The Synthesis and Diels-Alder Reactions of 2-Prop-2-enylidene-1,3-dioxolan

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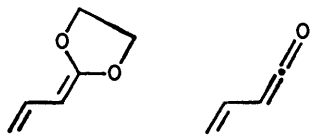
The synthesis and regiospecific Diels-Alder reactions of 2-prop-2-enylidene-1,3-dioxolan (1) are described. Reactions with 1,4-naphthoquinones (5) gave tetrahydroanthraquinones (6). The adduct of (1) with juglone (5d) could be further hydrolysed to 1,8-dihydroxy-9,10-anthraquinone (7).

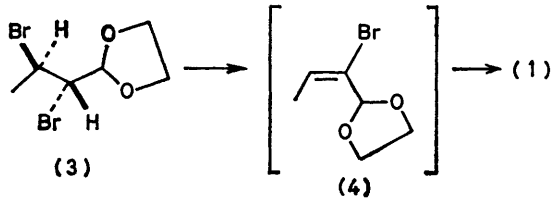
THE use of vinylketen acetals as dienes in the Diels-Alder reaction has considerable synthetic applications and has attracted much recent attention.[1]

Despite activity in this area very little is known about the Diels-Alder reaction of unsubstituted vinylketen acetals. For this reason we chose to prepare the novel acetal (1) which can be considered as a vinyl keten equivalent (2) and also to study its reactions with various dienophiles.



(1) (2)

The diene acetal (1) was first obtained in low yield (16%) by treatment of the dibromide (3) with potassium amide in boiling toluene. However as this procedure was not suitable for larger scale work an alternative preparation was sought. The most convenient was found to be the double dehydrobromination of (3) using freshly sublimed potassium t-butoxide at room temperature (Scheme).



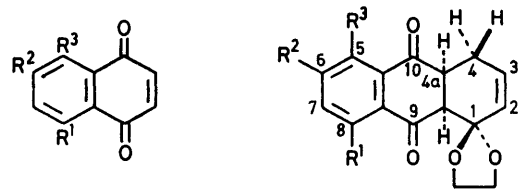
(3) (4) (1)

SCHEME

The diene acetal (1) was characterized spectroscopically. The ^{1}H n.m.r. spectra, for example, showed resonance at τ 3.61 (1 H, dt, J 10 and 17 Hz), 5.0—5.63 (3 H, m) corresponding to the olefinic protons, and at 5.74 (4 H, br s) for the methylene protons of the 1,3-dioxolan ring. The u.v. spectrum shows a characteristic diene chromophore at $\lambda_{max.}$ 244 nm (ε 13 900). It was not possible to prepare a sample of (1) of sufficient purity for micro-elemental analysis since it tended to decompose slowly at room temperature. Stabilization of the diene was achieved by the addition of a trace amount of quinol and triethylamine and the diene could be stored without serious decomposition at −23 °C for a period of some weeks.

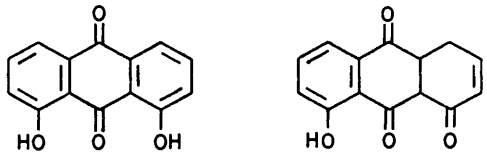
The dehydrobromination of (3) with KOBu^t to produce (1) is a stepwise process involving the intermediacy of the vinyl bromide (4). If only one equivalent of potassium t-butoxide was used in the dehydrobromination reaction it was possible to isolate (4) as the major product. The structure of (4) follows from its spectral parameters which show the vinyl proton resonating at typically τ 3.76 as a quartet (J 7 Hz) in the ^{1}H n.m.r. spectrum. The geometry was assumed on the basis of a *trans*-elimination of hydrogen bromide from (3).

Initial attempts at Diels-Alder coupling of (1) with



(5) (6)

(a) $R^1 = R^3 = OH$, $R^2 = H$
(b) $R^1 = R^3 = OAc$, $R^2 = H$
(c) $R^1 = R^2 = R^3 = H$
(d) $R^1 = OH$, $R^2 = R^3 = H$
(e) $R^1 = OH$, $R^2 = Me$, $R^3 = Cl$



(7) (8)

some common dienophiles were unsuccessful due mainly to the instability of the diene (1).

