

THERMAL DIMERIZATION OF NORACRONYCINE

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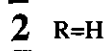
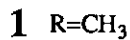
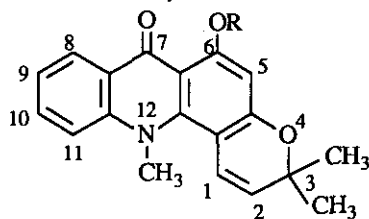
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Abstract - Thermal dimerization of the acridone alkaloid
noracronycine (**2**) leads to Diels-Alder adducts (**3**) and (**4**), possessing
a rearranged structure.

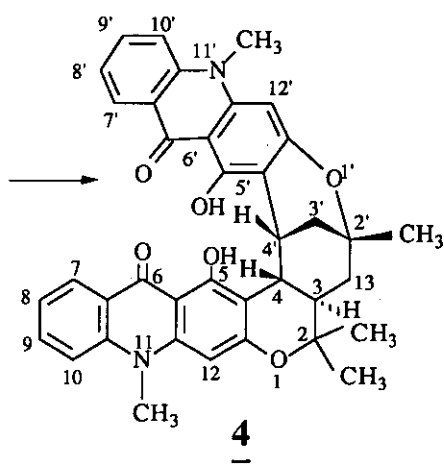
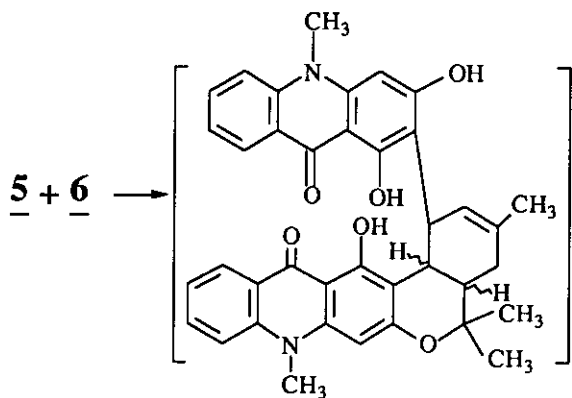
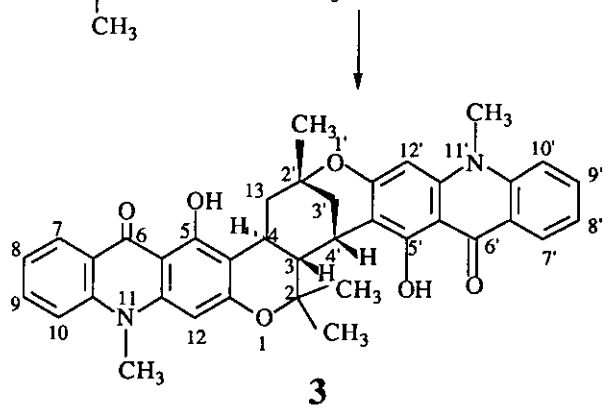
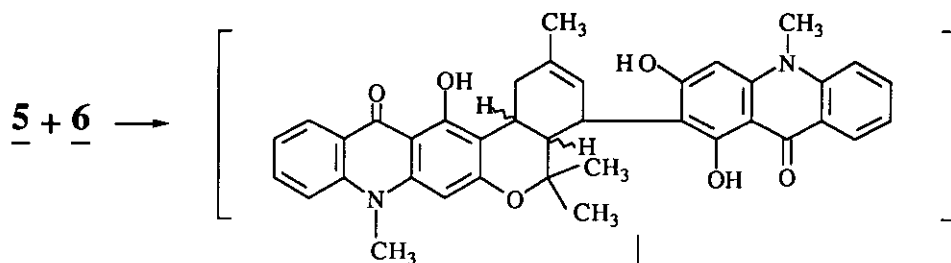
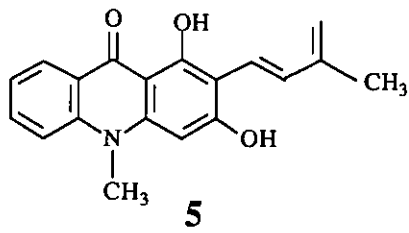
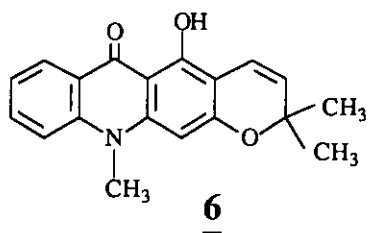
Acronycine (**1**) is a Rutaceous pyranoacridone alkaloid which exhibits a broad spectrum of antineoplastic activity.¹⁻³ It is easily converted into its *O*-demethyl derivative, noracronycine (**2**).⁴ Polymerization and rearrangement reactions of both compounds under acidic conditions have been recently 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 alkaloids⁶ 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**).



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 ¹H 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 ¹H



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.

ACKNOWLEDGEMENTS

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12. Compound **3**: ms (dci, reagent gas: NH₃) (m/z): 615 (M+H)⁺; ¹H nmr (CDCl₃) δ: 0.97 (3H, s, CH₃-2ax), 1.36 (1H, dd, J=13, 12 Hz, H-13ax), 1.49 (3H, s, CH₃-2'), 1.85 (3H, s, CH₃-2eq), 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, CH₃-11, CH₃-11'), 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, D₂O exch., OH-5, OH-5'); Anal. Calcd for C₃₈H₃₄N₂O: 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: NH₃) (m/z): 615 (M+H)⁺; ¹H nmr (CDCl₃) δ: 0.31 (3H, s, CH₃-2ax), 1.27 (3H, s, CH₃-2'), 1.43 (1H, dd, *J*=13, 12 Hz, H-13ax), 1.54 (3H, s, CH₃-2eq), 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, CH₃-11, CH₃-11'), 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, D₂O exch., OH-5, OH-5'); Anal. Calcd for C₃₈H₃₄N₂O: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.21; H, 5.62, N, 4.59.
14. For a discussion on the mechanism of this addition and of the *cis* to *trans* rearrangement of the ring junction of the intermediate forms, see: L. Jurd, R. Y. Wong, and M. Benson, *Aust. J. Chem.*, 1982, **35**, 2505.
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