BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (3), 826—829 (1978) [Vol. 51, No. 3

Regioselective, Abnormal Ring Opening of the Epoxide of Quinone Epoxide–Cyclopentadiene Adducts

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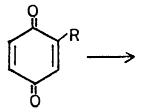
(Received June 28, 1977)

Treatment of quinone epoxide-cyclopentadiene adducts with sulfuric acid gave abnormal ring opening products, whose structures were determined by the spectral data and identification of the degradation product. Regioselectivity of the reaction was confirmed. The mechanism of the reaction is discussed.



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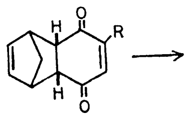
1b R=CH_3
1c R=H
1d R=CH_2OCOCH_3



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2d R=$CH_2OCOC_6H_5$
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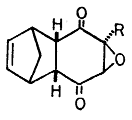

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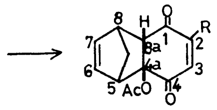

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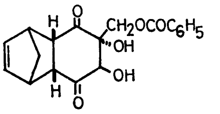

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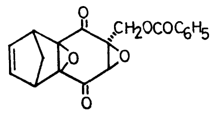

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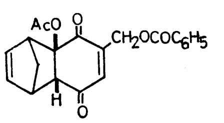


7

In the course of the synthetic studies of highly oxygenated cyclohexane derivatives,[1] it was needed to prepare compound **5** which would be served as a pertinent intermediate for the synthesis of crotepoxide[2] and senepoxide.[3] For this purpose, a derivative **3a** which was obtained by epoxidation of the benzoate **2d** of Diels-Alder adduct **2a** from cyclopentadiene and 2-(hydroxymethyl)-1,4-benzoquinone **1a** was prepared. The stereochemistry of **3a** was deduced from analogy and the spectral similarity with those of **3b** and **3c**, whose stereostructure has been unequivocally established.[4] Treatment of the epoxide **3a** with various acids yielded only complex mixtures resulting from polymerization and decomposition. However, when the epoxide **3a** was treated with acetic acid–sulfuric acid (10:1 v/v) at 25 °C for 3 days, an unknown product, $C_{21}H_{18}O_6$, was obtained. The infrared spectrum showed absorption bands at 1728 cm^{-1} due to acetoxy carbonyl group and at 1673 cm^{-1} attributed to enedione carbonyl and benzoyl carbonyl groups. In the PMR spectrum (Table 1), a signal at δ 6.65 (1H, t) due to a β-olefinic proton of enedione moiety and a signal at δ 2.04 (3H, s) due to an acetate methyl group were observed. Epoxidation of **4a** with hydrogen peroxide in alkaline solution gave, with loss of acetic acid, a diepoxide **6**, whose structure was supported by elemental analysis, $C_{19}H_{14}O_6$, and the spectral data. From these observations **4a** or **7** was deduced for the product as possible structures. At this stage, however, it was difficult to decide the correct structure on the basis of spectral data. In order to confirm the structure, further investigation was carried out on the adduct **3b** of toluquinone epoxide, since the quinone **1b** is easily available and retro Diels-Alder reaction of the product **4b** would yield known compound, 5-acetoxytoluquinone. Thus, the epoxide **3b** was prepared and treated with sulfuric acid in acetic acid at 25 °C for 3 days in the same manner. The resultant product, $C_{14}H_{12}O_4$, exhibited absorption bands at 1733 cm^{-1} ascribable to acetate carbonyl group and at 1688 cm^{-1} due to enedione system in the IR spectrum. In the PMR spectrum (Table 1), signals at δ 2.02 due to acetoxy methyl group and at δ 6.52 due to a vinylic proton in enedione moiety were observed. These data are certainly in accord with the structure of the abnormal ring opening product. In order to confirm the correct structure, retro Diels-Alder reaction was carried out by heating the compound **4b** at 350 °C under an atmosphere of nitrogen to give a product, mp 72—73 °C, whose structure is compatible to an acetoxyquinone. Since the location of the acetoxyl group was still not obvious, the acetoxyquinone was reduced with lithium aluminum hydride to yield a 1,2,4-benzenetriol. The PMR spectrum exhibited two signals at δ 6.38 and 6.56 as singlets, which indicate that these protons are located in a *para* position and the structure was deduced to be 5-methyl-1,2,4-benzenetriol. This means that the abnormal reaction product must be **4b**. Conclusive result was obtained by the direct comparison of the acetoxyquinone with an authentic sample, 2-acetoxy-1,4-benzoquinone, which was prepared according to the known procedure.[5] The sample thus prepared was identical with thermally decomposed product of **4b** in all respects. Accordingly, the structure of the abnormal reaction product was unambiguously identified as **4b**. The stereochemistry of **4b** was assigned to have the *endo*-configuration on the basis of following facts. Since in those compounds having *endo*-structure with 4a-substituent, the H-8a appears as a doublet with a coupling constant of 3 to 4Hz,[4] the signal at δ 2.95 with a coupling constant,