However on reaction with tetracyanoethylene, *p*-benzoquinone, and 2,6-dimethyl-1,4-benzoquinone adducts were obtained, as indicated by ^{1}H n.m.r. of the crude reaction mixtures but were unstable and could not be usefully isolated.

Reaction of (1) with naphthoquinones (5) gave stable crystalline adducts (6) in 48—81% yield. Under

optimum conditions an excess of the diene (2.0—2.5 equiv.) was mixed with the naphthoquinone in a minimum amount of chloroform as solvent at ≃ −62 °C and allowed to warm to room temperature.

The structure of these adducts follows from their ^{1}H n.m.r. spectra. As a representative example, the adduct (6c) shows a 3-H signal at τ 4.0 (ddd, $J_{2.3}$ 10 Hz, $J_{3.4\alpha}$ 2.5 Hz, and $J_{3.4\beta}$ 4.5 Hz). Irradiation of the 4β-proton causes the 3-H resonance to collapse to the expected double doublet.

The structure of the adduct (6d) was additionally proven by hydrolysis with aqueous acetic acid and oxidation to afford the known anthraquinone (7).[2]

The regiochemistry of addition of (1) to (5d) and (5e) is in accord with other examples[3] in that hydrogen bonding between the hydroxy-group and the neighbouring carbonyl group causes it to become more electron withdrawing and hence control the regioselectivity.

Attempts to unmask the carbonyl group in (6d) to provide the enone (8), which could serve as a useful precursor for biologically active anthraquinones such as Adriamycin,[4] were unsuccessful owing to preferential rapid conversion to (7) after aerial oxidation.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 257 spectrophotometer. U.v. spectra were recorded on a Unicam SP 800 or SP 1200 spectrophotometer. N.m.r. spectra were recorded in acid-free $CDCl_3$ on a Varian EM 360A at 60 MHz.

2-*Prop*-2-*enylidene*-1,3-*dioxolan* (1).—2-(1,2-Dibromopropyl)-1,3-dioxolan[5] (3) (20.0 g, 73 mmol) in ether (400 ml) was added with stirring to potassium t-butoxide (24.6 g, 220 mmol) in sodium-dried ether (800 ml) at 0 °C, under nitrogen. After stirring for 12 h at room temperature the mixture was *briefly* shaken with water (400 ml), separated, and the aqueous phase extracted with ether (2 × 200 ml). The combined organic extracts were dried (Na_2SO_4), stabilized by the addition of quinol (a few crystals), and the ether evaporated *at room temperature* under reduced pressure. The residual oil was distilled to yield 2-prop-2-enylidene-1,3-dioxolan (1) (3.09 g, 38%), b.p. 38—40 °C at 0.5 mmHg; $\lambda_{max.}$ (cyclohexane) 244 (ε 13 900); $\nu_{max.}$ (film) 1 800 (CH=CH_2, overtone), 1 684 (CH=C), 1 426 (CH=CH_2), 1 275 (CH=CH_2), 956 (CH=CH_2), 870 (CH=CH_2), and 790 cm^{-1} (CH=C); τ 3.61 (1 H, dt, *J* 10 and 17 Hz), 5.00—5.63 (3 H, m, olefinic), and 5.74 (4 H, s, OCH_2CH_2O); *m/e* 112 (M^+) and 73 ($C_3H_5O_2$). The diene (1) was not stable enough for a microanalysis to be obtained but could be stored at −23 °C in the presence of quinol (a few crystals) and triethylamine (1 drop) for a few weeks without serious decomposition.

