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CHEMISTRY OF ACRONYCINE, VII.[1] FACILE REARRANGEMENT OF DIHYDRONORACRONYCINE TO DIHYDROISONORACRONYCINE

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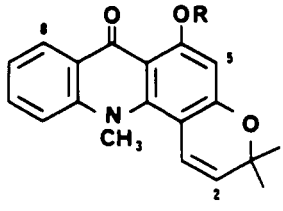
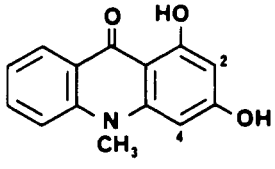
As part of our continuing studies of the reactions of acronycine (**1**), the antineoplastic alkaloid from *Baurella simplicifolia* (Endl.) Hartley (Rutaceae), and its derivatives noracronycine (**2**) and dihydronoracronycine (**3**) (2-5), we had the opportunity to examine the products of the reaction between acronycine (**1**) and dihydronoracronycine (**3**) with 98% H_2SO_4, whereupon it became apparent that two new compounds arose from **3** and/or the combination of **1** and **3**. Consequently, dihydronoracronycine (**3**) was treated with 98% H_2SO_4 at room temperature for 24 h under nitrogen to afford the same two products, which were purified by preparative tlc.

One of the isolates was identified as 1,3-dihydroxy-10-methyl acridone (**4**). The second displayed ir, uv, and mass spectroscopic properties comparable to those of dihydronoracronycine (**3**). In the ^{1}H-nmr spectrum, a geminal methyl singlet (δ 1.404), a N-CH_3 signal (δ 3.766), an aromatic singlet (δ 6.293), and a hydrogen-bonded phenolic proton (δ 15.127) were observed in addition to four coupled aromatic protons and two pairs of methylene protons.

The structure of this product was deduced on the basis of transient nuclear Overhauser experiments. Thus, when the three-proton singlet for the *N*-methyl group at δ 3.766 was irradiated, an enhancement was observed not only in the doublet at δ 7.464 (19%) but also in the singlet at δ 6.293 (22%). Significantly, no enhancement was observed at δ 2.775 (t, 2H, J=6.8 Hz). This compound, therefore, cannot have the angular structure of **3** but must have the linear structure found in isonorac-



	R
1	CH_3
2	H
3	H; 1,2-H_2



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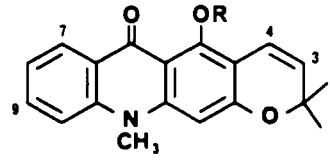

	R
5	H
6	H; 3,4-H_2
7	CH_3

[1]For Part VI see Funayama and Cordell (1).

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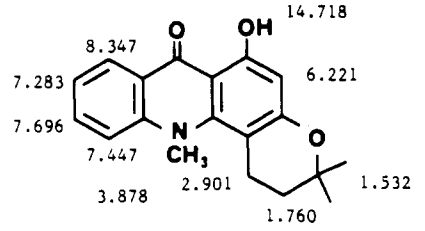
ronycine (**5**) (1). The structure of the product, was, therefore, envisaged as dihydroisonoracronycine (**6**). Direct comparison with dihydroisonoracronycine (**6**), formed by the catalytic hydrogenation of **5**, established the identity. Confirmation of the structure was achieved when **6** was found to undergo dehydrogenation to **5** with DDQ at room temperature for two days. A comparison of the ^{1}H-nmr spectral properties of **3** (1) and **6** is shown in Figure 1.



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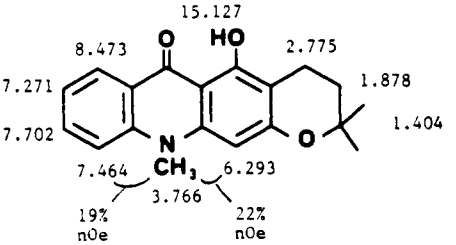

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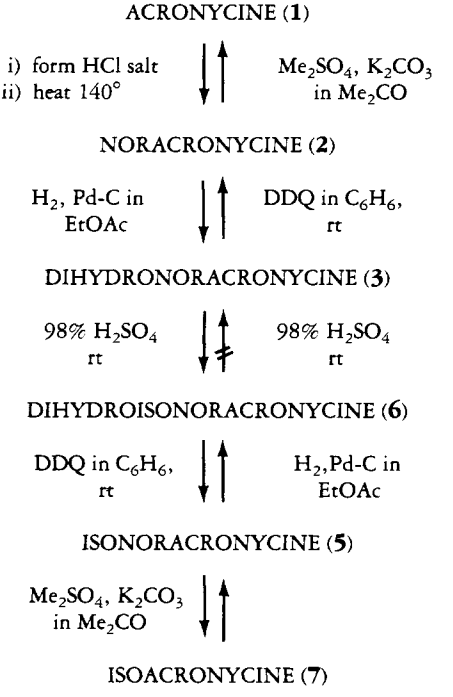
FIGURE 1. ^{1}H-nmr Spectral Comparison of Dihydronoracronycine (**3**) and Dihydroisonoracronycine (**6**).

