Hydroxyalkylation of 1,3-Dihydroxyanthraquinones

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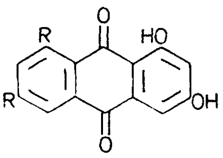
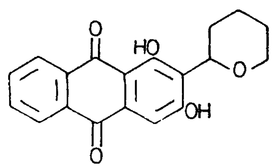
Summary Tetrahydropyranyl derivatives of xanthopurpurin (**1**), analogous to natural products isolated from some *Aspergillus spp.*, have been obtained by direct hydroxyalkylation of the parent quinone.

Several metabolites[1] of *Aspergillus spp.* can be considered formally as hydroxyalkylation products of 1,3,6,8-tetrahydroxyanthraquinone (**2**). Realization of this process in the laboratory would undoubtedly constitute the most convenient synthesis of this group of compounds.

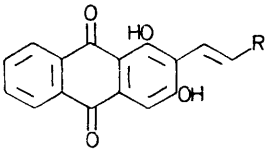
Data in the literature concerning the hydroxyalkylation of phenols or polyhydroxyanthraquinones did not at the outset show grounds for a successful use of this method. Hydroxymethylation of a number of 1,3-dihydroxyanthraquinones[2] has been carried out but to our knowledge no case involving higher homologues of formaldehyde has been recorded and in our hands the usual procedures were unsuccessful. Moreover it is well known that the reaction of phenolates with aldehydes in most cases yields only disubstituted derivatives (except in one case[3]).



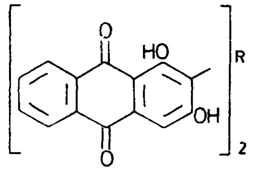
(1) R = H
(2) R = OH



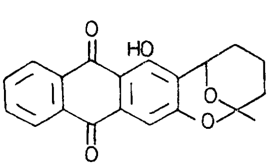
(3)



(4) R = $CH_2[CH_2]_2OH$
(8) R = $CH_2[CH_2]_2Me$



(5) R = $>CH[CH_2]_4OH$
(7) R = $>CH[CH_2]_3COMe$
(9) R = $>CH[CH_2]_4Me$



(6)

The desired products were obtained eventually, along with by-products, by treating xanthopurpurin (**1**) (480 mg, 2·0 mmol) with 1 equiv. of $NaHCO_3$ and the appropriate aldehyde (12·0 mmol, added in 3 portions) in water (4 ml) at *ca.* 95 °C for several hours. Dry column chromatography (silica gel) of the mixture obtained from a reaction with 5-hydroxypentanal (7 h) gave 2-(tetrahydropyran-2-yl)-xanthopurpurin (**3**), m.p. 190·5–191·5 °C (Et_2O) (20%), *m/e* 324 (M^+). Chromatography (dry column) of a slower-moving zone yielded the starting material (**1**) (26%), the dianthraquinonyl derivative (**5**) isolated as the trimethyl ether, m.p. 144—145 °C (EtOH), and an incompletely characterized product, probably the 2-(5-hydroxypent-1-enyl)xanthopurpurin (**4**), m.p. 212—213 °C (EtOAc–C_6H_6) (5%).

An analogous reaction using 5-oxohexanal (2·5 h) gave bisdeoxyaverufin (**6**), m.p. 179·0—179·5 °C (Et_2O–light petroleum, b.p. 30—60 °C) (11%), *m/e* 336 (M^+), starting material (40%), and the dianthraquinonyl derivative (**7**) (31%) characterized as the tetramethyl ether, m.p. 210—212 °C (aq. EtOH), *m/e* 632 (M^+).

When the foregoing aldehydes were replaced by compounds incapable of forming cyclic ethers or acetals, no secondary alcohols could be isolated. Thus a mixture of xanthopurpurin (**1**) (120 mg), 1 equiv. of $NaHCO_3$, and water (1 ml) was stirred at *ca.* 95 °C for 95 h and n-hexanal (600 mg) was added in portions over the first half of the reaction period. The work-up of the crude product gave the olefinic bisdeoxyaverythrin (**8**), m.p. 210—211·5 °C (Et_2O–light petroleum, b.p. 30—60 °C) (23%), *m/e* 322 (M^+), and the dianthraquinonylhexane (**9**) isolated as the tetramethyl ether, m.p. 214·5—215·0 °C (Et_2O–light petroleum, b.p. 30—60 °C).

All analyses and spectral data for compounds of definitive structure are concordant.

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