Table 1. PMR Spectra of abnormal ring cleavage products

PMR (δ) in $CDCl_3$

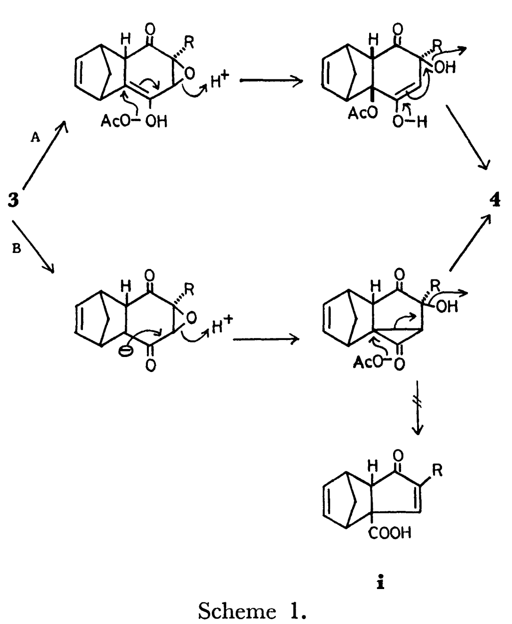
4 R	H-9	$\mathrm{O\underset{\displaystyle O}{\underset{\|}{C}}CH_3}$	H-8a	H-8	H-5	H-6,7	H-3	R
CH_2OCOPh (**4a**)	1.70 1.90 ABq J=9 Hz	2.04 s	2.98 d J=4 Hz	3.28 br s	3.41 br s	5.94, d d J=3 and 6 Hz 6.20, d d J=3 and 6 Hz	6.65 t J=2 Hz	5.07 d, J=2 Hz 8.03 7.42, J=5 Hz
CH_3(**4b**)	1.66 1.87 ABq J= 9Hz	2.02 s	2.95 d J=4 Hz	3.26 br s	3.46 br s	5.93, d d J=3 and 6 Hz 6.14, d d	6.52 q J=1.5 Hz	1.88 d J=1.5 Hz
H(**4c**)	1.68 1.90 ABq J=9 Hz	2.64 s	2·84 d J=4 Hz	3.28 br s	3.38 br s	5.93, d d J=3 and 6 Hz 6.19, d d J=3 and 6 Hz	6.61 d J=2 Hz	6.61 d J=2 Hz
CH_2OAc(**4d**)	1.64 1.86 ABq J=9 Hz	2.00 s	2.91 d J=4 Hz	3.22 br s	3.35 br s	5.93, d d J=3 and 6 Hz 6.19, d d J=3 and 6 Hz	6.46 t J=2 Hz	2.00 s 4.76 d, J=2 Hz

J=4Hz, in **4b** is also consistent with the *endo*-assignment. The structure of **4a** (**4c** and **4d**) was deduced from the PMR spectrum which shows similar spectral pattern with that of **4b** (Table 1).

For the purpose to investigate generality of this reaction, two more compounds, **3c** and **3d**, were prepared from **1c** and **1d** respectively and treated with sulfuric acid under the same conditions to yield analogous compounds, **4c** and **4d**. The PMR spectral data of the abnormal ring opening products are summarized in Table 1.

The results mentioned above are of quite interest since in the case of substituted quinone epoxide adducts (**3a**, **3b**, and **3d**), all of the reactions proceeded regioselectively to give **4a**, **4b**, and **4d**.

