreacted **1** were present. We have designated these substances as AB-1, AB-2, AB-3, *etc.*, according to their Rf value. We are, here, concerned with the formation and structure elucidation of the simplest products, AB-1 and AB-2

Closer examination of the reaction showed that a higher yield of the products could be obtained if noracronycine (**2**) were used as the starting material. Noracronycine (**2**) was formed in 65% yield by heating acronycine hydrochloride at 140° for 1 h according to the method of Brown *et al.* (10) and was reacted as described above with methanolic HCl. Column chromatography of the product, followed by extensive preparative tlc, afforded two compounds, AB-1 and AB-2, as crystalline products.

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[1]For Part 1 in this series see reference (1).

[2]This work was presented in part at the 23rd Annual Meeting of the American Society of Pharmacognosy held at the University of Pittsburgh, Pittsburgh, PA, August 2-6, 1982.

AB-1 crystallized as fine, yellow needles, mp 303.0-304.5° and displayed a uv spectrum similar to that of noracronycine (**2**). The molecular ion in the mass spectrum of AB-1 was observed at *m/z* 614, twice that of noracronycine. In the ^{1}H-nmr spectrum, there were four geminal methyl signals (δ 0.572, 1.141, 1.479, and 1.595), two N-CH_3 signals (δ 3.732 and 3.767), two H-bonded phenolic OH signals (δ 14.280 and 15.600), and eight aromatic protons. Three new resonances were observed, a triplet (J=12.4 Hz) at δ 1.865, and two doublets of doublets at δ 2.117 (J=7.2, 13.2 Hz) and δ 5.165 (J=7.3, 11.7 Hz). These signals were attributed to protons of a pyran ring. However, only one aromatic singlet (at δ 6.329) was observed, and only one pair of doublets (J=9.6 Hz) for the C_1-H and C_2-H (δ 5.116 and 6.171). These data suggested that AB-1 was a dimer of noracronycine where a new carbon-carbon bond had been formed between C-1 of one unit and C-5 of a second unit.

The spectral properties of AB-2 were almost identical to those of AB-1, including a molecular ion at *m/z* 614, and a ^{1}H-nmr spectrum which displayed the same multiplicities as the signals of AB-1. Some distinct differences were observed for the aliphatic triplet, which now was deshielded to δ 2.235, and an aromatic proton, which was shifted from δ 6.907 in AB-1 to δ 7.420 or 7.459 in AB-2. The doubly benzylic proton was now shifted slightly upfield to δ 4.904, but the multiplicity was unchanged. Eight distinct aromatic protons were observed.

Again, only one pair of doublets for the C_1 and C_2-H were observed, together with one singlet aromatic proton (δ 6.384) and two groups of four aromatic protons. Once again it appeared that AB-2 was a dimer of noracronycine, where a new carbon-carbon bond had also been formed between C-1 of one unit and C-5 of a second unit. In the ^{13}C-nmr spectrum, two N-CH_3 signals were observed at δ 43.72 and 33.76; the former resonance is very similar to that appearing in noracronycine (**2**) (δ 43.69) (1), but the latter signal was shifted to a higher field by approximately 10 ppm. A similar chemical shift (δ 33) had been observed previously for *N*-methyl acridone and related compounds (11,12). The remainder of the spectrum established AB-2 to be composed of two units of noracronycine but did not clarify how it might differ from AB-1.

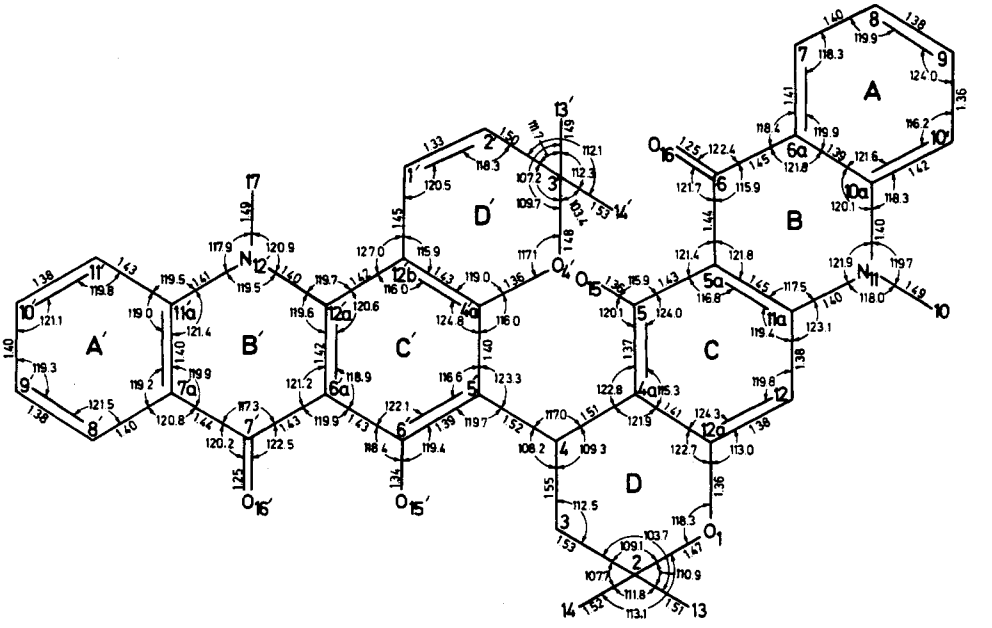
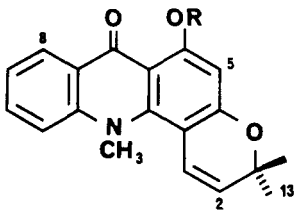


FIGURE 1. Atomic distances and angles of AB-2. Standard deviations of atomic distances are less than 0.01Å, and of the angles less than 0.9°.

X-Ray crystallographic analysis of AB-2 (Figure 1) indicated that it had the structure **3** and was composed of a noracronycine (angular) and an isonoracronycine (linear) unit. The higher field shift in the ^{13}C-nmr spectrum of one of the two N-CH_3 signals could now be explained as being that group in the linear system. The ^{1}H-nmr spectrum was also readily explained in terms of this structure.

