Substitution of Quinizarin and 5-Hydroxyquinizarin at C-2

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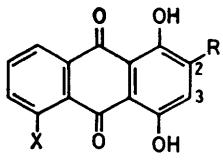
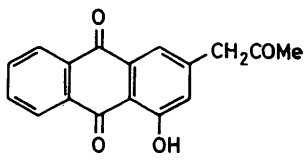
Summary Carbanions derived from ethyl acetoacetate, acetylacetone, and alkyl nitro-compounds add to C-2 of quinizarin and its 5-hydroxy-derivative.

IN previous work[1] we have shown that Marschalk (aldol) reaction of *leuco*-5-hydroxyquinizarin led, under appropriate conditions, to either predominant C-2 or C-3 alkylation. This selectivity has since been used in a synthesis of ξ-rhodomycinone.[2] We have since discovered that, while such alkylations are successful with simple aldehydes they are less successful with polyfunctional derivatives. The well established[3] Michael additions of quinones to stabilised carbanions led us to investigate such additions with quinizarin (**1**). Reaction of (**1**) in refluxing methanol with a



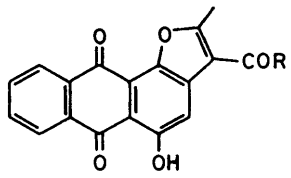


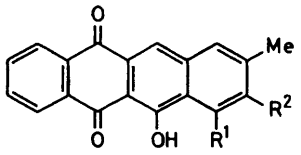
X = H
(**1**) R = H
(**2**) R = CH_2COMe
(**3**) R = CH_2CO_2Me
(**4**) R = CH_2CO_2H

X = OH
(**5**) R = H
(**6**) R = Me
(**7**) R = Pr^n
(**8**) R = Pr^i
(**9**) R = $CH_2CH_2C(OCH_2)_2Me$
(**10**) R = CH_2CH_2COMe

(**11**)

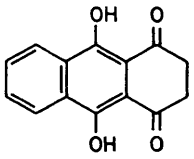
five-fold excess of sodium methoxide and ten-fold excess of ethyl acetoacetate unexpectedly yielded (**11**) (73%) [ν_{max} 1715, 1675, and 1638 cm^{-1}; λ_{max}^{EtOH} (ε) 257 (26200), 274 (13700), 330 (3000), and 408 nm (5200); τ −2·47 (1H, s, exch.), 1·75 (2H, m), 2·23 (2H, m), 2·40 (1H, d, *J* 1·7 Hz), 2·90 (1H, d, *J* 1·7 Hz), 6·21 (2H, s), and 7·76 (3H, s)]. This formal *cine*-substitution† is probably related mechanistically to our observation that when *leuco*-quinizarin (**16**) was allowed to react with pyrrolidine–toluene and the water was removed azeotropically then 1-hydroxyanthraquinone was formed in 83% yield. This was postulated (Scheme) to arise from the enamine (**17**) being in equilibrium with other tautomers of which (**18**) could undergo irreversible elimination to product. Similar equilibration and elimination of (**19**) would, after decarboxylation, yield (**11**). On prolonged reaction of (**1**) or (**11**) under the same reaction conditions a compound was formed (43%) which is formulated as (**14**) or (**15**) [ν_{max} 1725, 1670, and 1612 cm^{-1}; λ_{max}^{EtOH} (ε) 266 (21750), 289 (4750), 303 (3500), and 462 nm (2000); τ −5·72 (1H, s, exch.), 1·78 (2H, m), 2·02 (1H, s), 2·28 (2H, m), 2·52 (1H, s), 5·55 (2H, q), 7·13 (3H, s), 7·61 (3H, s), and 8·58 (3H, t)].

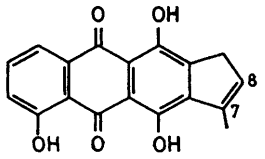




(**12**) R = OEt
(**13**) R = Me

(**14**) R^1 = Me, R^2 = CO_2Et
(**15**) R^1 = CO_2Et, R^2 = Me

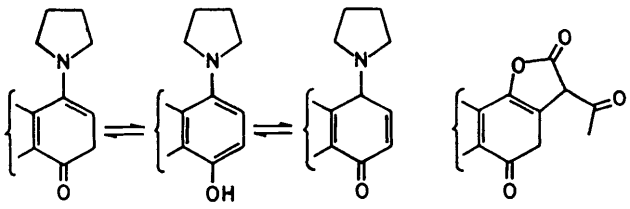




(**16**)

