Tetrahedron Letters No. 5, pp 477 - 480. 0040-4039/79/0129-0477$02.00/0

SYNTHESIS OF TETRACYCLIC HYDROXYQUINONES RELATED TO DAUNOMYCINONE

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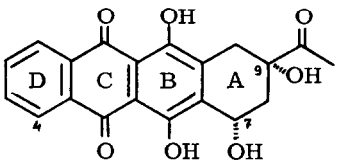
There is at present considerable interest in synthetic approaches to the anthracycline antibiotics daunomycin, adriamycin and carminomycin[1], which are widely used for the treatment of some types of human cancer[2]. The recent report that 4-demethoxydaunomycin is more active than daunomycin itself[3] has increased the interest in new synthetic routes to the aglycone 4-demethoxydaunomycinone (I).



I

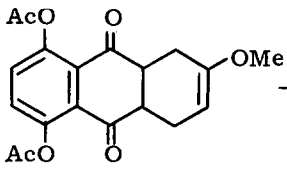
A major difficulty in the synthesis is the construction and functionalization of the alicyclic A ring. The functionalization of C-9 has already been achieved through a carbonyl group at the 9-position, which may be reacted to furnish the appropriate substituents[1c,4]. The introduction of the OH group at C-7 has generally been accomplished by benzylic bromination and subsequent solvolysis[1a-b,5]. In order to circunvent the difficulties of this approach a new method through a 7-trimethylsilyl group by a Diels-Alder reaction with quinizarinquinone has very recently been proposed[6].

In a previous work we developed a novel route to the tetracyclic system of anthracyclinones by two succesive Diels-Alder reactions starting from naphthazarin[7]. Our approach has been applied later by Kelly and coworkers[8] and recently by other authors[9] to the synthesis of anthracyclinone derivatives.

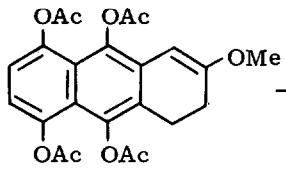
We now report the application of our previous method to the synthesis of several tetracyclic hydroxyquinones, the A ring of which is adequately functionalized in order to allow the conversion to 4-demethoxydaunomycinone.

The Diels-Alder adduct II (m.p. 153-154º) was obtained in nearly quantitative yield by refluxing 27 hr naphthazarin diacetate and 2-methoxy-1,3-butadiene in benzene. Acetylation of

II with Ac_2O + NaOAc afforded III (78%; m.p. 179-180º), with simultaneous isomerization of the double bond to the more stable conjugated position (the olefinic proton appeared in n.m.r. as a singlet at δ 5.60). Enol ether III was hydrolyzed by aqueous oxalic acid to the ketone IV (48%; m.p. 190-191º), easily converted into the dioxolane V (90%, m.p. 229-231º); air oxidation of V in 3% NaOH gave, after acidification, a quantitative yield of VI [m.p. 188º (subl.)],



II



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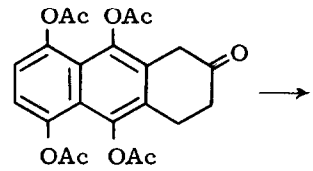

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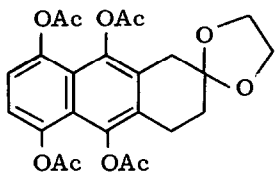
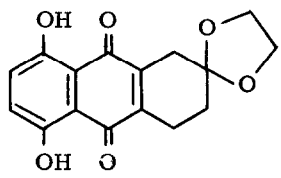


V



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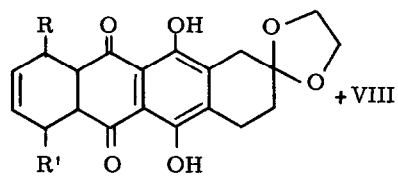
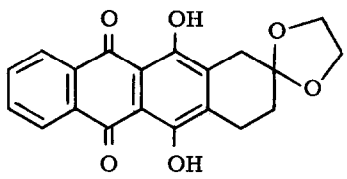
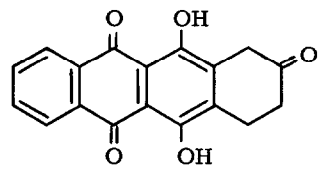