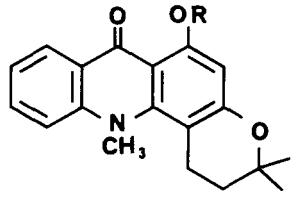
We envisaged AB-1 as having an angular-angular system and attempted to synthesize the dihydro derivative of AB-1 by coupling noracronycine with dihydronoracronycine (**4**). It was initially established that no reaction occurred when dihydronoracronycine (**4**) alone was refluxed with methanolic HCl, and only dihydronoracronycine (**4**) was produced under similar conditions from dihydroacronycine (**5**).



R

1 CH_3

2 H



R

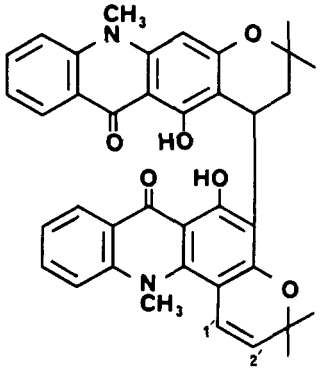
4 H

5 CH_3

Noracronycine (**2**) and dihydronoracronycine (**4**) were mixed in the ratio 1:10 and refluxed in methanolic HCl for 6 h. By mixing **2** and **4** in the ratio 1:10, we anticipated that a molecule of **2** would react preferentially with a dihydronoracronycine (**4**) molecule. In the event, a dimer of MW 616 was obtained in 86% yield. Catalytic hydrogenation of AB-1 afforded a dihydro derivative (M^+ 616), but direct comparison of this compound with the synthetic dimer indicated that these compounds were not identical. Therefore, either the postulated structure of dihydro-AB-1 or that of the synthetic dimer was incorrect.

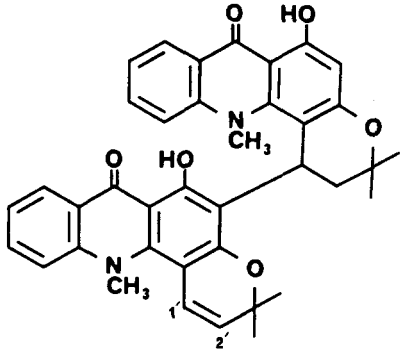
Reduction of AB-2 afforded a dihydro-derivative **6**, which was found to be identical to the synthetic dimer. Therefore, in the coupling reaction of **2** and **4**, rearrangement of an angular system to the linear system had also occurred.

The facile nature of this rearrangement led to a reaction in which AB-1 was refluxed in methanolic HCl. The linear-angular dimer AB-2 (**3**) and noracronycine (**2**) were produced, and under the same conditions, noracronycine (2) and isonoracronycine (**7**) were produced from AB-2. These data suggest that AB-1, having the structure **8**, is prob-



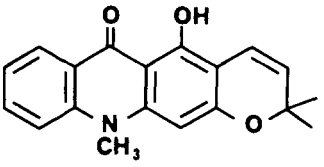
3 AB-2

6 1′,2′-H_2



8 AB-1

9 1′,2′-H_2



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ably an intermediate in the formation of AB-2 (**3**) and is constructed from two noracronycine moieties. A coupling reaction of noracronycine (**2**) and dihydronoracronycine (**4**) at room temperature for 3 days surprisingly afforded a 1:1 mixture of dihydro-AB-1 (**9**) and dihydro-AB-2 (**6**).

When noracronycine (**2**) was treated with methanolic HCl at room temperature for 24 h, AB-1 **8** and AB-3 were formed, but not AB-2. When the reaction was extended for 7 days, a small amount of AB-2 was formed. The results strongly suggest that AB-1 is the angular-angular isomer **8**, which can rearrange to AB-2, the linear-angular isomer **3**, either on prolonged treament with methanolic HCl at room temperature or more rapidly under reflux. Establishment of this structure was derived from single crystal X-ray analysis, as shown in Figure 2.

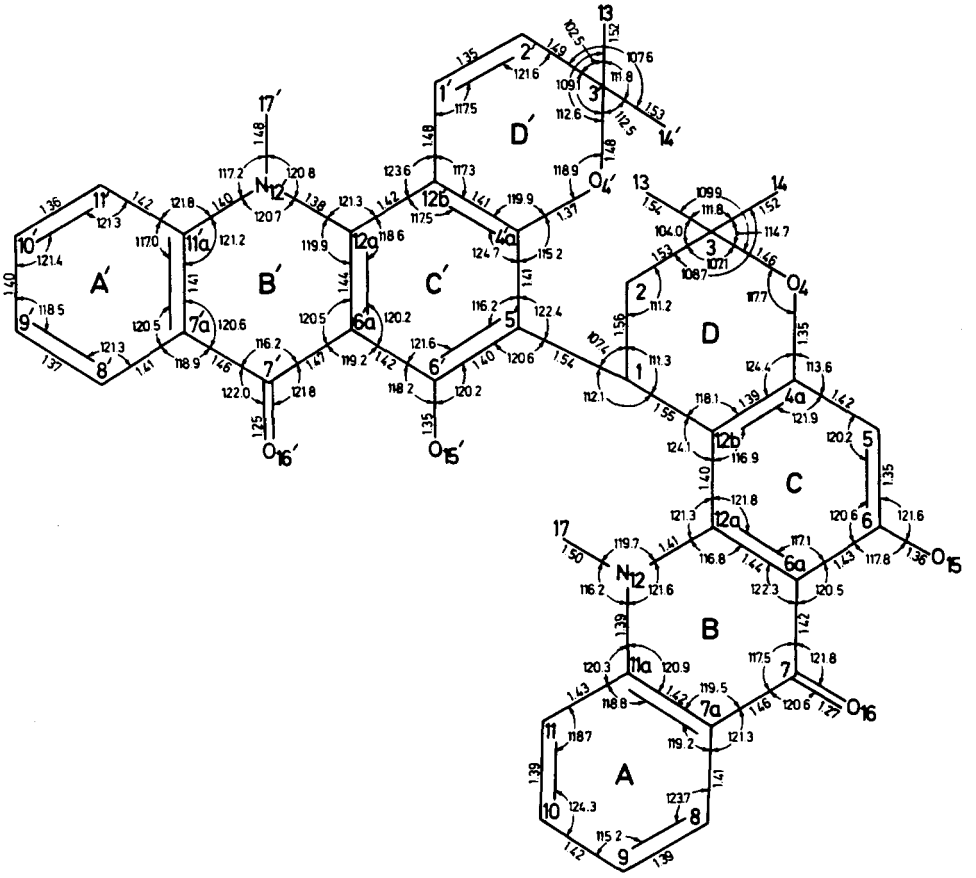


FIGURE 2. Atomic distances and angles of AB-1.

