Simple Novel Synthesis of the Anthracyclinone System Using a New Modification of the Marschalk Reaction and a Carbohydrate as a Chiral Centre Source

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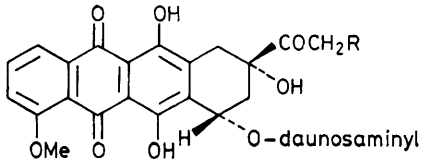
Summary *Leuco*-quinizarin (**4**) with ethanal in alkaline solution at 0 °C followed by aerial oxidation gave 2-(1-hydroxyethyl)quinizarin (**2c**) in high yield and similarly (**4**) with *aldehydo*-2,3 : 4,5-di-*O*-isopropylidene-D-arabinose (**3**) at 0 °C and aerial oxidation gave a good yield of the crystalline 2-(1-hydroxy-D-arabinityl)quinizarin (**5**) which after treatment with acid, periodate, and cold alkaline dithionite, aerial oxidation, and treatment with mild acid gave the crystalline anthracyclinone (**10**) in excellent yield.

IN recent years there has been intense interest[1] in the development of synthetic routes to the anthracyclinone system which includes the important and widely used anti-tumour antibiotics adriamycin (**1a**) and daunomycin (**1b**). A potential route to the tetracyclic system would

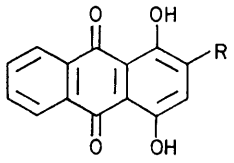


(1)

a; R = OH, adriamycin
b; R = H, daunomycin

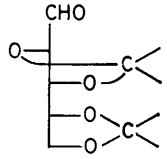
involve the extension of a suitable anthraquinone derivative such as quinizarin (**2a**) by attachment of a fourth ring and concomitant introduction of appropriate chiral centres. In an attempt to achieve such a synthesis we have been interested in using a carbohydrate as an aldehyde source in the Marschalk reaction.[2,3] This reaction involves the condensation of an aldehyde, R'CHO, with an anthraquinone, such as quinizarin (**2a**), in hot alkaline sodium dithionite solution followed by aerial oxidation of an intermediate *leuco*-form; good yields of the corresponding 2-alkylquinizarins (**2b**) are generally obtained.

In preliminary experiments which will be reported elsewhere, we obtained evidence which suggested that the proposed synthesis was feasible, but under the normal conditions of the Marschalk reaction, mixtures were obtained which proved difficult to separate and identify. However, we now report a new modification of the Marschalk reaction which has overcome these problems.



(2)

a; R = H
b; R = CH_2R'
c; R = CH(OH)Me



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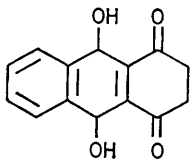
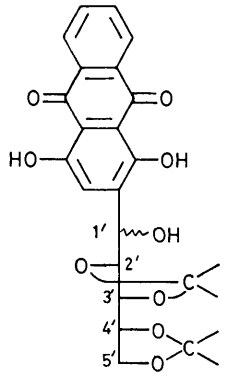


(4)

When the aldehyde (**3**)[4] was condensed with quinizarin (**2a**) under typical Marschalk conditions mixtures of products were obtained. However when the readily available *leuco*-quinizarin (**4**) was treated with the aldehyde (**3**) in aqueous sodium hydroxide containing methanol and tetrahydrofuran, at 0 °C for 30 min, followed by aerial oxidation, a good yield (56%) of the quinizarin (**5**) was obtained after a single chromatographic purification on silica gel. The compound readily crystallised from ethanol as orange-red laths, m.p. 167 °C. Compounds of this type have previously only been assumed to be intermediates in the Marschalk reaction and this appears to be the first



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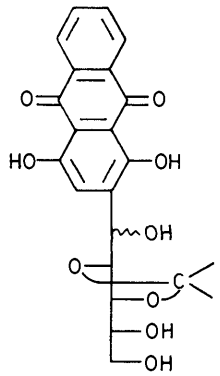

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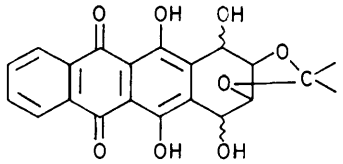

