Regioselective Synthesis of 2- and 3-Alkyl-5-hydroxyquinizarins

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Summary Condensation of *leuco*-5-hydroxyquinizarin with aldehydes in the Marschalk reaction leads to 2-alkyl-5-hydroxyquinizarins while condensation catalysed by piperidinium acetate yields the 3-alkyl derivatives.

IN the 1930's, Marschalk[1] showed that *leuco*-quinizarin[2] underwent an aldol-type condensation with a variety of aldehydes leading to 2-substituted quinizarins. This reaction is also applicable to *leuco*-5-hydroxyquinizarin[2] (**1**) and there is evidence from the work of Brockmann and Müller[3] that there is regio-selectivity in favour of the 2-position. It appeared that such regiospecificity might offer a possible solution to one of the long-standing problems in synthetic approaches[4] to the anthracycline antibiotics,[5]

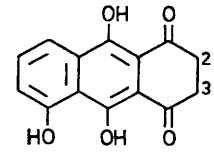
viz., how to introduce substituents specifically into the 2- and 3-positions of (**2**) in a molecule where the dissymetry is created by the distant 5-substituent. To this end we have made a general investigstion of the regiospecificity of the Marschalk and related reactions. Condensation of (**1**) (generated *in situ* by alkaline dithionite reduction) with propionaldehyde gave (**3**) (50%) with no detectable amount of the 3-isomer. The structure of (**3**) was established by degradation *via* the trimethyl ether (**7**) (NaH–MeI–glyme) which was cleaved[6] with $KOBu^t$–H_2O to give, after methylation of the acids formed, *m*-methoxybenzoic acid methyl ester (22%) and the alkyl compound (**8**) (28%), which was independently synthesised from quinol dimethyl ether. The results strongly suggest that cleavage occurs in the direction indicated in (**7**) but do not unambiguously establish the structure; this follows from degradation of the 3-alkyl compound. Reaction of the *leuco*-compound (**1**) with propionaldehyde in isopropyl alcohol–piperidinium acetate[7] gave mainly 3-substitution; cleavage of the trimethyl ether of (**4**) was complex† yielding (**9**) (6%) and the *m*-methoxybenzoic acid derivative (9%). With the structures unambiguously secured the minor chemical shift differences in the n.m.r. spectra of the trimethyl ether isomers can be used to assign structure; in the 2-alkyl series the 3-proton resonates at τ 3·00 and the three methoxy groups at τ 6·06, 6·09 and 6·17 while in the other isomer the 2-proton absorbs at τ 3·18 and the three methoxy groups at τ 6·06, 6·10 and 6·12. The various condensations we have effected are summarised in the Table. In addition, (**5**) was oxidised (pyridinium chlorochromate)[8] to the corresponding aldehyde which on exposure to dithionite and base gave the tetracycle (**6**).‡

TABLE

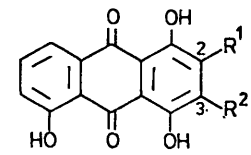
Aldehyde	Conditions[a]	Total yield[b]/%	Ratio 2-:3-alkylation
EtCHO	A	50	c
,,	B	46	1:9
$HO[CH_2]_3CHO$	A	44	7:1
$HO[CH_2]_4CHO$	A	44	9:1
$MeCH(OH)[CH_2]_2CHO$	B	49	1:7

[a] A, Marschalk conditions; B, isopropyl alcohol—piperidinium acetate. [b] Pure recrystallised material. [c] No 3-alkylation.

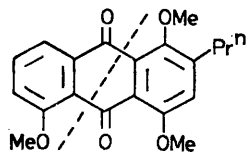
We have no definite proof as to the origin of the regioselectivity in these reactions but we propose a working hypothesis. Titration of (**1**) with NaOH shows that the predominant species present in aqueous sodium hydroxide is likely to be a mono-anion. The kinetically active species must be formed by proton abstraction from position-2. If the predominant species in solution is (**10**), which minimises electrostatic repulsions, then proton abstraction from position-2 giving rise to a hydrogen-bonded dianion might well be formed preferentially to the dianion arising from 3-proton loss, which is destablised by electrostatic repulsions. In isopropyl alcohol–piperidinium acetate, (**1**)



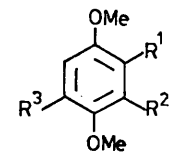
(1)



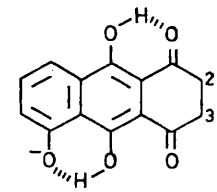
(2); $R^1 = R^2 = H$
(3); $R^1 = Pr^n, R^2 = H$
(4); $R^1 = H, R^2 = Pr^n$
(5); $R^1 = -[CH_2]_4OH, R^2 = H$
(6); $R^1, R^2 = -[CH_2]_4$



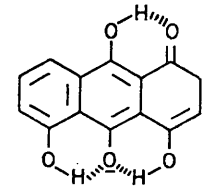
(7)



(8); $R^1 = Pr^n, R^2 = H, R^3 = CO_2Me$
(9); $R^1 = H, R^2 = Pr^n, R^3 = CO_2Me$
(12); $R^1 = Pr^n, R^2 = R^3 = H$



(10)



(11)

is most likely present as the neutral species in which 3-proton abstraction could be favoured over 2- by formation of a more extensively hydrogen-bonded anion, *e.g.* (**11**) or its tautomers. Such control of the regioselectivity of reactions may have more general implications.

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† The predominant cleavage in this case was to methoxyphthalic acid and the quinol ether (**12**), which was partially oxidised in the side chain (D. G. Davies, P. Hodge, and P. Yates, *J.C.S. Perkin I*, 1973, 850, 2299).

‡ The compound was also prepared by Marschalk condensation using succindialdehyde: J. R. Brown, Pharmacy Department, Manchester University, personal communication.

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