Most of the features of the ^{1}H-nmr spectrum of AB-1 could now be assigned with certainty. Thus, the doubly benzylic proton at C-1 was observed as a doublet of doublets (J=7.3, 11.7 Hz) at δ 5.165, and the adjacent methylene protons were observed at

δ 1.865 and 2.117. The aromatic protons were assigned initially by inference with other compounds in the series and subsequently through double irradiation techniques.

The short $C_{1'}$-$C_{2'}$ distances in ring D′ in both AB-1 and AB-2 (1.35 and 1.33 Å, respectively) establish the unsaturation in this ring. Thus A′B′C′D′ is an almost planar system, whereas ring D exists in an envelope conformation. One of the interesting features concerning compounds in the *N*-methyl acridone series is the angle that the *N*-methyl group subtends with the plan of the B-ring. Previous work in this area demonstrated that in bromodihydroacronycine the *N*-methyl group was 18° out of the plane (4), and although a lack of planarity was observed in *N*-methylacridone, the angle was not given (13). In AB-1, the angles between the B-rings and the *N*-methyl groups were found to be 24.4° and 19.2° for ring B and ring B′, respectively. For AB-2, the corresponding data were 14.3° and 19.5°, respectively. The out-of-plane angle of the *N*-methyl group in the linear noracronycine unit of AB-2 is substantially smaller than that for the other *N*-methyl groups and correlates with the shift to higher field observed for the methyl carbon in the ^{13}C-nmr spectrum.

AB-1 and AB-2 display decidedly different molecular shapes in the crystal structure. Whereas in AB-1 (Figure 3) the two ring systems are folded against each other, the conformation of AB-2 (Figure 4) is such that it is "stretched." This can be expressed in terms of the torsional angles around the connecting bond between the two units in the molecules:

AB-1	$C_{6'}$-$C_{5'}$-C_1-C_{12b}	139°
AB-2	$C_{6'}$-$C_{5'}$-C_4-C_{4a}	−138°

The sign is positive if vector $C_{6'}$-$C_{5'}$ is rotated clockwise to fit C_1-C_{12b} or C_4-C_{4a}, respectively.

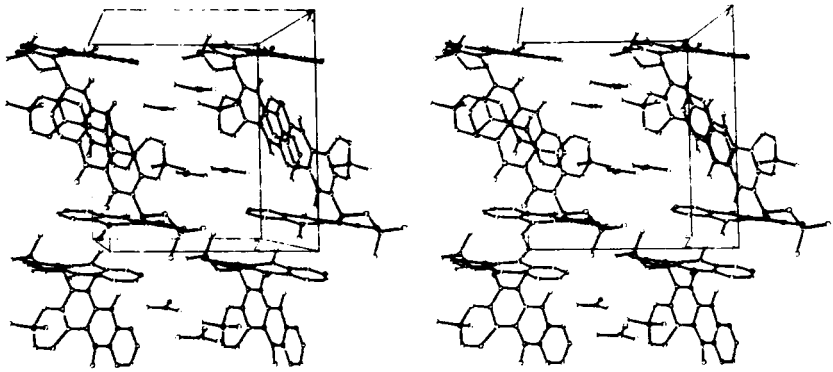


FIGURE 3. Crystal structure and molecular packing in the unit cell of AB-1. Acetone molecules are visible in the channel between the two layers of stacking.

As can be seen from the stereo structure of AB-1, one of the methyl groups on ring D′ (C-13′) lies above ring C and becomes influenced by the ring current. The distance from C-13′ to the ring system is only 3.3 Å. We assign the singlet of δ 0.572 in the ^{1}H-nmr spectrum to this methyl group, shielded by 0.9 ppm from its expected value of δ 1.50.

In the crystal of AB-1, the individual ring systems form an aggregation of sandwich layers such that ABCD always interfaces with A′B′C′D′ of another molecule. This results in two layers of stacking within the crystal, one parallel to the crystallographic XY-plane, and the other, according to the conformation of the molecule, is tilted by 68°. The distance between the two aggregated rings is approximately 3.3 Å. Between

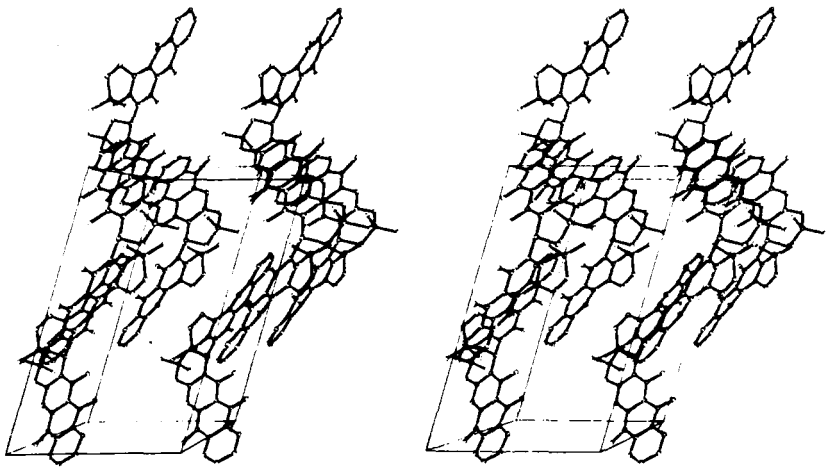
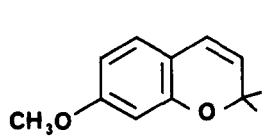


FIGURE 4. Crystal structure and molecular packing in the unit cell of AB-2.

the sandwich layers, around the crystallographic center, is a channel containing two acetone molecules per unit cell.

