THERMAL DIMERIZATION OF NORACRONYCINE

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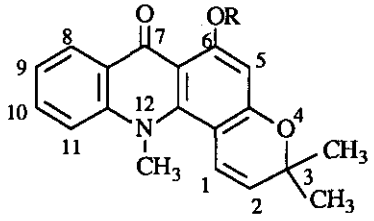
Abstract - Thermal dimerization of the acridone alkaloid noracronycine (**2**) leads to Diels-Alder adducts (**3**) and (**4**), possessing a rearranged structure.

Acronycine (**1**) is a Rutaceous pyranoacridone alkaloid which exhibits a broad spectrum of antineoplastic activity.[1-3] It is easily converted into its *O*-demethyl derivative, noracronycine (**2**).[4] Polymerization and rearrangement reactions of both compounds under acidic conditions have been recently extensively studied.[5] All the dimers, trimers and polymers obtained involve creation of a single carbon-carbon bond, between the positions 1 and 5 of two different units, sometimes with simultaneous rearrangement.[5] Nevertheless, the 2,2-dimethylpyran ring of these compounds led us to envisage the possibility of a different way of dimerization, leading to Diels-Alder derived alkaloid dimers. This type of reaction is known in the field of prenylated coumarins and alkaloids [6] and has been also studied in the case of

dimethylpyranoquinol-2-ones.[7,8] We report here the first reaction of this type involving an acridone alkaloid, noracronycine (**2**).

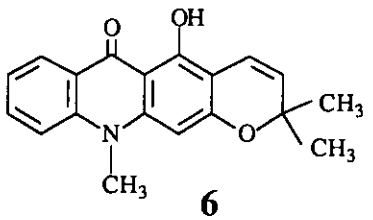


1 R=CH_3

2 R=H

Noracronycine (**2**) has been heated in a sealed tube under Ar for 24 h at different temperatures. At 150°C, the starting material was recovered unchanged. At 180°C, two dimers and one trimer could be isolated, but all of them belong to the series previously described by Funayama and Cordell and have been identified with the compounds AB-1, AB-2 and AB-3 of these authors.[9-11] At 210°C , the reaction products were completely different. The racemic dimers which were isolated in 12% overall yield, **3**[12] and **4**[13], arise from the two possible cyclodimerizations of the rearranged dienic form **5** on the chromene double-bond of norisoacronycine (**6**), followed by subsequent addition of the non-chelated OH phenolic group to the double-bond of each intermediate form.[14] The isoacronycine derivatives **9**,[15] involved in this reaction sequence are most probably produced by the previously described cleavage of dimers AB-1 and AB-2.[9] This statement is in good agreement with the isolation of norisoacronycine (**6**) itself in 3% yield from the reaction mixture. It most probably explains the moderate overall yield of the dimerization reaction.

The 'linear' structures of **3** and **4** were deduced from the strong correlations observed on the ^{1}H nmr 2D NOESY spectra between the signals of the N-Me groups and those of H-10, H-12, H-10' ,and H-12'.In both compounds, a large coupling constant (J=13 Hz) between the signals of H-3 and H-4 accounts for a *trans* relationship of these two protons. A chair conformation of the cyclohexane ring of **3** and **4** is consistent with the ^{4}J coupling (3Hz) of H-3'eq and H-13eq which exhibit a W relationship. The ^{1}H



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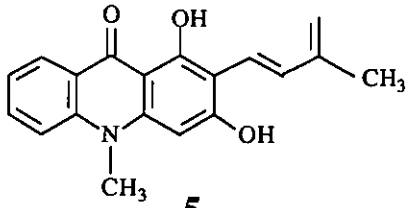

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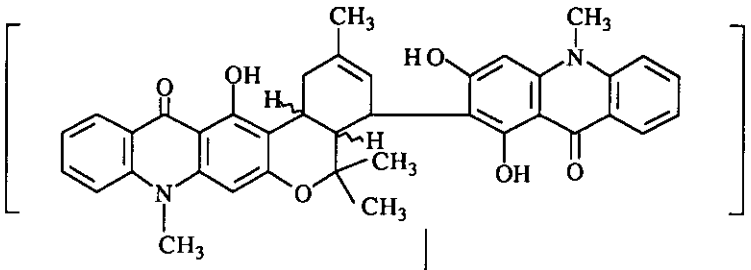
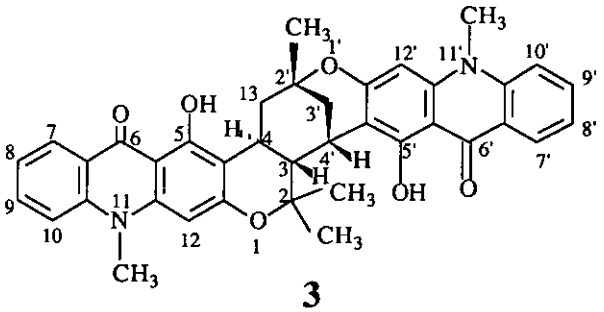
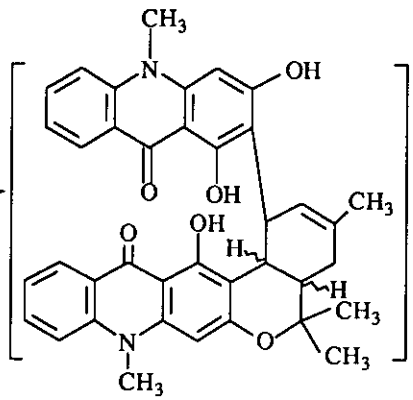
5 + **6** →

