A Simple Synthesis of Demethoxydaunomycinone

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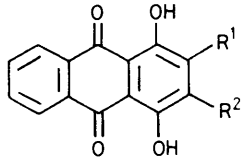
2-Acetylquinizarin has been converted into demethoxydaunomycinone by Michael addition with 3,3-dimethoxy-1-nitrobutan-2-one, aldol condensation, and reduction.

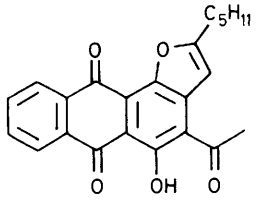
In unpublished work[1] we have shown that 2-acetylquinizarin (**1**) readily undergoes Michael addition with β-ketoesters and that *in situ* oxidation followed by aldol cyclisation generates anthracycline derivatives. If the alkoxycarbonyl group were replaced by a group with a similar acidifying effect on α-protons then addition should still occur and if this group could be eliminated by virtue of being β to a carbonyl function then the *in situ* oxidation to generate anthraquinone would not be required (Scheme 1).

Possible groups fulfilling these requirements are RSO–, RSO_2, $-NO_2$, and $-PO(OR)_2$. In the event, the sulphoxide and sulphone were found to be unsatisfactory. However, 2-acetylquinizarin (**1**) reacted with dimethyl 2-oxoheptylphosphonate in the presence of Et_3N–MeOH under an inert atmosphere to give the furan (**5**) (24%)† and with ethyl nitroacetate under similar conditions to give the ester (**2**) (57%); reaction in the presence of air gave the nitroester (**3**) (76%). Since these results suggested that NO_2 was the most suitable stabilising group, 3,3-dimethoxy-1-nitrobutan-2-one was prepared (73%) using the Seebach[2] method, by condensing the nitromethane dianion with methyl 2,2-dimethoxypropionate. Attempts to carry out the Michael addition–aldol condensation in a 'one-pot' process as in our previous work were unsuccessful, for reasons that will become apparent. However, reaction of the nitroketone with the quinone (**1**) in CH_2Cl_2–1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the diketone (**4**) (87%), $\nu_{max.}$ 1735, 1700 cm^{-1} δ_H 1.40 (3H, s), 2.56 (3H, s), 3.25 (6H, s), 4.19 (2H, s), 7.85 (2H, m), 8.36 (2H, m), 13.25 (1H, s), 13.28 (1H, s); δ_C 19.89, 31.56, 36.17, 49.79, 102.91, 202.32, 204.88, and 14 signals for the aromatic fragment. Attempts to effect the aldol condensation with a large variety of bases in MeOH and Lewis acids in CH_2Cl_2 were unsuccessful, mostly leading to the formation of a polar compound which reverted to starting material on attempted isolation. It was found that this material was also formed on dissolution of the diketone in Me_2NCHO. The ^1H n.m.r. spectrum of the isolated material measured in dry, acid-free

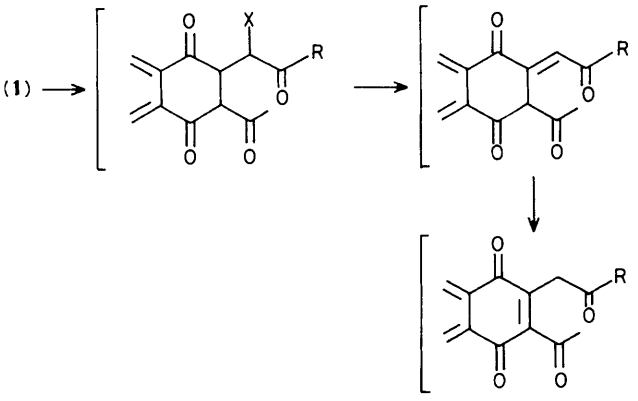
† All new compounds gave satisfactory combustion and/or accurate mass measurements on homogeneous samples as judged by t.l.c.



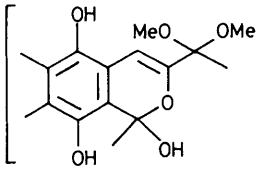
(1) R^1 = COMe, R^2 = H
(2) R^1 = CH_2CO_2Et, R^2 = COMe
(3) R^1 = $CH(NO_2)CO_2Et$, R^2 = COMe
(4) R^1 = $CH_2COC(OMe)_2Me$, R^2 = COMe



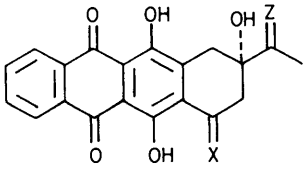
(5)



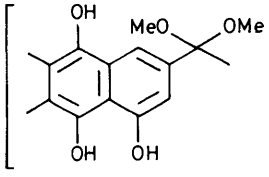
Scheme 1



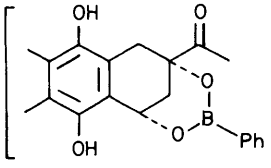
(6)



(7) X = O, Z = $(OMe)_2$
(8) X =  , Z = O
(9) X =  , Z = O



(10)



(11)

$CDCl_3$ showed it to be a 1 : 2 mixture of the diketone (**4**) and a compound showing δ_H 1.58 (3H, s), 2.18 (3H, s), 3.30 (3H, s), 3.31 (3H, s), 6.83 (1H, s), and the usual aromatic protons. These data, indicating an enol derivative probably containing a chiral centre, together with the absence of carbonyl absorption above 1625 cm^{-1} led us to assign structure (**6**). When the diketone (**4**) was hydrolysed with CF_3CO_2H–H_2O a stable enol derivative showing similar spectroscopic properties was isolated.

The aldol condensation can be successfully carried out, with minimal formation of the unproductive enol ether, by suspending the dione (**4**) in Pr^i_2NEt–H_2O to form the ketone (**7**) (46%), δ_H 1.44 (3H, s), 2.91 (3H, s), 3.13 (1H, d, *J* 19 Hz), 3.41 (3H, s), 3.42 (1H, d, *J* 19 Hz), 3.43 (3H, s). A small amount of the naphthacene (**10**) is also formed,‡ and is the major product when DBU is the base. Reduction of the ketone (**7**) with $NaBH_4$–$CeCl_3$–Pr^iOH followed by work-up with 3 M HCl gave a mixture of *cis* and *trans*-diols (**8**) and (**9**) (56%). Reaction of the mixture with $PhB(OH)_2$ using the Broadhurst, Hassall, and Thomas procedure[3] gave the boronate (**11**) (59%) which was cleaved with 2-methylpentane-2,4-diol to give demethoxydaunomycinone (**8**) (84%) identical with an authentic specimen.

This approach should have wide applicability for the enantioselective synthesis of anthracyclinones.

We thank Professor R. J. Stoodley, UMIST, for an authentic sample of demethoxydaunomycinone and the S.E.R.C. for financial support.

Received, 24th November 1986; Com. 1662

References

1 K. B. Mullah and J. K. Sutherland, unpublished results.
2 M. Eyer and D. Seebach, *J. Am. Chem. Soc.*, 1985, **110**, 3601.
3 M. J. Broadhurst, C. H. Hassall, and G. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2239.

‡ *Spectral data:* $\lambda_{max.}$ 564, 531, 495, 464 nm; δ_H 15.24, 14.33, 12.42 (all 1H, s), 8.17 (1H, s), 7.52 (1H, s), 3.23 (6H, s), 1.58 (3H, s).