REACTION OF THIOLS WITH EPOXIDES OF CONJUGATED 1,4-DIKETONES

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ABSTRACT

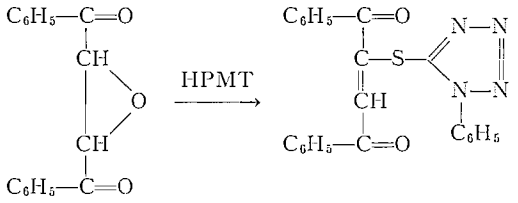
The reaction of thiols with 2,3-epoxides of bicyclo, conjugated 1,4-diketones was found to proceed readily to give the dehydrated thio-substituted enediones or their enolized isomers, depending upon the reaction conditions and the bicyclic bridging of the starting materials. In no case was a mixture of these isomers observed. Enediones generally resulted from these reactions with and without triethylamine catalysis, whereas the use of an equimolar amount of triethylamine generally gave hydroquinones. The ease of rearrangement of enedione to hydroquinone followed the order: 2,3-dimethylbutadiene adduct ≫ reduced cyclopentadiene adduct > cyclopentadiene adduct = 1,3-cyclohexadiene adduct.

Recent reviews on epoxides (1) reveal only one reference to the attack of a sulfhydryl group on an epoxide conjugated to a carbonyl group. In this case (2) hydrogen sulfide in the presence of barium hydroxide reacted with ethyl β,β-dimethylglycidate to give a small amount of ethyl 3-hydroxy-2-mercapto-3-methylbutyrate. The reactions of thiols with 2,3-epoxides of conjugated carbonyl or conjugated 1,4-dicarbonyl compounds have not been reported before. Alder *et al.* (3) have reported the preparation of several epoxides of cyclopentadiene–quinone adducts. The reactions of thiols with these and similar epoxides are reported in this paper.

The thiols that were studied were 1-phenyl-5-mercaptotetrazole (HPMT), 2-mercaptobenzthiazole (HMBT), *p*-toluenethiol (HPTT), 2-quinolinethiol (HQT), methanethiol (HMT), and ethanethiol (HET). Triethylamine (TEA) was often employed, either in catalytic or equimolar amounts. Trimethylamine or sodium salts of some mercaptans were also used.

In all but one case, the diketoepoxides were part of a cyclic system. The exception, *trans*-dibenzoylethylene epoxide (I), reacted with HPMT to produce 1,4-diphenyl-2-(1′-phenyl-5′-tetrazolylthio)-2-buten-1,4-dione (II), as shown in eq. [1]. The structure of II was assigned on the basis of a combustion analysis and an infrared spectrum which shows a conjugated carbonyl doublet at 1 630 and 1 650 cm^{-1}.

[1]



I II

The new diene adducts and epoxides used in this study are described in Tables I and II. Tables III and IV list the products obtained when these epoxides were treated with the various mercaptans. Two possible products of these reactions are the enedione III and the hydroquinone IV (eq. [2]). These structures were assigned on the basis of combustion

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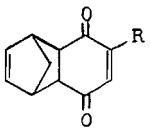
TABLE I

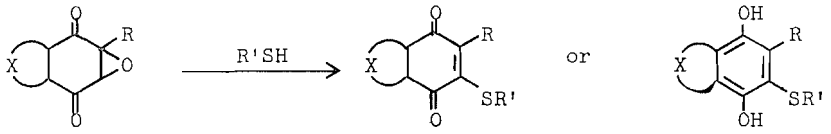
Adducts*



R	Yield, %	Melting point, °C, and crystallization solvent
4′-$C_6H_4CH_3$	76	128–129, methanol
$CH(CH_3)_2$	84	49–51, petroleum ether
$C(CH_3)_3$	82	81–82, ethanol
4′-$SC_6H_4CH_3$†	86	144–154, ethanol

*General procedure of Porter *et al.* (5).
†See Experimental section.

analyses and infrared spectra. In several cases, the products were known compounds synthesized in an unambiguous manner. The infrared spectra show conjugated carbonyl bands at 1 650 cm^{-1} for III and O—H bands at 3 325 cm^{-1} for IV.