Dehydrogenation of **3** to **2** could also be accomplished with DDQ under these conditions, although the yield was not as high as for the conversion of **6** to **5**. Methylation of **5** with dimethyl sulfate afforded isoacronycine (**7**), the linear nature of which was reestablished through difference nOe enhancement of H-10 (18%) and H-12 (24%) on irradiation of the *N*-methyl singlet at δ 3.788.

Although the rearrangement of the angular to the linear series of compounds has been observed previously in the dimeric series (1,3), this is the first report of the "direct" rearrangement (33% yield) of the angular to the linear array in the monomeric series.[3] Because this rearrangement does not occur in the monomers acronycine (**1**) or noracronycine (**2**), it is clear that the chroman unit is essential for the rearrangement. We are presently investigating the mechanism of the rearrangement and will report on the biological activity of the isolates subsequently.

It is worth noting that through these procedures it is possible to achieve the transformation of acronycine (**1**) to isoacronycine (**7**) (Scheme 1). However, thus far the reverse overall reaction cannot be carried out because the rearrangement of dihydronoracronycine (**3**) to dihydroisonoracronycine (**6**) is not reversible under these conditions.



SCHEME 1. Conversion of Acronycine (**1**) to Isoacronycine (**7**).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined using a Kofler

[3]The "indirect" rearrangement of the angular to the linear system has been observed previously through fragmentation of the dimeric species AB-2 (3,5).

hot stage microscope and are uncorrected. The ir spectra were recorded with a Beckman model IR 18-A spectrophotometer with polystyrene calibration at 1601 cm^{-1} or with a Nicolet MX-1 FT-IR interferometer; absorption bands are recorded in wave numbers (cm^{-1}). The uv spectra were measured with a Beckman model DB-G spectrophotometer. ^{1}H-nmr spectra were recorded in $CDCl_3$ at 360 MHz on a Nicolet NT-360 instrument at the Midwest Regional NMR Facility, University of Illinois at Urbana, or with a Varian T-60A instrument operating at 60 MHz with a Nicolet Model TT-7 Fourier Transform attachment. Mass spectra were obtained at 70 eV on a Varian MAT 112S double focusing spectrometer. The preparation of acronycine and dihydronoracronycine has been described previously (2), and isonoracronycine was also available from earlier work (1).

REACTION OF ACRONYCINE WITH 98% H_2SO_4.—Acronycine (**1**) (15.0 mg) was dissolved in 98% H_2SO_4 (4.0 ml), and the deep red solution was stirred under a N_2 atmosphere for 4 days. The reaction mixture was poured into cold H_2O (50 ml), neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (2×50 ml). The combined $CHCl_3$ layers were dried with Na_2SO_4 and concentrated in vacuo to afford unreacted acronycine (**1**) (13.0 mg) as shown by tlc and spectroscopic comparison.

REACTION OF DIHYDRONORACRONYCINE WITH 98% H_2SO_4.—Dihydronoracronycine (**3**) (103 mg) was dissolved in 98% H_2SO_4 (30 ml), and the orange-yellow solution was stirred under a N_2 atmosphere at room temperature. After 24 h, the reaction mixture was poured into cold H_2O (200 ml), neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (2×200 ml). The combined layers were dried with Na_2SO_4 and concentrated in vacuo to afford a brownish yellow powder (61 mg), which was subjected to preparative tlc on silica gel eluting with C_6H_6-EtOAc (1:1) to afford dihydroisonoracronycine (**6**) (29.7 mg) and 1,3-dihydroxy-10-methyl acridone (**4**) (3.0 mg). Dihydroisonoracronycine crystallized as yellow needles, mp 173-176°; ir ν max 1630, 1590, 1566, 1490, 1440, 1321, 1272, 1260, 1209, 1160, and 1115 cm^{-1}; uv λ max 251 (log ϵ 3.39), 267 (sh) (3.47), 278 (3.67), 331 (2.84), and 402 nm (2.79); ms *m/z* (% rel. int.) 310 (17), 309 (M^+, 63), 266 (19), 255 (21), 254 (100), 253 (30), 241 (17), and 225 (27); ^{1}H-nmr spectral data, see Figure 1.

