CHEMISTRY OF ACRONYCINE V. UNEXPECTED REACTIVITY OF DIHYDRONORACRONYCINE[1]

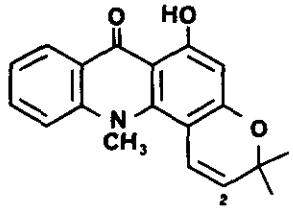
Shinji Funayama and Geoffrey A. Cordell*

Program for Collaborative Research in the Pharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612, U.S.A.

Abstract - Dihydronoracronycine (6) undergoes a condensation-disproportionation reaction in methanolic hydrochloric acid with the dimers of noracronycine 2 and 4 which leads to their corresponding dihydro derivatives 8 and 9, and to the trimers 5 and 7, respectively.

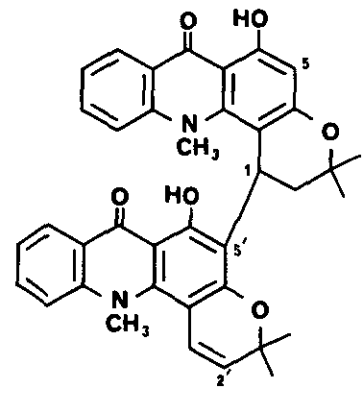
In previous reports from this laboratory we have described the dimerization[2] and trimerization[3] of noracronycine (1) when it is treated with methanolic hydrochloric acid. Noracronycine (1) possesses an angular arrangement of rings, and indeed in one of the dimers, AB-1 (2) and the trimer AB-3 (3) this molecular array was maintained. However, in the dimer AB-2 (4), which is formed from AB-1 (2)[2], a rearrangement has occurred in which one of the chromene rings has been modified to produce a linear four ring system in the upper part of the molecule.[2]

During a study of the trimerization of noracronycine (1),[3] an attempt was made to synthesize dihydro AB-3 (5) in order to demonstrate that AB-3 possessed an angular-angular-angular structure. The synthesis of 5 was attempted by coupling AB-1 (2) with dihydronoracronycine (6) in methanolic hydrochloric acid in the



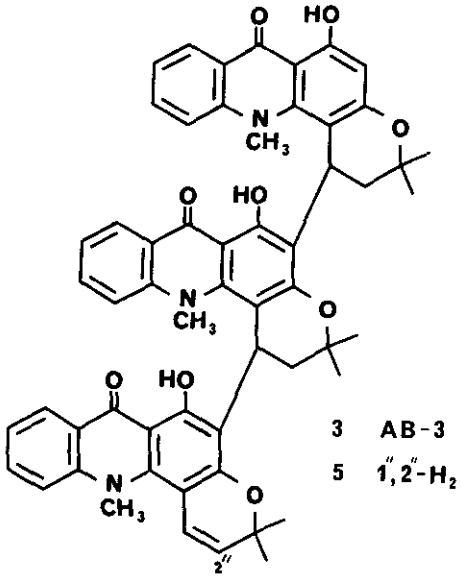
1 Noracronycine

6 1,2-H_2



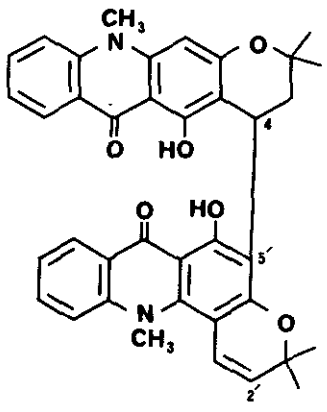
2 AB-1

8 1′,2′-H_2



3 AB-3

5 1″,2″-H_2



4 AB-2

9 1′,2′-H_2

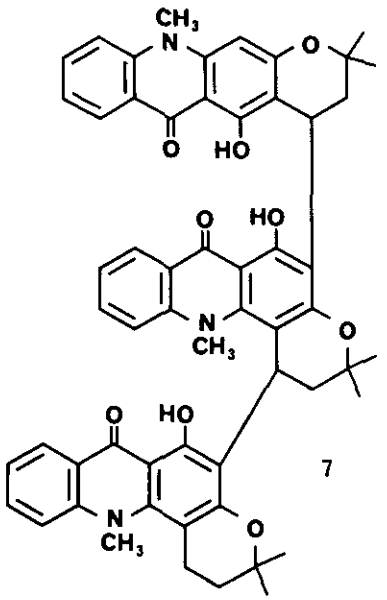
same manner as described previously [2] for the coupling of noracronycine (1) and dihydronoracronycine (6).