In the crystal of AB-2, the individual ring systems aggregate such that ABCD always interfaces with ABCD of another molecule and similarly A′B′C′D′ interfaces with A′B′C′D′ in a second molecule. This results in two distinct layers of stacking. One effect of this is that the 3′β-methyl group lies above the AB rings of another unit and, therefore, experiences some shielding. It is this methyl group (C-14′) that is assigned to δ 0.748. This apparent correlation between the ^{1}H-nmr spectral data and the X-ray crystallographic data suggests that AB-1 and AB-2 maintain the same conformations in their respective solution and crystal states.

There are two natural product examples of the nucleophilic attack of a 2,2-dimethyl chromene at the 4-position. Thus, treatment of precocene-I (**10**) with trichloroacetic acid afforded the dimer **11** (14), and it had previously been shown that the corresponding dimethoxy derivative ageratochromene (**12**) could be dimerized with either methanolic HCl or HOAc-H_2SO_4 (15). In this case, a 4′-3 bond is formed in the product **13**. We believe the reaction described herein to be the first example in any alkaloid system containing a chromene moiety.



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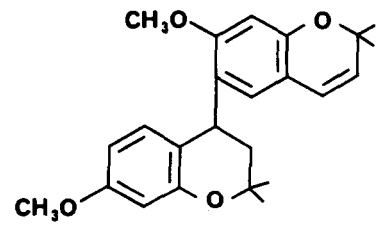

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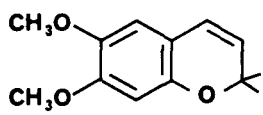

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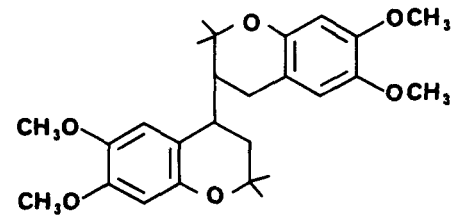

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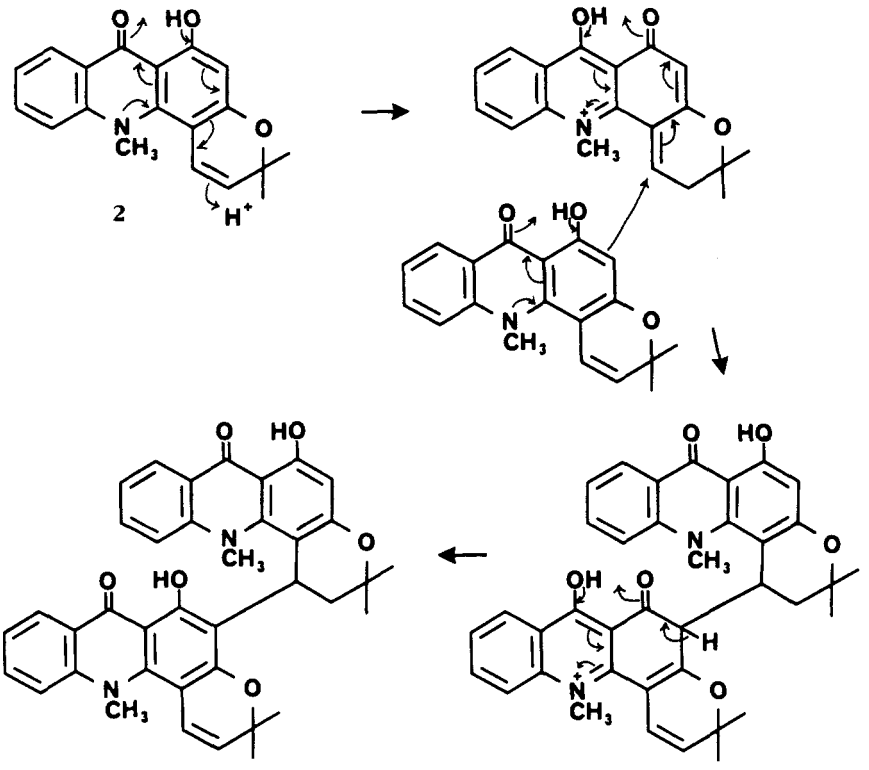


8 AB-1

SCHEME 1. Proposed mechanism for the dimerization of noracronycine (**2**) to AB-1 (**8**).