Finally, the mechanism of the abnormal reaction was presumed as follow. Ring contraction of piperitone epoxide, an α-epoxy ketone, under basic conditions was reported, for which Favorskii type mechanism was postulated.6) On the other hand, in the reaction of a steroid α-epoxy ketone with acids, another plausible mechanism which involves an enol intermediate was suggested.7) Since extremely strained structure resulted from Favorskii type reaction (path B in Scheme 1) excludes the possibility involving cyclopropanone intermediate and in fact, none of the compounds as **i** derived *via* the intermediate was obtained, enol intermediate (path A) might be involved in the present reaction as shown in Scheme 1. From the mechanistic point of view, it is interesting to note that another possible product **7** had not been recognized in the reaction.



Scheme 1.

The abnormal ring opening reaction would be useful for the synthesis of some 2-acetoxy-1,4-benzoquinones *via* retro Diels-Alder reaction.

Experimental

All melting points were uncorrected. The IR spectra were taken on a Hitachi EPI-S2 Spectrophotometer and the PMR spectra were measured with a Hitachi R-22 Spectrometer (90MHz), using tetramethylsilane as an internal standard.

*2-(Hydroxymethyl)-1,4-benzoquinone (**1a**).* This compound was prepared according to the known procedure involving oxidation of 2,5-dihydroxybenzyl alcohol with lead tertaacetate.8)

endo-*2-Hydroxymethyl-5,8-methano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (**2a**).* A solution of 1.5 g of the benzoquinone **1a** and 2 ml of cyclopentadiene in 6 ml of methanol was allowed to stand until the spot of the starting material disappeared on TLC. The reaction mixture was concentrated *in vacuo* to give a residue, which was recrystallized from benzene to yield pure **2a**, mp 65—66 °C; IR $\nu_{\max}^{\mathrm{KBr}}$ 1653, 3530 cm^{-1}; PMR ($CDCl_3$) δ 1.42 (2H, m, CH_2), 3.10 (2H, br s, $=\!/^{H}$), 6.52 (1H, t, J=3Hz, $=\!/^{H}$). Found: C, 70.72; H, 5.95%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; 5.92%.

endo-*2-(Benzoyloxymethyl)-5,8-methano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (**2d**).* A solution of 2.1 g of the adduct and 1.6 ml of benzoyl chloride in 10 ml of pyridine was allowed to stand at room temperature. The reaction mixture was washed with water and organic layer was separated. The water layer was extracted twice with benzene and the combined extracts were dried over anhydrous sodium sulfate and concentrated. The resultant crystals were recrystallized from benzene to give 2.86 g of the benzoate, mp 147—148 °C; IR $\nu_{\max}^{\mathrm{KBr}}$ 1723, 1664, 1636, 1600 cm^{-1}; PMR (CDCl$_3$) δ 1.34—1.58 (2H, m, CH$_2$), 3.22 (2H, m, CH), 3.52 (2H, br s, -CH), 5.08 (2H, d, J=2Hz, CH$_2$), 6.06 (2H, t, J=2Hz, $=\!/^{\mathrm{H}}$), 6.60 (1H, t, J=2Hz, $=\!/^{\mathrm{H}}$), 7.33—7.59 (3H, m, ArH), 8.03 (2H, dd, J=2Hz, J=8Hz, ArH). Found: C, 73.79; H, 5.17%. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23%.

r-*2-(Benzoyloxymethyl)-2,3-epoxy-*t-*5,8-methano-2,*c-*3,*t-*4a,5,8,*t-*8a-hexahydro-1,4-naphthoquinone (3a).* A mixture of 100 mg of the benzoate **2d** and 2 ml of solution made from 25 ml of hydrogen peroxide (30%) and 5 g of sodium carbonate in 125 ml of water was allowed to stand for *ca.* 40 min. The reaction mixture was extracted with benzene and the combined extracts were dried on anhydrous sodium sulfate. Removal of the solvent gave 66 mg of crystals which were recrystallized from benzene to yield the pure epoxide **3a**, mp 139—140 °C; IR $\nu_{\max}^{\mathrm{KBr}}$ 1715, 1600 cm^{-1}; PMR (CDCl$_3$) δ 1.22, 1.44 (2H, ABq, J=8Hz, CH$_2$), 3.25 (2H, br s, CH), 3.38 (2H, br s, CH), 3.52 (1H, s, $\overset{\mathrm{O}}{\angle\diagdown}\!/^{\mathrm{H}}$), 4.82, 4.54 (2H, ABq, J=13Hz, CH$_2$), 6.00 (2H, t, J=2Hz, $=\!/^{\mathrm{H}}$), 7.20—7.49 (3H, m, ArH), 7.90 (2H, dd, J=8Hz, J=2Hz, ArH); MS *m/e* 324 (M$^+$). Found: C, 70.21; H, 4.97%. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.98%.

