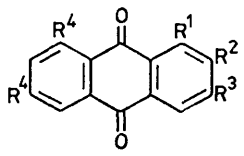
Amino Acid-catalysed Alkylation of Hydroxyanthraquinones with 2-Hydroxytetrahydropyrans

By ANDRE CASTONGUAY*
(*Department of Biochemistry, Brandeis University, Waltham, Massachusetts* 02154)
and YVES BERGER
(*Institut de Chimie, Université de Liège, Sart-Tilman,* B-4000 *Liège, Belgium*)

Summary 2-(Tetrahydropyran-2-yl)hydroxyanthraquinones have been produced in high yield by treatment of hydroxyanthraquinones with 2-hydroxytetrahydropyrans and with either (*S*)-(−)-proline or (*S*)-(−)-phenylalanine in dimethylformamide.

ALKYLATION of hydroxyanthraquinones was shown to be a very straightforward method of synthesis of some naturally occurring anthraquinones.[1] Furthermore, some approaches to the synthesis of the antineoplastic agents adriamycin and daunorubicin involved an anthraquinone alkylation.[2] In the course of the synthesis of (±)-averufanin and (±)-bipolarin it was noted that alkylation of xanthopurpurin (**1**) by aldehyde was promoted by the amino acid (*S*)-(−)-proline in dimethylformamide (DMF).[3] This communication shows the influence of amino acid and anthraquinone structures on the nature and yield of alkylation products.

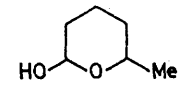


	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
(**1**);	OH	H	OH	H	(**6**);	OMe	X	OMe	**H**
(**2**);	OH	X	OH	OH	(**7**);	OH	H	OMe	H
(**3**);	OH	H	OH	OH	(**8**);	H	H	OH	H
(**4**);	OH	X	OH	H	(**9**);	OH	Y	OH	**H**
(**5**);	OH	X	OMe	H					

X = 6-Methyltetrahydropyran-2-yl
Y = Tetrahydropyran-2-yl

Synthesis of the orange pigment (+)-averufanin (**2**) isolated from *Aspergillus versicolor* (Vuillemin) Tirasboschi would require alkylation of 1,3,6,8-tetrahydroxyanthraquinone (**3**) with 2-hydroxy-6-methyltetrahydropyran (**10**), which was prepared as a mixture of two isomers (ratio 3 : 2) by treatment of freshly distilled glutaraldehyde with MeMgI. Preliminary studies carried out with xanthopurpurin (**1**) have shown that warming this hydroxyanthraquinone with an excess of (**10**) and 2 equiv. of (*S*)-(−)-proline quantitatively yielded the optically inactive bis-deoxyaverufanin (**4**). The stereochemistry of the methyltetrahydropyran rings of (**4**) and (**2**)[4] was found to be identical. In the ^{1}H n.m.r. ($CDCl_3$) spectrum of (**4**), H-4 absorbs as a singlet at δ 7·18. A doublet of doublets at δ 5·09 ($J_{2,3\ ax}$ 10·0 and $J_{2,3\ eq}$ 2·0 Hz) indicates that the anthraquinone residue occupies an equatorial position. Only one stereoisomer was obtained since the 6′-Me absorbs as a doublet centred at δ 1·28. Similarities in the ^{13}C n.m.r. ($CDCl_3$) spectra of (**4**) (δ C-2′, 76·36; C-3′, 29·99; C-4′, 23·28; C-5′ 32·79; C-6′, 75·83, and CH_3, 22·08 p.p.m.) and (**2**)[5] suggest that the 6′-Me of (**4**) is also equatorial[4] (the primed numbers refer to the tetrahydropyran ring).

Treatment of (**4**) with either 1 equiv. or an excess of $(MeO)_2SO_2$ gave (**5**) [m.p. 186·5—188.0 °C, ν_{max} 1625 cm^{-1}, *m/e* 352 (M^+)] and (**6**) [m.p. 166—167 °C, δ ($CDCl_3$) 3·98 and 4·02 (2 × s), *m/e* 366 (M^+)] respectively. It was of interest to observe that the amino acid-catalysed alkylation is specific for dihydroxyanthraquinones. Attempts to obtain (**5**) by alkylation of the xanthopurpurin methyl ether (**7**) with (**10**) were unsuccessful. Moreover, no alkylation occurred



(**10**)

when 2-hydroxyanthraquinone (**8**) was treated with an excess of (**10**) and 2-equiv. of (*S*)-(−)-proline. Only a small amount of (*S*)-(−)-proline is necessary to promote the alkylation. For instance, 2-(tetrahydropyran-2-yl)xanthopurpurin (**9**) was obtained in 72% yield by warming (**1**), 2-hydroxytetrahydropyran, and 0·1 equiv. of (*S*)-(−)-proline.[3]

The ability of various amino acids to catalyse the alkylation of (**1**) was also investigated. Bis-deoxyaverufanin (**4**) was obtained in 80% yield using 2 equiv. of (*S*)-(−)-phenylalanine. However, acetylation of the amino group of this amino acid eliminated its catalytic property. Increasing the temperature to 70 °C in this case led to the formation of (**4**) with only 14% yield. Other α-amino acids with higher or lower isoelectric point than proline (*e.g.*, glutamic acid or lysine) also failed to catalyse the alkylation of (**1**). These results suggest that this method of alkylation involves an intermediate formed by the reaction of an amino acid with 2-hydroxytetrahydropyrans.

We thank N.A.T.O. for financial support.

(*Received*, 13*th July* 1978; *Com.* 748.)

[1] N. R. Ayyangar and K. Venkataraman, *J. Sci. Ind. Res., India*, 1956, **15B**, 359; A. Castonguay and P. Brassard, *Canad. J. Chem.*, 1977, **55**, 1324.
[2] F. Suzuki, R. D. Gleim, S. Trenbeath, and C. J. Sih, *Tetrahedron Letters*, 1977, **27**, 2303.
[3] A. Castonguay and P. Brassard, unpublished results.
[4] Y. Berger and J. Jadot, *Bull. Soc. Roy. Sci. Liège*, 1975, **44**, 633; 1976, **45**, 157.
[5] C. P. Gorst-Allman, K. G. R. Pachler, P. Steyn, P. Wessels, and S. De Buys, *J.C.S. Perkin I*, 1977, 2181.