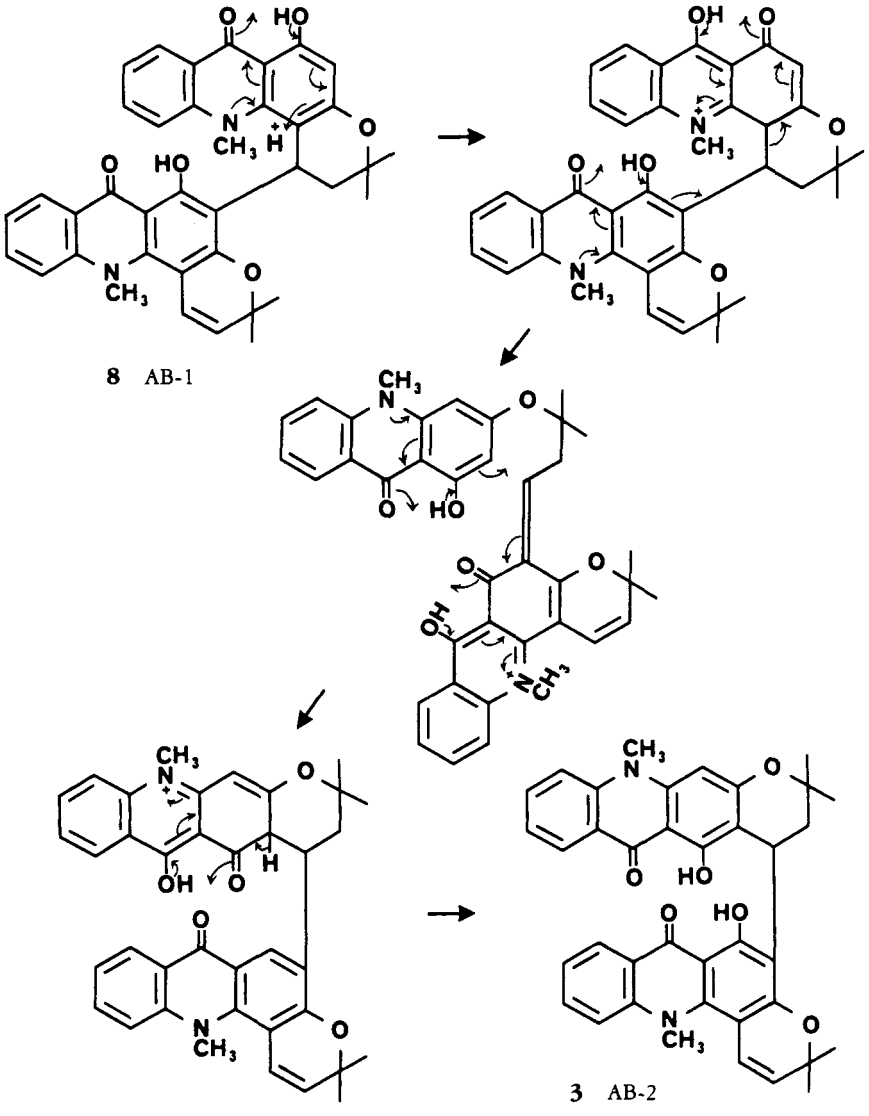
The proposed mechanism of formation of AB-1 (**8**) is shown in Scheme 1 and involves an initial protonation at C-2 of noracronycine (**2**), followed by nucleophilic attack of C-5 of the second unit and deprotonation.

In the experiments thus described, it is apparent that AB-2 (**3**) is formed from AB-1 (**8**), that is, one of the angular units of AB-1 is rearranged to a linear configuration. This apparently occurs intramolecularly, the C-1-C-12b bond being broken and C-1 being reattached to C-5. Because this rearrangement of the angular to the linear form does not occur in the monomers acronycine (**1**) and noracronycine (**2**), it is clear that the lower angular unit is essential for observing the rearrangement. Scheme 2 proposes a possible mechanism for this rearrangement. Crucial in this process is the protonation of C-12b followed by stabilization of an intermediate benzylic cation by way of the acridone nitrogen. Carbon-1 is thus available for nucleophilic attack at C-5, and deprotonation then leads to AB-2 (**3**).

We are presently investigating the mechanism of the reaction and the formation of other products from the reaction of noracronycine (**2**) with acid and will report on the biological activity of these compounds subsequently.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined using a Kofler hot-stage microscope and are uncorrected. Ir spectra were recorded with a Beckman model IR 18-A spectrophotometer with polystyrene calibration at 1601 cm^{-1} or with a Nicolet model MX-1 FT-IR interferometer; absorbtion bands are recorded in wave numbers (cm^{-1}). The uv spectra were measured with a Beckman model DB-G spectrophotometer. Mass spectra were taken on a Varian MAT 112S double focusing spectrometer. The ^{1}H- and ^{13}C-nmr spectra were obtained in $CDCl_3$ at the NSF Regional NMR Facili-



SCHEME 2. Proposed mechanism for the rearrangement of AB-1 (**8**) to AB-2 (**3**).

ty at the University of Illinois at Urbana on a Nicolet NT-360 instrument. Tetramethylsilane (TMS) was used as an internal standard and chemical shifts are recorded in δ ppm units. Single crystal X-ray data were measured on a computer-driven Nicolet-R3m diffractometer with CuK_{μ} radiation ($\theta_{max}=58°$ (AB-1), 56° (AB-2), Ω-scan, scan range 1°).

The preparation and properties of acronycine (**1**), noracronycine (**2**), dihydroacronycine (**5**), and dihydronoracronycine (**4**) were described previously (1).

FORMATION AND ISOLATION OF AB-1 (**8**) AND AB-2 (**3**).—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[3] followed by preparative tlc afforded as the two least polar products AB-1 (**8**, 13 mg) and AB-2 (**3**, 18 mg).

AB-1 (**8**) initially crystallized from $CHCl_3$ as fine yellow needles, mp 303.0-304.5°; ir (KBr): ν max 3440, 1633, 1587, 1558, 1501, 1463, 1396, 1329, 1266, 1172 and 1144 cm^{-1}; uv ($CHCl_3$): λ max 256

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

(log ε 3.68), 281 (3.81), 302 (sh) (3.67), 347 (sh) (3.20) and 412 nm (3.06); ms: *m/z* (% relative intensity) 615 (24.9), 614 (M^+, 58.4), 600 (14.9), 599 (34.6), 572 (10.1), 571 (24.3), 372 (13.4), 330 (21.4), 321 (15.7), 320 (32.7), 309 (19.6), 308 (88.7), 307 (56.1), 306 (22.1), 304 (14.3), 294 (10.1), 293 (23.5), 292 (100.0), 278 (23.4), 277 (30.1), and 146 (11.1); 360 MHz ^{1}H-nmr ($CDCl_3$): δ 0.572 (s, 3H, 13′-CH_3), 1.141 (s, 3H, 14′-CH_3), 1.479 (s, 3H, 13- or 14-CH_3), 1.595 (s, 3H, 14- or 13-CH_3), 1.865 (t, 1H, J=12.4 Hz, C_2-H_a), 2.117 (dd, 1H, J=7.2, 13.2 Hz, C_2-H_e), 3.732 (s, 3H, N-CH_3), 3.767 (s, 3H, N-CH_3), 5.116 (d, 1H, J=9.6 Hz, $C_{2'}$-H), 5.165 (dd, 1H, J=7.3, 11.7 Hz, C_1-H), 6.171 (d, 1H, J=9.6 Hz, $C_{1'}$-H), 6.329 (s, 1H, C_5-H), 6.907 (d, 1H, J=8.5 Hz, C_{11}-H), 7.111 (t, 1H, J=7.4 Hz, C_9-H), 7.369 (t, 1H, J=8.9 Hz, $C_{9'}$-H), 7.401 (t, 1H, J=8.7 Hz, C_{10}-H), 7.413 (d, 1H, J=8.7 Hz, $C_{11'}$-H), 7.752 (ddd, 1H, J=1.4, 7.8 and 7.9 Hz, $C_{10'}$-H), 8.225 (dd, 1H, J=1.4, 8.0 Hz, C_8-H or $C_{8'}$-H), 8.472 (dd, 1H, J=1.2, 8.0 Hz, $C_{8'}$-H or C_8-H), 14.280 (s, 1H, D_2O exchangeable, -OH), and 15.600 (s, 1H, D_2O exchangeable, -OH).