(**20**)
(**21**) 7,8-dihydro

We prefer (**14**) since the ester could not be hydrolysed with 40% NaOH–H_2O or 20% HCl–H_2O but was converted into the acid on adding a conc. H_2SO_4 solution of it to water. We were unable to lactonise this acid. When the addition of ethyl acetoacetate was carried out using NaOMe–MeOH the ester (**3**) [ν_{max} 1734 and 1612 cm^{-1}; τ −3·28 (1H, s, exch.), −2·81 (1H, s, exch.), 1·69 (2H, m), 2·19 (2H, m), 2·74 (1H, s), and 6·26 (5H, s)] was isolated (63% yield).‡ Reaction of (**1**) with an excess of acetylacetone and NaOEt–EtOH gave the furan§ (**13**) (35%) [ν_{max} 1670, 1635, and 1615 cm^{-1}; λ_{max}^{EtOH} (ε) 259 (32000), 270 (28000), 350 (6000), and 426 nm (8800); τ −2·8 (1H, s, exch.), 1·65 (2H, m), 2·07 (1H, s), 2·11 (2H, m), 7·03 (3H, s), and 7·34 (3H, s)], and the ketone (**2**) (45%) [ν_{max} 1725 and 1628 cm^{-1}; λ_{max}^{EtOH}



(**17**) (**18**) (**19**)

SCHEME

† The ^1H n.m.r. spectrum establishes the *meta*-relationship of two of the aromatic protons (*J* 1·7 Hz).

‡ In the derived acetate the methyl and methylene singlets were resolved in the ^1H n.m.r. spectrum.

§ When Et_3N was used as base and solvent then the furans (**12**) (79%) and (**13**) (72%) were the only products isolated from the addition of ethyl acetoacetate and acetylacetone, respectively.

(ε) 250 (16000), 256 (12900), 284 (6700), 458 (4900), and 484 nm (3100); τ −3·19 (1H, s, exch.), −2·26 (1H, s, exch.), 1·72 (2H, m), 2·22 (2H, m), 2·86 (1H, s), 6·18 (2H, s), and 7·70 (3H, s)]. When the base was changed to NaOMe–MeOH, (**2**) was the sole isolated product (73%).

Substitution of 5-hydroxyquinizarin (**5**) for (**1**) gives a parallel series of products; we cannot yet state with complete certainty that they are formed regiospecifically though existing evidence supports this. It has been our experience in the past that 2- and 3-regioisomers are not readily differentiated by the usual criteria. However, we can say that nitronate carbanions add specifically to C-2 of (**5**). Nitromethane, 1-nitropropane, and 2-nitropropane react with (**5**) and NaOMe in MeOH to yield, respectively, (**6**)¶ (84%), (**7**) (66%), and (**8**) (76%). Each product was converted into its trimethyl ether in which small reproducible differences between the 2- and 3-substituted compounds can be discerned in ^{1}H n.m.r. spectra.[1] The isomeric ethers can also be separated by t.l.c.; in no case were we able to detect 3-substituted compounds. Prolonged treatment of (**5**) with nitromethane gave 2,3-dimethyl-5-hydroxyquinizarin (65%). However, attempts to alkylate (**7**) using the nitroalkane, 1,3-dicarbonyl, or Marschalk methods failed. Intramolecular alkylation is possible. Compound (**5**) reacted with 1,4-dinitrobutane[4] to give the expected tetrahydronaphthacene (47%) and the ketone (**10**) under Marschalk conditions gave a mixture of (**20**) (59%) [τ −3·82 (1H, s, exch.), −2·70 (1H, s, exch.), −2·47 (1H, s, exch.), 2·05 (1H, dd, *J* 8·2, 1·1 Hz), 2·07 (1H, t, *J* 8·2 Hz), 2·66 (1H, dd, *J* 8·2, 1·1 Hz), 3·50 (1H, m), 6·46 (2H, m), and 7·54 (3H, br.s)] and (**21**) (17%) [τ −3·26 (1H, s, exch.), −2·22 (1H, s, exch.), −2·06 (1H, s, exch.), 2·42 (1H, dd, *J* 8·2, 1·1 Hz), 2·73 (1H, t, *J* 8·2 Hz), 2·83 (1H, dd, *J* 8·2, 1·1 Hz), 6·78 (1H, m), 7·28 (2H, m), 7·94 (2H, m), and 8·96 (3H, d, *J* 8·5 Hz)]. On reduction with dithionite, (**20**) was converted quantitatively into (**21**). The ketone (**10**) was prepared by alkylation of (**5**) with the ethylene acetal of 1-nitrobutan-3-one** to form (**9**) followed by acid hydrolysis to (**10**).

There are a number of possible explanations for the high regioselectivity observed but since one is not more convincing than another we shall not discuss them other than to note that the identical regioselectivity in the Marschalk and carbanion additions excludes both being controlled by formation of the more stable carbanion.

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¶ This constitutes an efficient synthesis of islandicin.

** Prepared from the bromoacetal (G. Büchi and H. Wüest, *J. Org. Chem.*, 1969, **34**, 1122) by reaction with $NaNO_2$–H_2O–DMF.

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[3] K. T. Finlay in 'The Chemistry of the Quininoid Compounds,' ed. S. Patai, Wiley, London, 1974, ch. 17.
[4] H. Feuer and G. Leston, *Org. Synth.*, 1963, (coll. vol.) **4**, 368.