1,1-*Ethylenedioxy*-5,8-*dihydroxy*-1,4,4aα,9aα-*tetrahydro*-9,10-*anthraquinone* (6a).—The diene (1) (367 mg, 3.27 mmol) in chloroform (1.3 ml) was added dropwise with stirring to naphthazarin (5a) (249 mg, 1.31 mmol) in chloroform (2.0 ml) containing quinol (a few crystals) at −62 °C under argon. The reaction was allowed to warm to room temperature and then stirred overnight. The solvent was evaporated and the residue crystallized from ethyl acetate to afford *compound* (6a) (189 mg, 48%), m.p. 156.5—158.5 °C; $\lambda_{max.}$ (THF) 234 (ε 16 500), 258 (9 800) and 399 nm (8 200); $\nu_{max.}$ (Nujol) 1 722, 1 640 (H-bonded C=O), 1 590 (aromatic) and 729 cm^{-1} (CH=CH, *cis*); τ −1.94 (1 H, s, OH), −1.47 (1 H, s, OH), 2.80 (2 H, s, olefinic), 4.04 (1 H, ddd, *J* 2, 4, and 10 Hz, H-3), 4.44 (1 H, ddd, *J* 0.5, 1 and 10 Hz, H-2), 5.70—7.33 (7 H, m, aliphatic) and 7.43—8.06 (1 H, m, H-4-β); *m/e* 302 (M^+) and 112 (base peak, $C_6H_8O_2$) (Found: C, 63.6; H, 4.6. $C_{16}H_{14}O_6$ requires C, 63.57; H, 4.67%).

5,8-*Diacetoxy*-1,1-*ethylenedioxy*-1,4,4aα,9aα-*tetrahydro*-9,10-*anthraquinone* (6b).—The diene (1) (293 mg, 2.62 mmol) in chloroform (1.5 ml) was added dropwise with stirring to naphthazarin diacetate (5b) (287 mg, 1.05 mmol) in chloroform (2.0 ml) containing quinol (a few crystals) at −62 °C, under argon. The reaction was allowed to warm to room temperature and then stirred overnight. The solvent was removed at room temperature and the residue crystallized from ethyl acetate to afford *compound* (6b) (319 mg, 80%), m.p. 183—185 °C; $\lambda_{max.}$ (MeCN) 232 (ε 18 600), 252 (7 700), and 301 nm (4 300); ν_{max} (Nujol) 1 769 (O_2CCH_3), 1 709 (C=O), 1 690 (C=O), 1 590 (aromatic), 1 363 (O_2CCH_3), and 724 (CH=CH, *cis*); τ 2.73 (2 H, s, olefinic), 4.11 (1 H, ddd, *J* 2, 4 and 10 Hz, H-3), 4.51 (1 H, dm, H-2), 5.96—8.26 (8 H, m, aliphatic), 7.60 (3 H, s, AcO), and 7.66 (3 H, s, AcO); *m/e* 386 (M^+) and 112 (base peak, $C_6H_8O_2$) (Found: C, 62.3; H, 4.65. $C_{16}H_{18}O_8$ requires C, 62.17; H, 4.70%).

1,1-*Ethylenedioxy*-1,4,4aα,9aα-*tetrahydro*-9,10-*anthraquinone* (6c).—1,4-Naphthoquinone (5c) (163 mg, 1.03 mmol) in chloroform (1.5 ml) was added with stirring to the diene (1) (289 mg, 2.58 mmol) in chloroform (2 ml) containing quinol (a few crystals) at −62 °C, under argon. The reaction was allowed to warm to room temperature and then stirred overnight. The solvent was evaporated and the residue crystallized from ethyl acetate to afford *compound* (6c) (227 mg, 81%), m.p. 144—147 °C; $\lambda_{max.}$ (MeOH) 233 (ε 24 800), 256 (21 200), and 303 nm (4 400); $\nu_{max.}$ (CH_2Cl_2) 1 695 and 1 603 cm^{-1}; τ 1.80—2.55 (4 H, m, aromatic), 4.0 (1 H, ddd, *J* 2.5, 4.5 and 10 Hz, H-3), 4.47 (1 H, ddd, *J* 1.5, 2.5, and 10 Hz, H-2), 5.90—7.16 (7 H, m, aliphatic) and 7.56—8.26 (1 H, m, H-4β); *m/e* 270 (M^+) and 112 (base peak, $C_6H_8O_2$) (Found: C, 70.95; H, 5.2. $C_{16}H_{14}O_4$ requires C, 71.09; H, 5.23%).