AB-2 (**6**) initially crystallized from $CHCl_3$-C_6H_6 as fine yellow needles, mp 275.0-280.5°; ir (KBr): ν max 3443, 1632, 1591, 1558, 1500, 1451, 1400, 1328, 1267, 1185 and 1139 cm^{-1}; uv ($CHCl_3$): λ max 255 (log ε 3.76), 283 (3.92), 303 (sh) (3.79) and 412 nm (3.11); ms: *m/z* (% relative intensity) 615 (27.4), 614 (M^+, 65.8), 596 (19.5), 595 (11.8), 581 (14.2), 571 (18.3), 527 (12.1), 309 (10.4), 308 (54.3), 307 (43.7), 306 (25.3), 298 (10.6), 293 (22.3), 292 (100.0), 278 (12.4), 277 (24.0), and 146 (12.9); 360 MHz ^{1}H-nmr ($CDCl_3$): δ 0.748 (s, 3H, 14′-CH_3), 1.231 (s, 3H, 13′-CH_3), 1.423 (s, 3H, 13- or 14-CH_3), 1.498 (s, 3H, 14- or 13-CH_3), 2.104 (dd, J=7.7, 13.4 Hz, C_3-H_e), 2.235 (t, 1H, J=12.0 Hz, C_3-H_a), 3.804 (s, 3H, N-CH_3), 3.868 (s, 3H, N-CH_3), 4.904 (dd, 1H, J=7.7, 11.5 Hz, C_4-H), 5.309 (d, 1H, J=9.6 Hz, $C_{2'}$-H), 6.384 (s, 1H, C_{12}-H), 6.463 (d, 1H, J=9.6 Hz, $C_{1'}$-H), 7.218 (t, 1H, J=7.5 Hz, C_8-H or $C_{9'}$-H), 7.313 (t, 1H, J=7.5 Hz, $C_{9'}$-H or C_8-H), 7.420 (d, 1H, J=8.4 Hz, C_{10}-H or $C_{11'}$-H), 7.459 (d, 1H, J=8.7 Hz, $C_{11'}$-H or C_{10}-H), 7.676 (dd, 1H, J=6.9, 8.6 Hz, C_9-H or $C_{10'}$-H), 7.681 (dd, 1H, J=6.9, 8.6 Hz, $C_{10'}$-H or C_9-H), 8.406 (dd, 1H, J=1.4, 8.0 Hz, C_7-H or $C_{8'}$-H), 8.447 (dd, 1H, J=1.4, 8.1 Hz, $C_{8'}$-H or C_7-H), 14.779 (s, 1H, D_2O exchangeable, -OH), and 15.371 (s, 1H, D_2O exchangeable, -OH); 90.54 MHz ^{13}C-nmr ($CDCl_3$): δ 23.57, 24.16, 24.58, and 29.85 (gem. CH_3), 27.55 (C_4), 33.76 (N_{11}-CH_3), 38.05 (C_3), 43.72 ($N_{12'}$-CH_3), 91.45 (C_{12}), 96.14 ($C_{5'}$), 100.68, 106.54, 106.55 and 112.03 (C_{4a}, C_{5a}, $C_{6'a}$, and $C_{12b'}$), 114.09 and 115.98 (C_{10} and $C_{11'}$), 120.69, 120.97, 121.61 and 122.38 (C_8, $C_{1'}$, $C_{2'}$ and $C_{9'}$), 121.74 and 122.04 (C_{6a} and $C_{7'a}$), 126.46 and 126.95 (C_7 and $C_{8'}$), 133.58 and 133.63 (C_9 and $C_{10'}$), 142.25, 142.73, 142.86 and 144.92 (C_{10a}, C_{11a}, $C_{11'a}$ and $C_{12'a}$), 162.11, 162.22, 162.33 and 162.85 (C_5, C_{12a}, $C_{4'a}$ and $C_{6'}$), and 180.50 and 181.29 (C_6 and $C_{7'}$).

HYDROGENATION OF AB-1 (**8**).—AB-1 (**8**, 0.5 mg) was dissolved in EtOAc (5 ml), 10% Pd/C (1 mg) was added, H_2 gas was introduced after flushing with N_2, and the mixture stirred at room temperature for 24 h. The reaction mixture was filtered and concentrated to afford a yellow powder that was purified by preparative tlc on silica gel eluting with $CHCl_3$ to afford dihydro AB-1 (**9**, 0.4 mg); uv ($CHCl_3$): λ max 253, 280, 337 and 405 nm, ms: *m/z* (% relative intensity) 616 (M^+, 86.8), 601 (92.2), 323 (54.2), 322 (100.0), 318 (39.4), 308 (64.5), 307 (37.3), 294 (15.0), 293 (16.9), 292 (73.0), 280 (39.8), 278 (17.8), 277 (15.9), 266 (30.1), 254 (20.0), 252 (30.9), 242 (17.0), 241 (39.3), and 225 (15.4).