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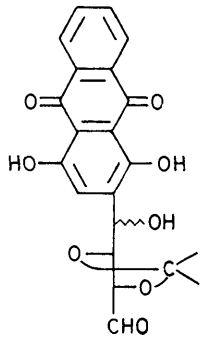

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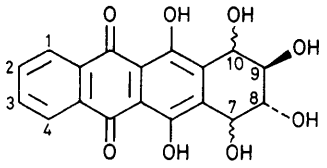

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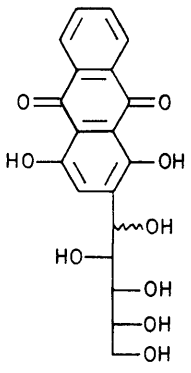

(7)

recorded example of the isolation of such a substance in a pure form. A similar reaction of *leuco*-quinizarin (**4**) with ethanal readily produced a high yield (80%) of the corresponding quinizarin (**2c**) which readily crystallised from ether as orange-red needles, m.p. 110 °C.

The structure assigned to the quinizarin (**5**) was confirmed by elemental analysis, its i.r. spectra (*e.g.* ν_{max} 1380 cm^{-1}, CMe_2), mass spectrometry (*e.g.* M^+ *m/e* 470), its u.v. absorption spectra which were typical of mono-substituted quinizarins, its ^1H n.m.r. spectra [*e.g.* absence of signal for H-2; signals at δ 7·52 (H-3) and 3·0 (d, 1′-OH), and full assignment of all other protons], and by its subsequent reactions.

The spectroscopic data and homogeneity of the material on t.l.c. in several solvent systems suggested that it was a single diastereoisomer and although we have not assigned chirality of the new asymmetric centre produced at C-1′ the OH group probably has the *trans*-configuration with respect to the C(2′)–O bond.

Treatment of the di-isopropylidene derivative (**5**) with aqueous acetic acid at 48 °C for 1 h readily removed the terminal isopropylidene group to produce in high yield (95%) the mono-isopropylidene derivative (**6**) which crystallised readily from propan-2-ol–ether as orange-red prisms, m.p. 178 °C. Further treatment of the mono-isopropylidene derivative (**6**) with refluxing 80% aqueous acetic acid over 1 h gave (100% yield) the fully deprotected compound (**7**) which readily crystallised from ethanol as orange-red silky needles, m.p. 229 °C.

The structure assigned to the mono-isopropylidene derivative (**6**) was confirmed by spectroscopic data and in addition by its reaction with 1 mol equiv. of periodate to give the aldehyde (**8**) which was obtained in solid form and which was homogeneous on t.l.c. This compound [M^+ *m/e* 398, ν_{max} 1380 (CMe_2) and 1700 cm^{-1} (CHO)] did not readily cyclise but when it was converted into the *leuco*-form with sodium dithionite in alkaline solution at 0 °C it very rapidly gave the solid cyclic isopropylidene derivative (**9**) which after treatment with aqueous acetic acid gave the fully deblocked anthracyclinone derivative (**10**) in high yield (70%). This readily crystallised from aqueous acetic acid as orange-red laths, m.p. 240 °C (decomp.). It was homogeneous on t.l.c. and the assigned structure was confirmed by elemental analysis and spectroscopic data [M^+ *m/e* 358; no ^1H n.m.r. signal at δ 7·5, corresponding to loss of H-3, full assignment of all other ^1H n.m.r. signals; u.v. absorption spectra typical of a 2,3-disubstituted quinizarin]. The tetracyclic compound contains two new chiral centres at C(7) and C(10) to which we have not assigned configurations but the spectroscopic data suggest that the OH groups have a *transoid* arrangement with respect to those at the known chiral centres at C(8) and C(9).

The reactions outlined clearly have many applications and we believe that this particular method is the best yet recorded for the synthesis of a wide variety of anthracylinone derivatives and of many related naturally occurring anthraquinone derivatives. In particular, the ability to introduce centres of known chirality at all four positions on the fourth alicyclic ring is in itself novel and of considerable value since hydroxy-groups in these positions are capable of much modification.

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[2] C. Marschalk, F. Koenig, and N. Ourousoff, *Bull. Soc. Chim. Fr.*, 1936, **3**, 1545.
[3] C. Marschalk, *Bull. Soc. Chim. Fr.*, 1939, **6**, 655.
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