endo-*4a-Acetoxy-2-(benzoyloxymenthyl)-5,8-methano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4a).* To a solution of 139.7 mg of the epoxide **3a** in 2 ml of acetic acid was added a mixture of 2.2 ml of sulfuric acid–acetic acid (1 : 10 v/v), and the mixture was stand for 3 days at 25 °C and the completion of the reaction was checked by TLC. The reaction mixture was extracted with chloroform and washed with water. The combined extracts were dried on anhydrous sodium sulfate and concentrated *in vacuo.* The residue was chromatographed on silicic acid and eluted with benzene–ethyl acetate (95 : 5 v/v) to give 34.5 mg of a crystalline material. The crude crystals were recrystallized from benzene to give a pure compound, **4a**, mp 166—167 °C. IR $\nu_{\max}^{\mathrm{KBr}}$ 1728, 1673, 1640 cm^{-1}; PMR spectra are cited on Table 1. MS *m/e* 367 (M$^+$ + 1). Found: C, 67.89; H, 4.75%. Calcd for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95%.

Epoxidation of **4a**. To a solution of 546 mg of **4a** in 6 ml of tetrahydrofuran was added a mixture of 0.2 g of potassium carbonate and 1 ml of hydrogen peroxide (30%) in 5 ml of water. After 10 min, the reaction mixture was extracted with chloroform and the extracts were dried on anhydrous sodium sulfate and concentrated. The residue was chromatographed on 20 g of silicic acid using benzene–ethyl acetate (95 : 5 v/v) as eluent to give 82 mg **6** as crystals, mp 132—133 °C; IR $\nu_{\max}^{\mathrm{KBr}}$ 1732, 1704, 1604 cm^{-1}; PMR (CDCl$_3$) δ 1.47 (2H, m, CH$_2$), 3.23 (2H, m, CH), 3.65 (1H, s, $\overset{\mathrm{O}}{\angle\diagdown}\!/^{\mathrm{H}}$), 4.53, 4.76 (2H, ABq, J=13Hz, -CH$_2$O), 6.42 (2H, t, J=2Hz, $=\!/^{\mathrm{H}}$), 7.32—7.57 (3H, m, ArH), 7.92 (2H, dd, J=8Hz, 2Hz, ArH); MS *m/e* 338 (M$^+$). Found C, 67.53; H, 4.16%. Calcd for $C_{19}H_{14}O_6$: C, 67.45; H, 4.17%.

2-Methyl-5,8-methano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (2b). This compound was prepared from toluquinone **1b** and cyclopentadiene in methanol heating at 50 °C for 4 h.[4] Mp 61—62.4 °C.

r-*2,3-Epoxy-2-methyl-*c-*5,8-methano-2,3,*c-*4a,5,8,*c-*8a-hexahydro-1,4-naphthoquinone (3b).* This compound was prepared in the same way used for the synthesis of **3a** starting from toluquinone.[4]

endo-*4a-Acetoxy-2-methyl-5,8-methano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4b).* To a solution of 8 g of the epoxide **3b** in 40 ml of acetic acid was added a mixture of 70 ml of acetic acid and 7 ml of sulfuric acid. After allowing to stand for two days at room temperature, the reaction mixture was extracted with chloroform and the extracts were concentrated *in vacuo* to give a residue which was chromatographed on silicic acid to yield 10 g of the product. Pure **4b** was obtained by recrystallization from benzene, mp 61—62 °C, IR $\nu_{\max}^{\mathrm{KBr}}$ 1733, 1668 cm^{-1}; PMR data, see Table 1. MS *m/e* 246 (M$^+$); Found: C 68.50; H, 6.00%, Calcd for $C_{14}H_{12}O_4$: C, 68.28; H, 5.73%.