[2] 

III IV

Inspection of Tables III and IV reveals that when no catalyst was used the product was the enedione III. Only one exception was noted: the 2,3-dimethylbutadiene–quinone adduct epoxide (XVII), which gave a substituted hydroquinone. This result is not surprising in view of the ease of rearrangement of the dimethylbutadiene–quinone adducts to the aromatic system (4). Since the enedione from XVII is a known compound, it was prepared by a different synthetic route (5).

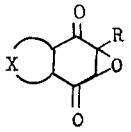
The use of a catalytic amount of triethylamine generally gave enediones III. When an equimolar amount of triethylamine was used, the products were naphthohydroquinones. The enediones XXXIV and XXXV are not exceptions to this reaction, since they cannot rearrange to hydroquinones. The use of the sodium salt of the thiol also led to the naphthohydroquinone, as shown by XXIII.

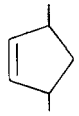
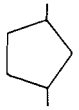
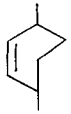
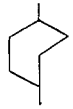
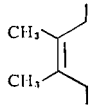
In a previous paper (6) it is shown that the diene–quinone adducts have the *endo-cis* configuration and that the epoxide ring has the *exo* configuration. To determine whether the isolated double bond at the 6,8-position, because of its possible close proximity, had any effect on the reactivity of the epoxide and on the reaction mechanism, several examples of saturated epoxides were prepared. It is clear from the reactions of these epoxides (XLI–L) that the isolated double bond does not affect the reaction course. To verify this type of structure, XLVI was also prepared from the known quinone LIV (7), as shown in eq. [3]. The reduction of the isolated double bond appears to have decreased the strain on the bicyclic ring system, for the enedione XLV readily rearranged after the addition of a trace of mineral acid or after a long reflux period; the corresponding unsaturated enediones of XIX, XXVII, and XXXI required a base for rearrangement (4, 5).

A phenyl or *p*-tolyl substituent did not exhibit any appreciable steric hindrance, as was shown by the reactions of epoxides V, VI, and XIV. When the substituent was isopropyl

TABLE II

Epoxides prepared by the procedure of Alder *et al.* (3)

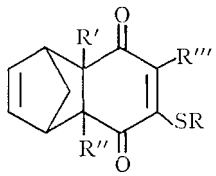
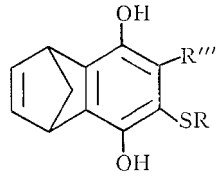


Compound No.	Starting material	X	R	Reaction conditions	Yield, %	Melting point, °C
V	See ref. 5		C_6H_5	60 min, room temp.	90	143–144
VI	See Table I		4′-$C_5H_4CH_3$	60 min, room temp.	88	134–136
VII	See Table I		$CH(CH_3)_2$	30 min, room temp.	90	119–120
VIII	See Table I		$C(CH_3)_3$	60 min, room temp.	84	144–146
IX	See ref. 2		H	*	83	111.5–113.5
X	See ref. 2		CH_3	*	82	132–134
XI	V		C_6H_5	*	62	127–130
XII	See ref. 3		H	10 min, 5 °C	80	137–138
XIII	See ref. 5		CH_3	30 min, 5 °C	80	116–117
XIV	See ref. 5		C_6H_5	30 min, room temp.	84	142.5–143
XV	XII		H	*	51	119–122
XVI	XIII		CH_3	*	75	130–132
XVII	See ref. 10		H	10 min, 5 °C	30	77–79

*Obtained by hydrogenation of the parent epoxides with Raney nickel – ethyl acetate at room temperature and 40 p.s.i.

