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1,2-DIHYDRO-3,10-DIHYDROXYCYCLOBUT[b]ANTHRACENE-4,9-DIONE A KEY INTERMEDIATE FOR 4-DEMETHOXYANTHRACYCLINONES

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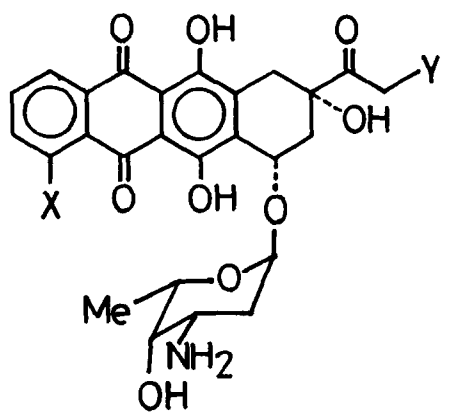
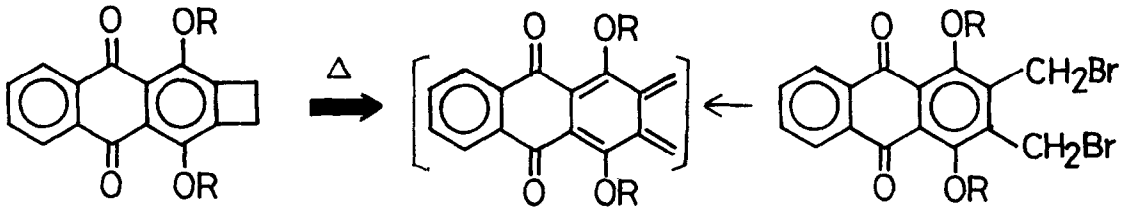
Summary: The title compound synthesized in four steps from bicyclo[4.2.0]octane-2,5-dione and *o*-phthaldehyde undergoes cleanly thermolytic intermolecular Diels-Alder reactions providing a general synthesis of 7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenediones, the compounds being related to anthracyclinones.

Potent anticancer activity of the anthracycline antibiotics such as daunomycin 1, 4-demethoxydaunomycin 2, and adriamycin 3 has stimulated much research on the synthetic methods for the tetracyclic aglycons.[1] The dose-dependent cardiotoxicity[2] of these agents has also made it important to search for less toxic structural analogues. Accordingly, it would be useful to develope a common synthon which allows to prepare a variety of analogues as well as anthracyclinones. Cava *et al.* have reported a Diels-Alder approach in which the *o*-quinodimethane analogues 6 generated from the corresponding bis(bromomethyl)quinizarins 5 by action of zinc or sodium iodide were key intermediates.[3] Although 6 thus generated gave Diels-Alder adducts in moderate yields with simple dienophiles, it did in rather poor yields with more functionalized dienophiles even in the presence of a large excess of reagents. Since 1,2-dihydrobenzocyclobutenes undergo ring-opening to *o*-quinodimethanes under purely thermal conditions, it would be expected that thermolytic Diels-Alder reactions of the cyclobutene-ring fused quinizarin 4a, the title compound, could render improvements in respect to yield and applicability. We wish here to report the synthesis of 4a ∿ c and their promising thermolytic Diels-Alder reactions leading to the precursors of 4-demethoxydaunomycinone and the related compounds.



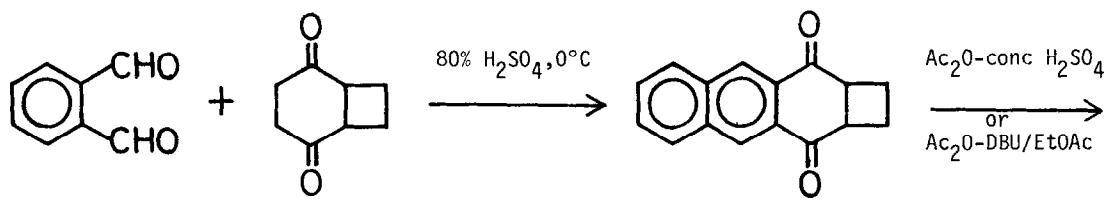
1: X=OMe, Y=H
2: X=H, Y=H
3: X=OMe, Y=OH



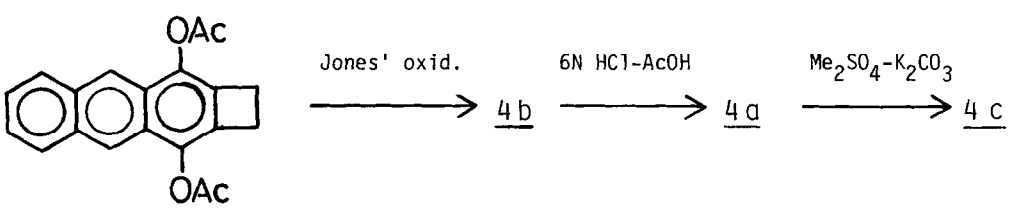
a: R=H
4 b: R=OAc 6 5
c: R=OMe

We previously reported an efficient and general synthesis of bicyclo[4.2.0]octane-2,5-diones.[4] Our synthesis of 4a ∿ c starts from the diketone 7.