1,1-*Ethylenedioxy*-6-*hydroxy*-1,4,4aα,9aα-*tetrahydro*-9,10-*anthraquinone* (6d).—Juglone (5d) (184 mg, 1.06 mmol) in deuteriochloroform (1.5 ml) was added dropwise with stirring to the diene (1) (296 mg, 2.64 mmol) in deuteriochloroform (2 ml) containing quinol (a few crystals) at −62 °C, under nitrogen. The solution was allowed both to warm to room temperature and then react overnight. The solvent was then removed and the residue crystallized from benzene to afford *compound* (6d) (201 mg, 66%), m.p. 154—157 °C (from ethyl acetate); $\lambda_{max.}$ (MeCN) 234 (ε 22 000), 265 (5 400), and 351 nm (5 200); $\nu_{max.}$ (Nujol) 1 698, 1 647, 1 602, and 1 581 cm^{-1}; τ($CDCl_3$) 2.10—3.07 (3 H, m, aromatic), 4.02 (1 H, ddd, *J* 1.0, 2.5, and 10 Hz, H-3), 4.42 (1 H, dm, *J* 10 Hz, H-2), 5.73—7.16 (7 H, aliphatic), and 7.48—8.30 (1 H, m, H-4 β); *m/e* 286 (M^+) and 112 (base peak, $C_6H_8O_2$) (Found: C, 66.85; H, 4.85. $C_{16}H_{14}O_5$ requires C, 67.12; H, 4.94%).

5-*Chloro*-1,1-*ethylenedioxy*-8-*hydroxy*-6-*methyl*-1,4,4aα,-9aα-*tetrahydro*-9,10-*anthraquinone* (6e).—5-Chloro-8-hydroxy-6-methyl-1,4-naphthoquinone[6] (5e) (326 mg, 1.47 mmol) in deuteriochloroform (5 ml) was added dropwise with stirring to the diene (1) (328 mg, 2.93 mmol) in deu-

teriochloroform (2 ml) containing quinol (a few crystals) at −62 °C, under nitrogen. The reaction was allowed to warm to room temperature and then stirred for 2 days, after which time the quinone still remained (n.m.r.). At −62 °C, further diene (52) (65.6 mg, 0.59 mmol) in deuteriochloroform was added. The reaction was warmed to room temperature and stirred for 3 h. The solvent was removed and the residue crystallized from ethyl acetate to afford *compound* (6e) (285 mg, 58%), m.p. 132—134 °C; $\lambda_{max.}$ (MeCN) 237 (ε 25 900), 252sh (13 900), 271sh (6 300), and 359 nm (6 000); $\nu_{max.}$ (Nujol) 1 704 (C=O), 1 640 (H-bonded C=O and *trans* CH=CH) and 726 cm^{-1} (CH=CH, *trans*); τ −2.57 (1 H, s, OH), 2.90 (1 H, s, aromatic) 4.02 (1 H, ddd, *J* 2.2, 5, and 10 Hz, H-3), 4.56 (1 H, ddd, *J* 1.5, 3 and 10 Hz, H-2), 5.68—8.14 (8 H, m, aliphatic), and 7.53 (3 H, s, CH_3); *m/e* 335 (M^+) and 112 (base peak, $C_6H_9O_2$) (Found: C, 61.0; H, 4.4. $C_{17}H_{15}ClO_5$ requires C, 61.00; H, 4.52%).

1,8-*Dihydroxy*-9,10-*anthraquinone* (7).—The adduct (6d) (50 mg, 0.175 mmol) was heated in aqueous acetic acid for 20 min at 100 °C. On cooling, the solid which precipitated was collected and dried *in vacuo*. The mother liquors were poured into aqueous saturated sodium hydrogen carbonate and extracted with dichloromethane. The dried (Na_2SO_4) extracts were added to the solid above, and the resultant solution evaporated. The residue was crystallized from ethanol, affording 1,8-dihydroxy-9,10-anthraquinone (7) (17 mg, 40%), m.p. 192—193 °C (lit.,[2] 192—193 °C).

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