VIIa: R = H; R' = OMe
VIIb: R = OMe; R' = H



VIII

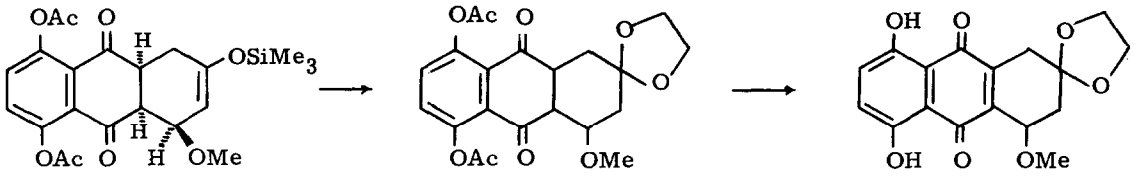


IX

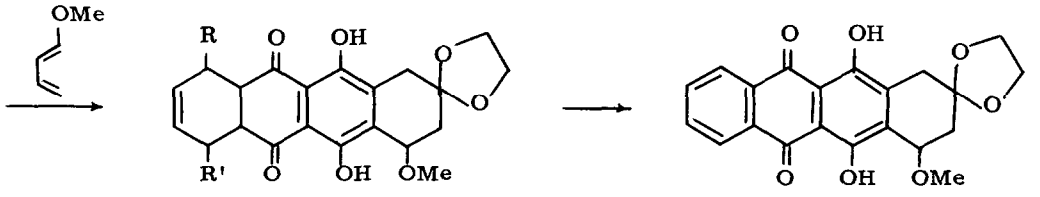
which possesses a naphthazarin chromophore (λ_{max}^{EtOH}: 285, 478, 508, 545). A new Diels-Alder reaction through the less stable tautomer of VI with (E)-1-methoxy-1,3-butadiene afforded a mixture of regioisomers VIIa + VIIb and aromatized product VIII, which we have been unable to separate. By treatment of this mixture with 3% NaOH and subsequent acidification, the regioisomers VII were transformed in VIII [m.p. 210-212º; n.m.r. ($CDCl_3$): δ 13.50 (s, 2H); 8.30 (m, 2H); 7.90 (m, 2H); 4.10 (s, 4H); 3.30 (m, 2H); 3.10 (m, 2H); 2.00 (m, 2H); yield VI → VIII: 90%]. Acid hydrolysis of VIII afforded IX (99% yield; m.p.> 310 d.) the spectroscopic data of which are identical as those reported[10].

On the other hand, functionalization of both 7- and 9-positions of ring A was accomplished with a 1,3-disubstituted diene. Diels-Alder addition of naphthazarin diacetate to (E)-1-methoxy-

3-trimethylsilyloxy-1,3-butadiene[11] at room temperature in benzene led to the adduct X [73%; m.p. 168-170º; n.m.r. ($CDCl_3$): δ 7.30 (s, 2H); 5.10 (m, 1H); 4.15 (m, 1H); 3.30 (m, 2H); 3.00 (s, 3H); 2.40 (s, 3H); 2.30 (s, 3H); 2.20-2.50 (m, 2H); 0.20 (s, 9H)][12,13]. Treatment of X with ethylenglycol in the presence of conc. HCl afforded a mixture of two products the major component of which XI was isolated, after silica gel chromatography, in 60% yield[14] (m.p. 179-181º).



X XI XII



XIIIa: R = H; R' = OMe
XIIIb: R = OMe; R' = H

XIV

Treatment of XI with cold 1% NaOH and subsequent acidification (50% aq. HOAc) gave 93% of XII [m.p. 104-105º (dec.)][15]. Reaction of XII through the less stable tautomer with (E)-1-methoxy-1,3-butadiene by refluxing 5 days in benzene yielded a red oil. The crude mixture of XIIIa + XIIIb was aromatized by treatment with cold 1% NaOH and acidified (50% HOAc) giving 70% of XIV [m.p. 130-132º (dec.); n.m.r. ($CDCl_3$): δ 13.50, 13.30 (s, 1H each); 8.50-8.10 (m, 2H); 8.00-7.70 (m, 2H); 5.10-4.80 (m, 1H); 4.10 (broad s, 4H); 3.60 (s, 3H); 3.10 (broad s, 2H); 2.50-2.20 (m, 2H); MS: m/e 382 (M^+)].

The ready availability of the key intermediates IX and XIV by the Diels-Alder route starting from naphthazarin diacetate shows that this approach is a valuable alternative for the anthracyclinone synthesis.

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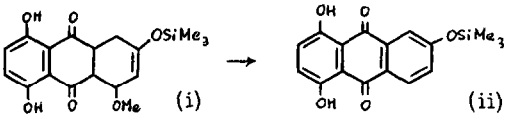
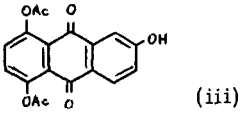
12. A detailed study of the n.m.r. spectrum in the 4.0-5.5 region demonstrated the stereo chemistry of adduct X in accord with the expected endo addition.
13. Diels-Alder addition of naphthazarin to (E)-1-methoxy-3-methylsilyloxy-1,3-butadiene in benzene solution, in the cold, yielded the expected adduct, the spectroscopic data of which



are consistent with the structure (i). The adduct (i) is less stable than diacetate X and under mild conditions, undergoes aromatization to afford 1,4-dihydroxy-6-trimethylsilyloxy-9,10-anthraquinone (ii), m.p. 250-252 (dec.).

14. The minor component, m.p. 200-203º, was isolated in only 5% yield and its structure (iii),



was established on the basis of the spectroscopic data.

15. The presence of a singlet at δ 7.20 (2 aromatic H) in n.m.r. spectrum indicates that XII is the predominant tautomer.
16. All new compounds gave satisfactory combustion and/or mass spectrometric analyses and spectroscopic data consistent with the assigned structures.

(Received in UK22 November 1978)