AB-1 (2) and dihydronoracronycine (6) were mixed in this ratio 1:10 and refluxed in methanolic hydrochloric acid for 6 h. By mixing 2 and 6 in this ratio , it was anticipated that a molecule of AB-1 (2) would preferentially react with a dihydronoracronycine (6) molecule. In the event, when the reaction was completed, two products were detected by tlc. One of the two compounds was readily identified as unreacted dihydronoracronycine (6), and it was thought that the other compound was a trimer, namely dihydro AB-3 (5). However, direct comparison of the product with authentic dihydro AB-3 (5), synthesized by the catalytic hydrogenation of AB-3 (3), indicated that these compounds were not identical.

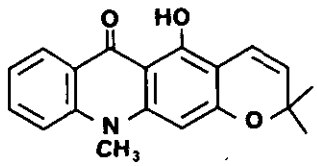
Consequently, we envisaged this new compound to possess the linear-angular-angular structure 7, since it was known that AB-1 (2) could be rearranged to AB-2 (4) under these reaction conditions.[2] In order to confirm the structure 7, a synthetic route involving the coupling of AB-2 (4) and dihydronoracronycine (6) was studied.

AB-2 (4) and dihydronoracronycine (6) were mixed in the ratio 1:10 and refluxed in methanolic hydrochloric acid. A compound identical with the product of the coupling of AB-1 (2) and dihydronoracronycine (6) under reflux was isolated, as well as unreacted 6.

However, dihydro AB-3 (5) was synthesized by coupling AB-1 (2) and dihydronoracronycine (6) at room temperature for 24 h. As expected, [3] no rearrangement occurred under these reaction conditions. From this reaction mixture, in addition to dihydro AB-3 (5) and unreacted dihydronoracronycine (6), a compound with m/z 616 (M^+) was also isolated. Closer examination of this compound indicated that it was a dimer comprised of one molecule of noracronycine (1) and one molecule of dihydronoracronycine (6), namely dihydro AB-1 (8).