HYDROGENATION OF AB-2 (**3**).—AB-2 (**3**, 1.3 mg) was dissolved in EtOAc (5 ml), 10% Pd/C (1 mg) was added, H_2 gas was introduced after flushing with N_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 $CHCl_3$ to afford dihydro AB-2 (**6**, 0.9 mg); uv ($CHCl_3$): λ max 253, 283, 335 (sh) and 405 nm; ms: *m/z* (% relative intensity) 616 (M^+, 100.0), 309 (16.6), 308 (39.4), 307 (10.4), 306 (11.9), 292 (28.8), 280 (11.2), 271 (29.8), 254 (7.7), 242 (4.8), 241 (9.0), 225 (3.5), and 146 (3.9).

REACTION OF DIHYDROACRONYCINE (**5**) WITH METHANOLIC HCL.—Dihydroacronycine (**5**, 17.0 mg) was dissolved in MeOH (8 ml) and 10 N aqueous HCl (3 ml) and the yellow solution refluxed on a steam bath for 6 h. The cooled reaction mixture was diluted with H_2O, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. After drying (Na_2SO_4), the $CHCl_3$ layer was concentrated *in vacuo* to yield a yellow powder (14.6 mg). Dihydronoracronycine (**4**) and unreacted dihydroacronycine (**5**) were detected in the product by tlc analysis on comparison with authentic samples (1), but no other products were observed.

REACTION OF DIHYDRONORACRONYCINE (**4**) WITH METHANOLIC HCL.—Dihydronoacronycine (**4**, 13.2 mg) was dissolved in MeOH (8 ml) and 10 N aqueous HCl (3 ml) and the deep yellow solution refluxed on a steam bath for 6 h. The cooled reaction mixture was diluted with H_2O, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. After drying (Na_2SO_4), the $CHCl_3$ layer was concentrated *in vacuo* to afford unreacted dihydronoracronycine (**4**, 13.1 mg) as shown by comparison with an authentic sample (1). No other products were observed.

COUPLING OF NORACRONYCINE (**2**) AND DIHYDRONORACRONYCINE (**4**).—Noracronycine (**2**, 14.0 mg) and dihydronoracronycine (**4**, 140.0 mg) were dissolved in MeOH (56 ml) and 10 N aqueous HCl (21 ml) and the solution heated on a steam bath for 6 h. The cooled reaction mixture was concentrated *in vacuo* to about 25 ml and diluted with H_2O (225 ml). After neutralization with $NaHCO_3$, the solution was extracted with $CHCl_3$ (2×250 ml), and the $CHCl_3$ layer was dried (Na_2SO_4). The crude binary product was purified by preparative tlc on silica gel and crystallized from $CHCl_3$ to afford **6** (24.1 mg), mp 193-195°; ir (KBr): ν max 3370, 2930, 1630, 1618, 1585, 1558, 1490, 1451, 1322, 1261, 1185, and 1161 cm^{-1}; uv ($CHCl_3$): λ max 253 (log ϵ 4.08), 283 (4.22), 338 (3.66), and 408 nm (3.45); ms: *m/z* (% relative intensity) 616 (M^+, 45.1), 309 (43.5), 308 (24.9), 307 (26.1), 306 (8.1), 292 (100.0), 280 (7.4), 271 (19.4), 254 (20.1), 242 (9.6), 241 (48.5), 225 (13.8), and 146 (31.7); 360 MHz ^{1}H-nmr ($CDCl_3$): δ 0.700 (s, 3H, 14′-CH_3), 1.157 (s, 3H, 13′-CH_3), 1.435 (s, 3H, 13- or 14-CH_3), 1.495 (s, 3H, 14- or 13-CH_3), 1.511-1.625 (m, 2H, 2′-H_2), 2.103 (dd, 1H, J=7.8, 13.2 Hz, C_3-H_e), 2.163 (t, 1H, J=11.1 Hz, C_3-H_a), 2.733-2.855 (m, 2H, 1′-H_2), 3.795 (s, 3H, N-CH_3), 3.831 (s, 3H, N-CH_3), 4.906 (dd, 1H, J=7.9, 11.2 Hz, 4-H), 6.366 (s, 1H, 12-H), 7.215 (t, 1H, J=7.5 Hz, C_8-H or $C_{9'}$-H), 7.264 (t, 1H, J=7.5 Hz, $C_{9'}$-H or C_8-H), 7.398 (d, 1H, J=8.4 Hz, C_{10}-H or $C_{11'}$-H), 7.454 (d, 1H, J=8.7 Hz, $C_{11'}$-H or C_{10}-H), 7.674 (ddd, 2H, J=0.9, 7.2 and 8.2 Hz, C_9-H and $C_{10'}$-H) 8.389 (dd, 1H, J=1.4, 7.9 Hz, C_7-H pr $C_{8'}$-H), 8.411 (dd, 1H, J=1.5, 7.9 Hz, $C_{8'}$-H or C_7-H), 14.721 (s, 1H, -OH), and 14.931 (s, 1H, -OH).

REACTION OF AB-1 (**8**) WITH METHANOLIC HCL.—AB-1 (**5**, 1.1 mg) was dissolved in MeOH (5 ml) and 10 N aqueous HCl (2 ml) and the mixture refluxed over a steam bath for 6 h. After cooling, the reaction mixture was diluted with H_2O to about 50 ml and neutralized with $NaHCO_3$. This solution was extracted with $CHCl_3$ (2×50 ml), and the combined layers were dried (Na_2SO_4), filtered, and concentrated to give a yellow powder. Tlc analysis using the solvent systems $CHCl_3$, $CHCl_3$-Et_3N, (49:1) and C_6H_6-EtOAc (9:1) (Table 1) indicated the presence of AB-2 (**3**) and noracronycine (**2**) in addition to unreacted AB-1 (**8**).