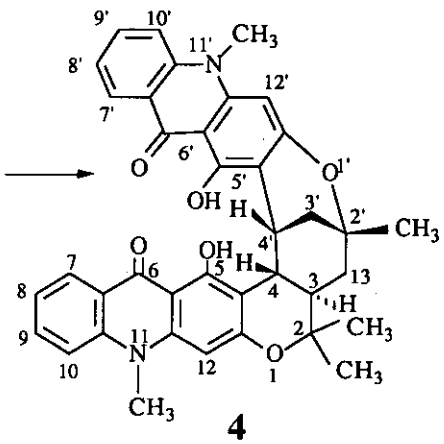




3

5 + **6** →





4

nmr data of **3** and **4** are closely related to those of paraensidimerin F [16] and vepridimerine E [7] which have an equivalent stereochemistry. Cross-peaks between CH3-2eq and H-4' on the 2D NOESY spectrum of **3** and between CH3-2eq and H-13eq on that of **4** agree with their structural differences. In addition, when compared with those of **3**, significant differences appear for **4** in the chemical shifts of H-4' and CH3-2ax. They account for the influence of the *peri* OH groups on H-4' and for the shielding effect of the aromatic rings on CH3-2ax in the latter compound.

In conclusion, thermal dimerization of noracronycine (**2**) has led to Diels-Alder adducts possessing a rearranged structure. This result should prove useful in further studies of this group of antineoplastic acridones and help to establish the structures of new natural Rutaceous alkaloids.

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12. Compound **3**: ms (dci, reagent gas: NH_3) (m/z): 615 $(M+H)^+$; ^1H nmr ($CDCl_3$) δ: 0.97 (3H, s, CH_3-2ax), 1.36 (1H, dd, *J*=13, 12 Hz, H-13ax), 1.49 (3H, s, CH_3-2'), 1.85 (3H, s, CH_3-2eq), 1.89 (1H, dt, *J*=13, 3 Hz, H-3'eq), 2.05 (1H, dd, *J*=13, 2 Hz, H-3'ax), 2.05 (1H, dd, *J*=13, 2 Hz, H-3), 2.94 (1H, td, *J*=13, 3 Hz, H-4), 3.73 (1H, dt, *J*=3, 2 Hz, H-4'), 3.78 (1H, dt, *J*=12, 3 Hz, H-13eq), 3.72, 3.79 (2x3H, 2s, CH_3-11, CH_3-11'), 6.22, 6.42 (2x1H, 2s, H-12, H-12'), 7.22, 7.28 (2x1H, 2t, *J*=8 Hz, H-8, H-8'), 7.40, 7.44 (2x1H, 2d, *J*=8 Hz, H-10, H-10'), 7.65, 7.67 (2x1H, 2td, *J*=8, 1 Hz, H-9, H-9'), 8.41, 8.43 (2x1H, 2dd, *J*=8, 1 Hz, H-7, H-7'), 12.90, 13.00 (2x1H, 2s, D_2O exch., OH-5, OH-5'); Anal. Calcd for $C_{38}H_{34}N_2O$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.38; H, 5.47, N, 4.53.

13. Compound **4**: ms (dci, reagent gas: NH_3) (m/z): 615 $(M+H)^+$; ^1H nmr ($CDCl_3$) δ: 0.31 (3H, s, CH_3-2ax), 1.27 (3H, s, CH_3-2'), 1.43 (1H, dd, *J*=13, 12 Hz, H-13ax), 1.54 (3H, s, CH_3-2eq), 2.05 (1H, dd, *J*=13, 2 Hz, H-4), 2.10 (1H, dd, *J*=13, 2 Hz, H-3'ax), 2.27 (1H, dt, *J*=13, 3 Hz, H-3'eq), 2.86 (1H, td, *J*=13, 3 Hz, H-3), 3.74 (1H, dt, *J*=12, 3 Hz, H-13eq), 3.69, 3.80 (2x3H, 2s, CH_3-11, CH_3-11'), 3.82 (1H, dt, *J*=3, 2 Hz, H-4'), 6.14, 6.89 (2x1H, 2s, H-12, H-12'), 7.26 (2H, t, *J*=8 Hz, H-8, H-8'), 7.31, 7.40 (2x1H, 2d, *J*=8 Hz, H-10, H-10'), 7.66, 7.73 (2x1H, 2td, *J*=8, 1 Hz, H-9, H-9'), 8.32, 8.43 (2x1H, 2dd, *J*=8, 1 Hz, H-7, H-7'), 12.90, 14.00 (2x1H, 2s, D_2O exch., OH-5, OH-5'); Anal. Calcd for $C_{38}H_{34}N_2O$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.21; H, 5.62, N, 4.59.

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