Enolate Ion Reactions of Leucoquinizarin. Michael Additions

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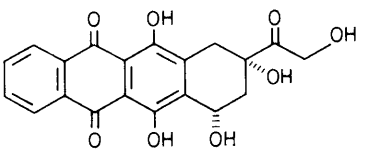
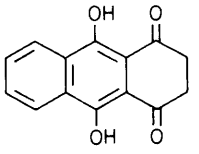
The base-catalysed reaction of leucoquinizarin with various Michael acceptors gives derivatives of potential value as anthracyclinone precursors.

Owing to the cardiotoxic effects of anthracycline antibiotics, such as adriamycin, there is interest in the synthesis of analogues with improved chemotherapeutic properties.[1] A simple strategy for the synthesis of tetracyclic aglycones starts with a 1,4-dihydroxy-9,10-anthracenedione (quinizarin) derivative. Previously, the alkylation reactions used to introduce the alicyclic ring were carried out *via* the Marschalk reaction.[2] This is a base-catalysed, crossed-aldol reaction, in which the reduced quinizarin [leuco compound, (**1**)] reacts with an aldehyde to give, after air oxidation, the 2-hydroxyalkyl or alkyl (**2**), depending upon the reaction temperature.[3] Since this is a typical enolate ion reaction of (**1**), the possibility of Michael additions was considered. This is a new approach to the synthesis of compounds (**2**), which might serve as anthracyclinone precursors. Reactions of leucoquinizarins with crotonaldehyde have been reported to give low yields of products, which could only arise by the enolate ion of (**1**) adding to the double bond, prior to either intra- or intermolecular Marschalk reaction of the aldehyde,[3,4] but the potential of the initial Michael addition has not been previously recognized.

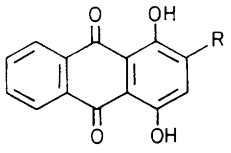
Leucoquinizarin (**1**) was allowed to react with excess of ethyl acrylate (12 mol, added in 4—5 portions over 24 h) in ethanol, under N_2 at 50 °C, using EtONa (1.8 mol) as base. After 48 h, the products were isolated by re-oxidation with air, acidification, and filtration of the precipitate. They were separated by dry-column chromatography[5] on silica gel ($CHCl_3$) owing to contamination with 40% quinizarin, to give (**2**) [R = $CH_2CH_2CO_2Et$, 50% yield based on (**1**)]; i.r. ($CHCl_3$): ν_{max} 1732 (ester CO), 1628 cm^{-1} (quinone CO); ^1H n.m.r. ($CDCl_3$): δ 2.82 (A_2B_2, m), 7.02 (s, aromatic, 3-H), 12.62 and 13.12 (2 s, HO); proton decoupled ^{13}C n.m.r. ($CDCl_3$): 19 peaks; δ 186.6, 185.8 (quinone CO), 172.2 (ester



Adriamycin aglycone



(**1**)



(**2**)

Table 1. Conditions and yields for the formation of the compounds (**2**).

Michael acceptor	Conditions	M.p./°C	Yield (%)	Substituent R
Ethyl acrylate	EtONa/50 °C	122—123	50	$CH_2CH_2CO_2Et$
Acrylonitrile	EtONa/25 °C	211—213	56	CH_2CH_2CN
Methacrylonitrile	EtONa/reflux	172—173	55	$CH_2CH(Me)CN$
Ethyl methacrylate	EtONa/reflux	217—219	49	$CH_2CH(Me)CO_2Et$
Diethyl maleate	KOH/25 °C	110—111	22	$CH(CO_2Et)CH_2CO_2Et$

CO), 157.3, 156.5 (ring C-1 and C-4), 142.3 p.p.m. (ring C-2); m.s. m/z (80 eV): 340 (M^+), minor fragments at 295, 266, 240.

The compounds (**2**) listed in Table 1 gave satisfactory i.r. and ^{1}H Fourier transform n.m.r. spectra but, apart from the ethyl acrylate adduct, were insufficiently soluble for ^{13}C n.m.r. spectroscopy. The singlets (1H) at δ 7.3, 12.8, and 13.3 in their ^{1}H n.m.r. spectra, and i.r. absorptions characteristic of the 2-R substituents, established their identities. Purification by dry column chromatography was required owing to the presence of quinizarin (25—45%). Reactions conducted in refluxing ethanol gave better conversions but the products were then contaminated with an insoluble polymer. The initial low yields were a consequence of back-oxidation of (**1**) to quinizarin, polymerisation of the alkenes, and the competitive addition of the base to the alkenes. In the reaction with diethyl maleate, using EtONa, diethyl ethoxysuccinate[6] was isolated (b.p. 87—87.5 °C/0.3 mmHg). The ^{1}H n.m.r. spectrum of this compound was interesting because the chiral centre not only resulted in absorptions characteristic of an ABX spin system but also of an ABX_3 system, arising from the non-equivalence of the diastereoisotopic protons of the methylene group of the ethoxy substituent.

This type of reaction shows promise for the preparation of a variety of substituted quinizarin derivatives, which could prove to be valuable anthracyclinone precursors, and are not readily accessible by the Marschalk reaction.

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