Condensation of 7 and *o*-phthaldehyde in 80% H_2SO_4 (0°C, 1 h) gave the tetracyclic diketone 8[5] in 80% yield. Condensation under basic conditions resulted in much poorer yield of 8 due to the formation of several by-products.[6] The diketone 8 was then converted into the diacetoxyanthracene 9[5] by treatment with either acetic anhydride and a trace of conc. H_2SO_4 (100°C, 2 h, 81%) or acetic anhydride and 1,8-diazabicyclo[5.4.0]undec-7-ene in ethyl acetate (reflux, 5 h, 88%). Oxidation of 9 with Jones' reagent (3 mol. equiv., room temp., acetone, 1 day) provided the desired quinone 4b[5] in 90% yield. Under these conditions the oxidation proceeded cleanly, whereas the oxidation with CrO_3 in aqueous acetic acid which had been employed in similar oxidations[7] produced a hardly separable mixture of products though 4b was a major component (*ca.* 50% by ^1H NMR). Hydrolysis of 4b with 6N HCl-AcOH (1:1; reflux, 0.5 h) cleanly gave 4a[5] as orange-red needles in 97% yield. The dimethoxyquinone 4c[5] was obtained by methylation of 4a (Me_2SO_4-K_2CO_3-2-butanone, reflux, 2 h, 98%).



7 8



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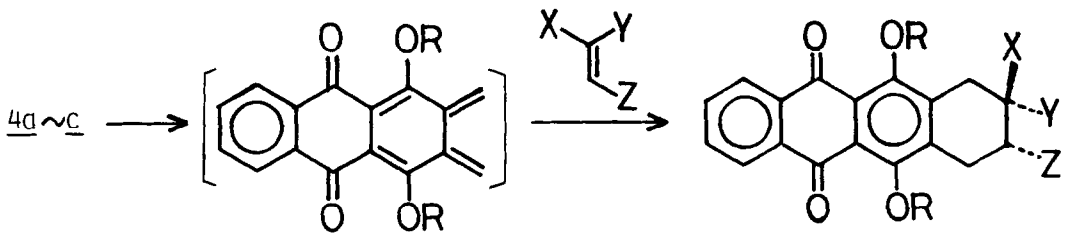
Thermolytic Diels-Alder reactions of 4a ∿ c turned out encouraging, and the results with a number of dienophiles are summarized in Table 1. The dihydroxyquinone 4a shows better prospects than 4b and 4c for the anthracyclinone synthesis: i) while 4b and 4c undergo the ring-opening at about 200°C, 4a does at lower temperature, even at 160°C, and ii) 4a appears to give cycloadducts in better yields than 4b and 4c. The tautomerism between 4a and 4a'

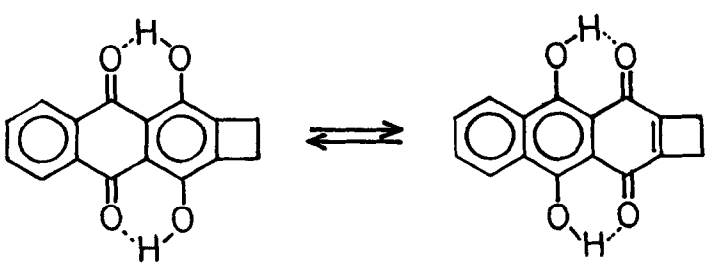


6a~c 10~17

Table 1. Thermolytic Diels-Alder reactions of 4a ~ c with dienophiles[a]

Entry No.	Compd.	Dienophile	Mol. equiv.	Temp. °C	Time h		Product	Mp. °C	Yield %
1	4a	Methyl vinyl ketone	4	200	5	10	R=H, X=$COCH_3$ Y=Z=H	198-202[b]	98
2	4b	Methyl vinyl ketone	4	200	5	11	R=X=$COCH_3$ Y=Z=H	200-201[c]	88
3	4c	Methyl vinyl ketone	4	220	5	12	R=CH_3, X=$COCH_3$ Y=Z=H	146-148[d]	89
4	4a	Methyl acrylate	4	200	5	13	R=H, X=$COOCH_3$[6] Y=Z=H	196-197	98
5	4a	Methyl methacrylate	4	180	6	14	R=H, X=$COOCH_3$[6]	202-204	78
			10	180			Y=CH_3, Z=H		93
6	4a	Methyl crotonate	4	180	6	15	R=H, X=$COOCH_3$[6] Y=H, Z=CH_3	199-202	53
7	4a	3-Acetoxy-3-buten-2-one	4	180	6	16	R=H, X=$COCH_3$[e] Y=OH, Z=H	210-213[f]	41[e]
8	4a	3-Benzoyloxy-3-buten-2-one	4	180	6	16			51[e]
9	4a	N-Phenylmaleimide	2	200	5	17	R=X=H Y-Z=CONPhCO	*ca.*300 dec.[g]	91

