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FACILE SYNTHESIS OF QUINONE EPOXIDES AND EPOXYCYCLOHEXENONES VIA RETRO DIELS-ALDER REACTION[1)]

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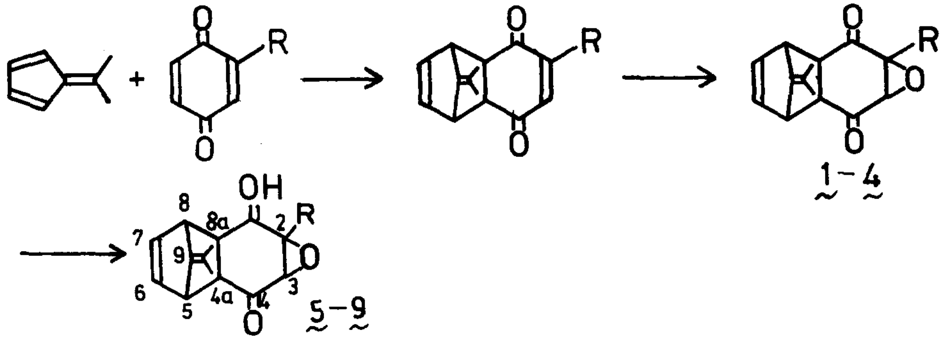
In previous papers, we reported the synthesis of phyllostine and an antitumor substance[2)], epoxydon. In this communication, we would like to describe facile synthetic method of quinone epoxides and epoxycyclohexenones, closely related compounds of epoxydon and useful synthetic intermediates for some natural products[3)], by retro Diels-Alder reaction of epoxy derivatives of quinone-dimethylfulvene adducts. Although it was noted that quinone epoxides were prepared from epoxides of cyclopentadiene-quinone adducts along this line, in practice it involved decomposition of products because of drastic conditions (420°C) during retro Diels-Alder reaction[4)].

Diels-Alder reaction of quinones with dimethylfulvene in ethanol at 4 — 5°C for 2 days gave adducts, which, without isolation, were oxidized with hydrogen peroxide to yield epoxides **1**-**4**. The reactions proceeded in a stereoselective manner to give predominantly endo compounds **3** and **4** except in the case of benzoquinone, which afforded exo and endo compounds **1** and **2** in a ratio of 1 : 1. The stereochemistries at ring juncture 4a-H and 8a-H in the epoxides **1**-**4** were determined easily by NMR spectra[5)], in which the signals due to the protons 4a-H and 8a-H appeared at ca. δ 3.40 (multiplet) in endo compounds **2**, **3**, **4**, but at

δ 2.70 (singlet) shielded by C-6 double bond in *exo* compound **1**. The relative configuration of the epoxides **1**-**4** was confirmed as described later.

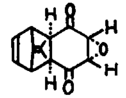
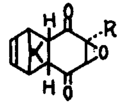
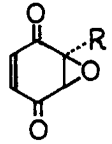
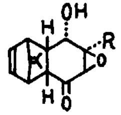
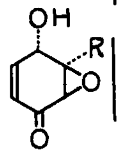
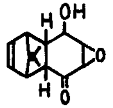
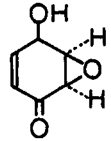
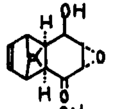
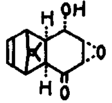


Reduction of the epoxides **1**, **2** and **4** with sodium borohydride in tetrahydrofuran gave ketols **5**-**9** : though the reduction of **4** afforded regio- and stereoselectively **5** because of neighboring hydroxyl group effect, the same treatment of **2** and **1** yielded two epimeric isomers, **6**, **7** and **8**, **9**, respectively. Assuming o-axial conformation[6] of β epoxy group in *endo* structure, a large coupling constant (9Hz) due to 8a-H in compound **7** indicates that the protons 8a-H and 1-H occupy *trans* diaxial positions. The result is compatible with β-configuration of epoxy group in **2**, together with consideration of unhindered β side attack of hydroperoxide and the stereochemistry of **7** must be as shown and the other isomer as **6**. In *exo* compounds **8** and **9**, the coupling constant (9Hz) of 8a-H in **9** consists with diaxial relationship to 1-H. In the IR spectra under high dilute condidions, there was a strong hydrogen bond (3550 cm^{-1}) between hydroxyl group and C-9 double bond in **8** but none in **9**. These data demonstrate that the stereochemistry of epoxy group in **1** must be α and the stereostructure **9** was assigned. The other isomer must be depicted as **8**. These structures were further supported by the fact that **6**, **8** and **7**, **9** were led to **14** and **15** by retro Diels-Alder reaction, respectively.

Retro Diels-Alder reaction under pyrolytic conditions without solvents

Table

Retro Diels-Alder reaction of epoxy derivatives of quinone–dimethylfulvene adducts

starting material*		method	reaction temp(°C)	solvent	reaction time(min)	product		yield(%)
	1	B	180	toluene	40		10 R = H	100
	2 R = H	B	160	toluene	30		10 R = H	95
	3 R = CH_3	B	150	benzene	30		11 R = CH_3	100
	4 R = CH_2OH	A	165	diglyme	30		12 R = CH_2OH	22**)
	5 R = CH_2OH	A	190	diglyme	60		13 R = CH_2OH	43**)
	6 R = H	B	160	THF	40		14 R = H	100
	7	B	160	THF	30		15	100
	8	B	180	THF	40		14	100
	9	B	180	THF	40		15	100

* Satisfactory analytical data were obtained for all these compounds.

** The yields may be improved if we use method B.

failed because of decomposition of products. Successful conditions were method A and B and summerized in Table. Method A is refluxing the adduct in diglyme under nitrogen atmosphere and method B is heating the adduct in low boiling organic solvents such as benzene, toluene and THF etc. in a sealed tube. Since both methods were carried out under rather mild conditions at 150~190°C in organic solvents, most of the reaction proceeded quantitatively. The resultant products **10**-**15** were characterized by IR, NMR, and MS spectra. The relative configuration of compounds **13** and **14** must be *trans*, since a long range coupling due to W-configration[6] was observed in these compounds. This synthetic method is not only useful for the general synthesis of quinone epoxides and epoxycyclohexenones but also made possible to synthesize senepoxyde[3]. Further investigation on biological and antitumor activities of all synthetic compounds are in progress.

References and footnotes

1) This paper constitutes part V of "Synthetic studies of highly oxygenated cyclohexane derivatives". Part IV. A. Ichihara, R. Kimura, and S. Sakamura, *Agr. Biol. Chem.*, submitted for publication.

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3) A. Ichihara, K. Oda, M. Kobayashi, and S. Sakamura, submitted for publication.

4) K. Alder, F. H. Flock, and H. Beumling, *Ber.*, **93**, 1896 (1960).

5) P. F. O'Brien and J. W. Gates, Jr. *J. Org. Chem.*, **30**, 2593 (1965).

6) G. Read and V. M. Ruiz, *J. Chem. Soc.*, (C) 1970, 1945.