1,3-Dihydroxy-10-methyl acridone (**4**) was obtained as fine yellow rhomboids, mp 262-264°; ir ν max 3258, 3252, 1625, 1599, 1552, 1513, 1470, 1339, 1276, 1227, 1172, and 1152 cm^{-1}; uv λ max 247, 261, 270, 292, 327, and 392 nm; ms *m/z* (% rel. int.) 241 (M^+, 71), 213 (12), 198 (15), 184 (15), 170 (8), 154 (2), and 106 (2); ^{1}H-nmr (60 MHz, acetone-d_6) δ 3.87 (s, 3H, N-CH_3), 6.19 (d, 1H, J=2 Hz, C_2-H or C_4-H), 6.51 (d, 1H, J=2 Hz, C_4-H or C_2-H), 7.16-7.80 (m, 4H, C_5-H, C_6-H, C_7-H and C_3-OH), 8.38 (d, 1H, J=7.8 Hz, C_8-H), and 14.9 (s, 1H, C_1-OH).

CATALYTIC HYDROGENATION OF ISONORACRONYCINE.—*Isonoracronycine* (**5**) (1.0 mg) was reduced with H_2 gas in EtOAc (3.0 ml) in the presence of a 10% palladized charcoal catalyst (0.5 mg) 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 C_6H_6-EtOAc (1:1) to afford dihydroisonoracronycine (**6**) (0.9 mg) identical in its physical and spectral properties to the material obtained previously.

DEHYDROGENATION OF DIHYDROISONORACRONYCINE.—A mixture of dihydroisonoracronycine (**6**) (16.5 mg) and DDQ (35.0 mg) in dry C_6H_6 (63 ml) was stirred under N_2 at room temperature. After 2 days, the reaction mixture was diluted with C_6H_6 (300 ml) and washed with H_2O (3×150 ml), dried over Na_2SO_4, and concentrated in vacuo to afford isonoracronycine (**5**) (6.5 mg) after preparative tlc. Identification of the product was accomplished by direct comparison with an authentic sample.

REACTION OF DIHYDROISONORACRONYCINE WITH 98% H_2SO_4.—Dihydroisonoracronycine (**6**) (0.2 mg) was dissolved in 98% H_2SO_4 (1.0 ml) and the solution stirred under N_2 at room temperature. After 24 h, the reaction mixture was poured into cold H_2O (20 ml) and extracted with $CHCl_3$ (2×20 ml). The combined $CHCl_3$ layers were washed successively with 5% $NaHCO_3$ solution (20 ml) and H_2O (20 ml) and dried (Na_2SO_4). Concentration of the $CHCl_3$ layer in vacuo afforded a yellow powder (0.2 mg). Tlc analysis, on several systems, indicated the product to be mostly unreacted **6** together with some minor products, but dihydronoracronycine (**3**) could not be detected.

TREATMENT OF DIHYDRONORACRONYCINE WITH DDQ.—A mixture of dihydronoracronycine (**3**) (5.6 mg) and DDQ (12.5 mg) in dry C_6H_6 was stirred under N_2 at room temperature. After 2 days, the reaction mixture was diluted with C_6H_6 to 200 ml and the C_6H_6 layer washed with H_2O (3×200 ml), dried over Na_2SO_4, and concentrated in vacuo to afford a yellow powder. Through preparative tlc using $CHCl_3$-MeOH (99:1) as the eluting solvent, noracronycine (**2**) (1.5 mg) and unreacted dihydronoracronycine (**3**) (1.9 mg) were obtained. Identification of these compounds was accomplished through direct comparison with authentic samples.

METHYLATION OF ISONORACRONYCINE.—Isonoracronycine (**5**) (6.0 mg) was dissolved in

Me_2CO (5.0 ml) and to this solution was added anhydrous K_2CO_3 (200 mg) and dimethyl sulfate (0.15 ml) and the mixture refluxed on a steam bath for 7 h. Additional anhydrous K_2CO_3 (200 mg) and dimethyl sulfate (0.15 ml) were added and refluxing was continued for a further 14 h. The pale yellow reaction mixture was diluted with H_2O (25 ml) and stirred for 15 min. Acetone was removed in vacuo, the aqueous layer was extracted with $CHCl_3$ (2×50 ml) and the $CHCl_3$ layer dried over Na_2SO_4. Preparative tlc of this fraction afforded isoacronycine (**7**) (4.5 mg) as yellow needles, mp 162.5-164°; ir, uv, and ^{1}H-nmr data are in agreement with the literature values (6).

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