7



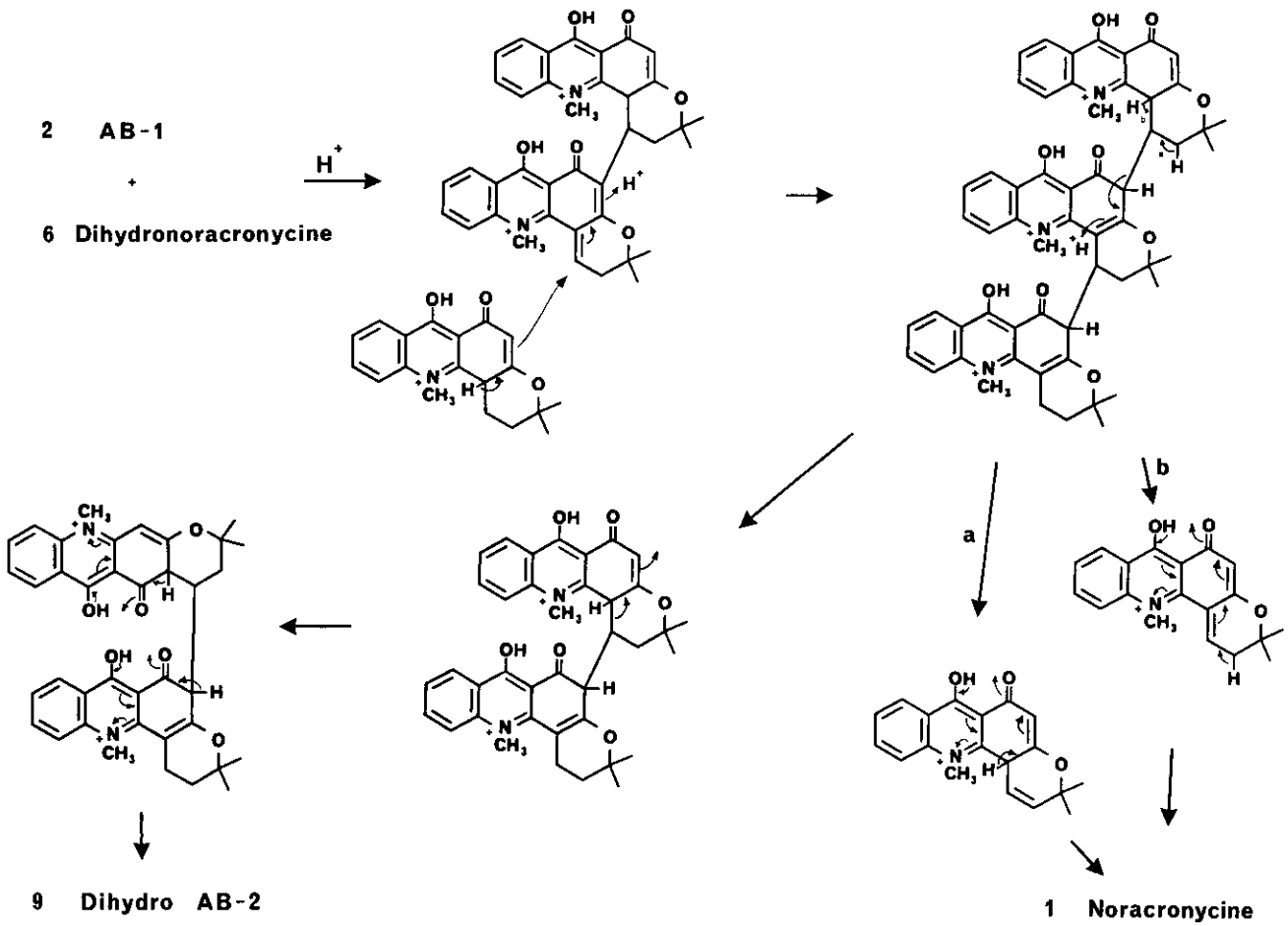
10

We were consequently stimulated to re-examine of the nature of the products obtained from coupling AB-1 (2) and dihydronoracronycine (6), and of AB-2 (4) and dihydronoraconycine (6) under reflux. In the course of this analysis it was established that the products were identical and exhibited a molecular ion at m/z 616. Clearly, our evaluation that this compound was a trimer possessing the linear-angular-angular system 7 was erroneous. Through direct comparison with an authentic sample, these products were identified as dihydro AB-2 (9), a dimer composed of one molecule each of isonoracronycine (10) and dihydronoracronycine (6).

From these results, it was evident that during the reaction under reflux, the C_1-C_5' bond of AB-1, and the C_4-C_5' bond of AB-2 have been cleaved, and that a new bond with C_5 of dihydronoracronycine (6) and, as necessary, a rearrangement had occurred. Scheme 1 indicates a plausible mechanism for this process in the case of 2 and 6. A similar scheme can be written for the reaction of 4 and 6. Additionally, in the coupling reaction at room temperature, partial cleavage (about 50%) of the C_1-C_5' junction of AB-1 was estimated because dihydro AB-3 (5) and dihydro AB-1 (8) were obtained in about 40% yield, respectively.

Because, when AB-1 (2) or AB-2 (4) was refluxed with methanolic hydrochloric acid for 8 h, these compounds were only partially destroyed to give noracronycine (1), or (1) and isonoracronycine (10), respectively, dihydronoracronycine (6) must perform a very important role in the cleavage reaction of AB-1 (2) and AB-2 (4) described above.

Dihydro AB-1 (8) can be synthesized by the catalytic hydrogenation of AB-1 (2)[2] or through the coupling of noracronycine (1) and dihydronoracronycine (6) at room temperature[2]. Through the experiments



Scheme 1. Formation of Dihydro AB-2 (9) from AB-1 (2).

herein it has been found, unexpectedly, that 8 can be also synthesized by coupling AB-1 (2) and dihydronoracronycine (6) at room temperature.

Three procedures were described previously for the formation of dihydro AB-2 (9),[2] namely, catalytic hydrogenation of AB-2 (4), coupling of noracronycine (1) and dihydronoracronycine (6) at reflux and coupling of 1 and 6 at room temperature. Now it has been demonstrated that dihydro AB-2 (9) can be produced by coupling AB-1 (2) or AB-2 (4) with dihydronoracronycine (6) under reflux with methanolic hydrochloric acid.

A summary of the reactions of dihydronoraconycine (6) is given in TABLE 1 below.

TABLE 1. REACTIONS OF DIHYDRONORACRONYCINE (6)

Reactant	Conditions[a]	Products
Noracronycine	reflux, 6h	Dihydro AB-2 (9), 6
	room temp., 24 h	Dihydro AB-1 (8), Dihydro AB-2 (9), 6
AB-1 (2)	reflux, 6 h	Dihydro AB-2 (9), 6
	room temp., 24 h	Dihydro AB-1 (8), Dihydro AB-3 (5), 6
AB-2 (4)	reflux, 6 h	Dihydro AB-2 (9), 6
	room temp., 24 h	Dihydro AB-1 (8), Dihydro AB-2 (9), 4, 6

[a] Methanolic hydrochloric acid, 2.5 :1 (v/v) was used in all cases; reactions at room temperature were conducted under nitrogen; refluxing was conducted on a steam bath.

EXPERIMENTAL

Preparation of Noracronycine (1) and Dihydronoracronycine (6) - The preparation and physical and spectral properties of these compounds were described previously.[4]

Formation of AB-1 (2), AB-2 (4), Dihydro AB-1 (8), Dihydro AB-2 (9), Dihydro AB-3 (5) and Isonoracronycine (10) - The formation and properties of these compounds were described previously[2-3].