TABLE 1. Thin-Layer Chromatographic Comparison of Acronycine Derivatives[a]

Compound	Solvent System			
	$CHCl_3$	$CHCl_3$-MeOH (99:1)	C_6H_6-EtOAc (9:1)	$CHCl_3$-Et_3N (49:1)
Acronycine (**1**)	0.06	0.30	0.05	0.26
Dihydroacronycine (**5**)	0.05	0.22	0.03	0.26
Noracronycine (**2**)	0.36	0.73	0.58	0.40
Dihydronoracronycine (**4**)	0.25	0.66	0.48	0.30
Isonoracronycine (**7**)	0.42	0.75	0.65	0.47
AB-1(**8**)	0.16	0.59	0.46	0.28
Dihydro-AB-1 (**9**)	0.14	0.54	0.34	0.27
AB-2 (**3**)	0.13	0.54	0.42	0.26
Dihydro-AB-2 (**6**)	0.12	0.50	0.36	0.27

[a]Silica gel plates (0.25 mm thickness) supplied by E. Merck, Darmstadt, W. Germany, were used.

REACTION OF AB-2 (**3**) WITH METHANOLIC HCL.—AB-2 (**3**, 1.0 mg) was dissolved in MeOH (5 ml) and 10 N aqueous HCl (2 ml) and the mixture refluxed on a steam bath for 6 h. The cooled reaction mixture was diluted with H_2O to about 50 ml and neutralized with $NaHCO_3$. This solution was extracted with $CHCl_3$ (2×50 ml), and the combined $CHCl_3$ layers were dried (Na_2SO_4), filtered, and concentrated to give a yellow powder. By preparative tlc, noracronycine (**2**) and isonoracronycine (**7**) were isolated, as well as unreacted AB-2 (**3**). Identification of these compounds was accomplished by tlc and comparision of their spectral properties.

COUPLING OF NORACRONYCINE (**2**) AND DIHYDRONORACRONYCINE (**4**) AT ROOM TEMPERATURE.—Noracronycine (**2**, 2.0 mg) and dihydronoracronycine (**4**, 20.0 mg) were dissolved in MeOH (8 ml) and 10 N aqueous HCl (3 ml) and the mixture stirred under N_2 at room temperature. After 3 days, the reaction mixture was diluted with H_2O, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4) and concentrated. By preparative tlc, dihydro AB-1 (**9**, 2.1 mg) and dihydro AB-2 (**6**, 2.8 mg) were isolated as well as unreacted dihydronoracronycine (**4**, 18.1 mg). Identity with dihydro AB-1 (**9**), dihydro AB-2 (**6**), and dihydronoracronycine (**4**) was accomplished by direct comparison with authentic samples.

REACTION OF NORACRONYCINE (**2**) WITH METHANOLIC HCL AT ROOM TEMPERATURE.—Noracronycine (**2**, 20 mg) was dissolved in MeOH (8 ml) and 10 N aqueous HCl (3 ml) and the solution stirred under N_2 at room temperature. After 24 h, the reaction mixture was diluted with H_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4) and concentrated to afford a yellow powder. By tlc analysis, AB-1 (**8**) and AB-3 were detected, as well as unreacted noracronycine (**2**) and other minor products. AB-2 (**3**) was not detected in this reaction mixture.

X-RAY STRUCTURE ANALYSIS.—*AB-1*: The compound was crystallized from Me_2CO-H_2O (20:1) to give thin, rhombic, orange plates, size $0.3\times0.3\times0.05$ mm, in the triclinic P1 system with unit cell constants a=10.717 (4) Å, b=12.479 (6) Å, c=14.431 (8) Å, α=91.06 (4)°, β=103.53 (4)°, γ=110.77 (4)°. The density measured by floatation in KI/H_2O was 1.284 g/cm^3 and showed z=2 molecules in the unit cell. From a total of 4925 measured reflections, 3033 were observed ($\geq 2\sigma$ (I)). The crystals dissolved in air within 12 d, and therefore the measurements were taken rapidly with a scan speed of 8°/min.

The structure was solved using SHELXTL (16). First attempts in $P\bar{1}$ with direct methods failed, even using several different starting reflections and increasing the size of the starting set. Because of this quite common problem in $P\bar{1}$, we tried the solution in P1, and also raised the limit for "observed" reflections to 4σ (I). An E-map from the phase set with the best figure of merit (NQEST=−0.76) showed reasonable fragments of the two molecules. By partial structure expansion and a subsequent difference fourier synthesis, all 92 atoms were found for the two molecules in the cell. The partial structure expansion consisted of a cyclic procedure in which trial atoms from the fragments were taken and an *R*-index based on the strongest E-values optimized by eliminating some of the input atoms. Then a sum-weighted difference E-map was calculated with a peak search to find new trial atoms to serve as input for the next cycle. The two molecules in P1 were now transformed to $P\bar{1}$, with one molecule in the asymmetric unit and the atomic positions and thermal parameters refined. After refinement, two molecules of Me_2CO were found in the unit cell, and we surmise that this is the reason for the instability of the crystals in air. The *R*-factor converged at 8.7%, including hydrogens calculated from the C-atoms to which they are bound (except the two phenolic H) (17). Distances and angles are shown in Figure 2.

AB-2: The structure of this compound was solved in a similar manner as that described for AB-1. The compound was crystallized from Me_2CO-H_2O (20:1) to give thin, rhombic, orange plates, size $0.3\times0.2\times0.06$ mm, in the triclinic $P\bar{1}$ system, with unit cell constants a=9.479(2)Å, b=10.443(3)Å, c=17.836(7)Å, α=74.16(2)°, β=79.39(2)°, γ=63.04)2)°. The density measured by floatation in KI/H_2O was 1.318 g/cm^3 and showed z=two molecules in the unit cell. From a total of 3902 measured reflections, 2686 were observed [$\geq 2\sigma$ (I)].

The structure was solved using SHELXTL (16). The best E-map (NQEST-criterion) out of 1024 phase set revealed two still incomplete ring systems. Following partial structure expansion and difference fourier maps, the complete structure was revealed. Refinements anisotropically converged at *R*=9.3%, and hydrogen atoms were calculated (17). The distances and angles are given in Figure 1. Cocrystallized mother liquor was not found in this case.

THIN-LAYER CHROMATOGRAPHIC ANALYSIS.—For comparison purposes, tlc data of the compounds **1-9** were obtained on silica gel G 0.25 mm plates.[3] The results are shown in Table 1.

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