5-Acetoxy-2-methyl-1,4-benzoquinone. A column packed with glass beads was evacuated from lower end of the column with an aspirator at 0.4 mmHg and heated at 350 °C. From the bottle equipped on the column, 100 mg of **4a** was dropped five times into the column, and after cooling, the reaction vessel was washed with chloroform to give a crude product, which was chromatographed on silicic acid using benzene–ethyl acetate (95 : 5 v/v) to yield 53 mg of 5-acetoxytoluquinone, mp 72—73.5 °C (lit,[5]) 74.5—76 °C).

Reduction of 5-Acetoxy-2-methyl-1,4-benzoquinone. A mixture of 20 mg of the quinone in 7 ml of anhydrous ether and 17 mg of LiAlH$_4$ was refluxed for 2 h. To the reaction mixture was added ethyl acetate to decompose excess LiAlH$_4$, and then 10%-sulfuric acid to acidify. The mixture was extracted with ethyl acetate and the extracts were dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give a residue. PMR (CDCl$_3$) δ 6.38 (1H, s, ArH), 6.55 (1H, s, ArH), 7.90—6.78 (3H, br, ArOH).

endo-*4a-Acetoxy-5,8-methano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4c).* The epoxide **3c** prepared from 1 g of *p*-benzoquinone (**1c**) according to the known procedure[5] was dissolved into 10 ml of acetic acid. To the solution was added a mixture of 3 ml of concd sulfuric acid and 30 ml of acetic acid. After allowing to stand for 3 days at room temperature, the reaction mixture was extracted with chloroform and the extracts were washed with brine and dried over anhydrous sodium sulfate, evaporated *in vacuo* to give a crude residue. The residue was chromatographed on silicic acid to give 600 mg of **4c**, mp 102—103 °C, IR $\nu_{\max}^{\mathrm{KBr}}$ 1736, 1683, 1671 cm^{-1}; PMR data (Table 1); MS *m/e* 232 (M$^+$). Found: C, 67.31; H, 5.34%. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%.

r-*2-(Acetoxymethyl)-2,3-epoxy-*t-*5,8-methano-2,*c-*3,*t-*4a,5,8,*t-*8a-hexahydro-1,4-naphthoquinone (3d).* A solution of 13 g of 3-(acetoxymethyl)-1,4-benzoquinone (**1d**) and 8 ml of cyclopentadiene was allowed to stand for 1 h at room temperature. The reaction mixture was concentrated *in vacuo.* To the residue dissolved into tetrahydrofuran was added 100 ml of hydrogen peroxide (30%) under ice-cooling. The mixture was heated at 55—60 °C for 1 h and then cooled at room temperature. After excess hydrogen peroxide had been decomposed with sodium bisulfite, the reaction mixture was extracted twice with benzene and the extracts were dried on anhydrous sodium sulfate and concentrated *in vacuo* to yield a product, which was recrystallized from benzene to give 3.07 g of the epoxide **3d**, mp 125—126 °C, IR $\nu_{\max}^{\mathrm{KBr}}$ 1725, 1260 cm^{-1}; PMR (CDCl$_3$) δ 1.27, 1.47 (2H, ABq, J=9Hz, CH$_2$), 2.02 (3H, s, COCH$_3$), 3.32 (2H, br s, CH), 3.49 (2H, br. s, CH), 3.54 (1H, s, $\overset{\mathrm{O}}{\angle\diagdown}\!/^{\mathrm{H}}$), 4.69, 4.31 (2H, ABq, J=13Hz, CH$_2$OAc), 6.09 (2H, t, J=2Hz, $=\!/^{\mathrm{H}}$); MS *m/e* 262 (M$^+$): Found C, 64.22; H, 5.39%. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38%.

endo-*4a-Acetoxy-2-(acetoxymethyl)-5,8-methano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4d).* To a solution of 3.07 g of the epoxide **3d** in 10 ml of acetic acid was added a mixture of 6 ml of concd sulfuric acid and 60 ml of acetic acid, and the reaction mixture was allowed to stand for 3 days at room temperature and extracted with chloroform. The extracts were washed with brine and dried on anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silicic acid eluting with benzene-ethyl acetate (95 : 5 v/v) to yield 1 g of the product, **4d**, mp 102—103 °C. IR $\nu_{\max}^{\mathrm{KBr}}$ 1752, 1732, 1682 cm^{-1}; PMR data, see Table 1. MS *m/e* 304 (M^+). Found: C, 67.31; H, 5.34%. Calcd for $C_{16}H_{16}O_6$: C, 67.23; H, 5.21%.

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