Preparation of Dihydro AB-2 (8) by Coupling Noracronycine (1) and Dihydronoracronycine (6) - The reaction procedures and the physical and spectral properties of dihydro AB-2 (8) were described previously.[2]

Preparation of Dihydro AB-1 (8) and Dihydro AB-2 (9) by Coupling Noracronycine (1) and Dihydronoracronycine (6) at Room Temperature -The reaction procedures and physical and spectral properties of dihydro AB-1 (8) and dihydro AB-2 (9) were described previously.[2]

Coupling of AB-1 (2) and Dihydronoracronycine (6) under Reflux - AB-1 (2, 1.1 mg) and dihydronoracronycine (6, 5.9 mg) were dissolved in MeOH (8.0 ml) and 10 N aqueous hydrochloric acid (3.0 ml), and the solution heated on a steam bath for 6 h. The cooled reaction mixture was diluted with water (50 ml), neutralized with $NaHCO_3$ and the solution extracted with $CHCl_3$ (2 x 50 ml). The combined $CHCl_3$ layers were dried (Na_2SO_4), filtered and concentrated in vacuo to give a yellow powder (7.3 mg). By preparative tlc, dihydro AB-2 (9, 0.9 mg) and unreacted dihydronoracronycine (6, 3.8 mg) were isolated. Identification of these compounds was accomplished by direct comparison with authentic samples.[2,4]

Coupling of AB-1 (2) and Dihydronoracronycine (6) at Room Temperature - AB-1 (2, 1.1 mg) and dihydronoracronycine (6, 6.2 mg) were dissolved in MeOH (5.0 ml) and 10 N aqueous hydrochloric acid (3.0 ml) and the solution stirred under N_2 at room temperature. After 24 h, the reaction mixture was diluted with water (50 ml), neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (2 x 50 ml). The combined $CHCl_3$ layers were dried (Na_2SO_4) and concentrated in vacuo to afford a yellow powder (7.7 mg). By preparative tlc, dihydro AB-1 (8, 0.8 mg) and dihydro AB-3 (5, 0.7 mg) were isolated, as well as unreacted dihydronoracronycine (6, 5.1 mg) and other minor products. Identity was accomplished by direct comparison with authentic samples.[2,3]

Coupling of AB-2 (4) and Dihydronoracronycine (6) under Reflux - AB-2 (4, 1.3 mg) and dihydronoracronycine (6, 5.6 mg) were dissolved in MeOH (8.0 ml) and 10 N aqueous hydrochloric acid (3.0 ml), and the solution heated on a steam bath for 6 h. The cooled reaction mixture was diluted with water (50 ml). After neutralization with $NaHCO_3$, the solution was extracted with $CHCl_3$ (2 x 50 ml), and the combined $CHCl_3$ layers were dried (Na_2SO_4), filtered and concentrated in vacuo to give a yellow powder (7.1 mg). By preparative tlc, dihydro AB-2 (9, 0.8 mg) and unreacted dihydronoracronycine (6, 3.9 mg) were isolated. Identification of these compounds was accomplished by direct comparison with authentic samples.[2,4]

Reaction of AB-1 (2) with Methanolic Hydrochloric Acid - Reaction procedures were given in a previous paper.[2] Noracronycine (1) and AB-2 (4) were detected as well as unreacted AB-1 (2).

Reaction of AB-2 (4) with Methanolic Hydrochloric Acid - Reaction procedures were given in a previous paper.[2] Noracronycine (1) and isonoracronycine (10) were isolated in addition to unreacted AB-2 (4).

ACKNOWLEDGEMENTS

This work was supported at the University of Illinois, in part, by grant CA-20164 from the Division of Cancer Treatment, National Cancer Institute. High field nuclear magnetic resonance spectra were obtained at the Midwest Regional NMR facility, University of Illinois at Urbana, Urbana-Champaign. This facility is funded, in part, by the National Science Foundation, grant number CHE 79-16100. The authors would like to thank Mr. Gary T. Marshall and Mr. Cesar M. Compadre for FT-IR and MS data, respectively.

REFERENCES

1. For part IV in the series see: S. Funayama and G.A. Cordell, J. Nat. Prod., in press.
2. S. Funayama, G.A. Cordell, H. Wagner and H.L. Lotter, J. Nat. Prod., in press.
3. S. Funayama and G.A. Cordell, Planta Med., in press.
4. S. Funayama, R.P. Borris and G.A. Cordell, J. Nat. Prod., in press.

Received, 19th April, 1983