[a]Reactions were performed in a sealed tube using *o*-dichlorobenzene as solvent. [b]Lit. 198-202°C[2a]. [c]Lit. 197-199°C[2b]. [d]Lit. 147-149°C[2a]. [e]After alkaline hydrolysis. [f]Lit. 160-162°C[2a,7a], 190-193°C[2a], 210-212°C[7b]. [g]Lit. >290°C[2a]



4a 4a'

might be responsible for the easier ring-opening of 4a in view of much ready thermal ring-opening of 1,2-dihydrobenzocyclobutene-3,6-dione relative to that of 1,2-dihydrobenzocyclobutene.[8] Accordingly, the cycloadditions were studied mostly on 4a. With simple and/or typical dienophiles (entries 1 ∿ 4 and 9), 4a ∿ c gave the adducts, 10 ∿ 13 and 17, in high yields. With more substituted and less reactive dienophiles (entries 5 ∿ 8), the yields of adducts 14 ∿ 16 were lower but still fair to excellent. In the cases of entries 7 and 8, the product was isolated as 4-demethoxy-7-deoxydaunomycinone 16 after alkaline hydrolysis (2N NaOH-aq THF) because of some difficulty in purification of the primary adducts.

Thus, Diels-Alder reactions from 4 show considerable improvements compared to those from 5[2], *i.e.* the better yields of adducts, the requirement of much smaller quantity of dienophiles, and a wider applicability.

The present synthetic scheme of 4 should allow to prepare a number of its derivatives or analogues by choice of other aromatic 1,2-dialdehydes and substituted bicyclo[4.2.0]octane-2,5-diones, and further studies on 4a ∿ c and the related compounds are in progress.

References and Notes

1) For reviews of synthetic approaches to the anthracyclines, see a) T. R. Kelly, Annu. Rep. Med. Chem., 14, 288 (1979); b) T. Kametani and K. Fukumoto, Med. Res. Rev., 1, 23 (1981); c) S. Terashima, Yuki Gosei Kagaku Kyokaishi, 40, 20 (1982).

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4) M. Oda, H. Oikawa, Y. Kanao, and A. Yamamuro, Tetrahedron Lett., 4905 (1978).

5) Satisfactory elemental analyses and spectroscopic data were obtained for all the new compounds. The melting points and/or ^{1}H NMR data are following. 8: mp 121-122°C; δ($CDCl_3$) 2.0 ∿ 3.0 (4H, m), 3.70 (2H, m), 7.68 (2H, m), 8.06 (2H, m), 8.67 (2H, s); 9: mp 197°C decomp.; δ ($CDCl_3$) 2.46 (6H, s), 3.30 (4H, s), 7.44 (2H, m), 7.96 (2H, m), 8.43 (2H, s); 4a: mp 186°C decomp.; δ ($CDCl_3$) 3.22 (4H, s), 7.80 (2H, m), 8.30 (2H, m), 13.10 (2H, s); 4b: mp 200°C decomp.; δ ($CDCl_3$) 2.48 (6H, s), 3.16 (4H, s), 7.71 (2H, m), 8.12 (2H, m); 4c: mp 184-185°C; δ ($CDCl_3$) 3.52 (4H, s), 4.07 (6H, s), 7.70 (2H, m), 8.10 (2H, m); 13: δ ($CDCl_3$) 1.5 ∿ 2.5 (3H, m), 2.6 ∿ 3.2 (4H, m), 3.76 (3H, s), 7.81 (2H, m), 8.20 (2H, m), 13.22 (1H, s), 13.25 (1H, s); 14: δ ($CDCl_3$) 1.36 (3H, s), 1.76 (1H, m), 2.23 (1H, m), 2.58 (1H, d, J=19 Hz), 2.86 (2H, m), 3.37 (1H, dd, J=19, 1 Hz), 3.69 (3H, s), 7.73 (2H, m), 8.25 (2H, m), 13.36 (1H, s), 13.43 (1H, s); 15: δ ($CDCl_3$) 1.12 (3H, d, J=6 Hz), 1.8 ∿ 2.5 (3H, m), 2.5 ∿ 3.2 (3H, m), 3.77 (3H, s), 7.69 (2H, m), 8.18 (2H, m), 13.17 (2H, s).

6) The structures of the by-products have not yet been fully elucidated and will be described in a full paper.

7) a) A. S. Kende, D. P. Curran, Y. Tsay, and J. E. Mills, Tetrahedron Lett., 3537 (1977); b) J. R. Wiseman, N. I. French, R. K. Hallmark, and K. G. Chiong, Tetrahedron Lett., 3765 (1978); c) Y. Bessiere and P. Vogel, Helv. Chim. Acta, 63, 232 (1980).

8) 1,2-Dihydrobenzocyclobutene-3,6-dione readily undergoes ring-opening at 140°C; Y. Kanao and M. Oda, Bull. Chem. Soc. Japan, in press.

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