TABLE III

Reaction products

Compound No.	R′	R″	R‴	Thiol reagent*	Yield, % 	Yield, % 	Melting point, °C
XIX	H	H	H	HPMT – cat. TEA†	70	—	133–134
XX	H	H	H	HMBT‡	27	—	141–142
XXI	H	H	H	HQT§	33	—	126–128
XXII	H	H	H	TEAPMT	—	94	179–181.5
XXIII	H	H	H	HMBT – cat. TEA‖	—	78	240–241
	H	H	H	NaMBT¶	—	77	
XXIV	H	H	H	TEAPTT§	—	89‡‡	144–145
XXV	H	H	H	TEAMT**	—	87‡‡	135–137
XXVI	H	H	H	TEAET**	—	30‡‡	95–96
XXVII	H	H	CH_3	HPMT – cat. TEA§	43	—	140–141
XXVIII	H	H	CH_3	TEAPMT	—	41	182–183
XXIX	H	H	CH_3	TEAMBT	—	90	213–214
XXX	H	H	CH_3	TEAPTT§	—	80‡‡	118–119
XXXI	H	H	C_6H_5	TEAPMT	—	50	125–134 (decomp.)
XXXII	H	H	C_6H_5	TEAPTT**	—	76	151–153 (decomp.)
XXXIII	H	H	4′-$C_6H_4CH_3$	HPMT – cat. TEA††	48	—	178–180 (decomp.)
XXXIV	CH_3	H	CH_3	TEAPMT	22	—	129–130
XXXV	H	CH_3	CH_3	TEAPMT	16	—	119–122 (decomp.)

*GENERAL PROCEDURE: Equimolar amounts of the reactants were refluxed for ¼ to 48 h in ethanol. A solid was obtained when the solution was allowed to cool or when the solvent was concentrated, and recrystallization was effected from ethanol or dilute acetic acid.

†Reaction time, 2 weeks at room temperature.

‡Reaction time, 3 weeks at room temperature.

§Refluxed for 1 h.

‖Refluxed for 48 h.

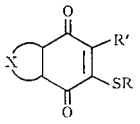
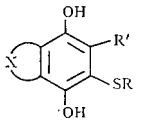
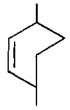
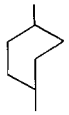
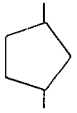
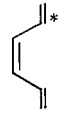
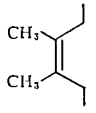
¶Reaction time, 18 h at room temperature in 50% ethanol.

**Refluxed for ½ h.

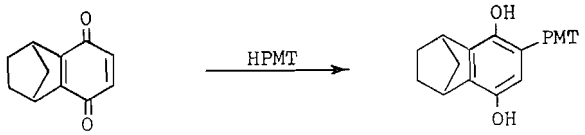
††Refluxed for 1½ h.

‡‡Isolated as the diacetate by acetylation of the solvent-stripped reaction mixture, with acetic anhydride and a catalytic amount of pyridine.

TABLE IV
Reaction products

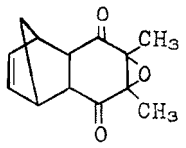
Compound No.	X	R′	Thiol reagent†	Yield, % 	Yield, % 	Melting point, °C
XXXVI		H	HPMT – cat. TEA	—	70	204–205 (decomp.)
XXXVII		H	HMBT – cat. TEA‡	—	25	217–218 (decomp.)
XXXVIII		CH_3	HPMT – cat. TEA§	60	—	145–146
XXXIX		CH_3	TEAPMT	—	40	185–186
XL		C_6H_5	TEAPMT	—	58	211–213 (decomp.)
XLI		H	HPMT – cat. TEA	44	—	135–136
XLII		H	TEAPMT	—	52	201–202 (decomp.)
XLIII		CH_3	HPMT – cat. TEA	77	—	121–122
XLIV		CH_3	TEAPMT	—	79	195–196 (decomp.)
XLV		H	HPMT‖	62	—	132–133
XLVI		H	HPMT¶	—	52	179–181
XLVII		CH_3	HPMT – cat. TEA‖	54	—	150–152
XLVIII		CH_3	TEAPMT	—	85	120–122
XLVIX		C_6H_5	HPMT – cat. TEA‖	100	—	Oil
L		C_6H_5	TEAPMT‖	—	70	132–134
LI		H	HPMT	78	—	144–145
LII		H	HMBT	64	—	171–173 (decomp.)
LIII		H	HPMT¶	—	65	185–186

*Epoxide was obtained by the procedure of Wertz *et al.* (11).
†General procedure is that of Table III.
‡Refluxed for 1½ h in benzene.
§Refluxed for 2 h.
‖Refluxed for 1 h.
¶Refluxed for 4 h in benzene.

[3] 

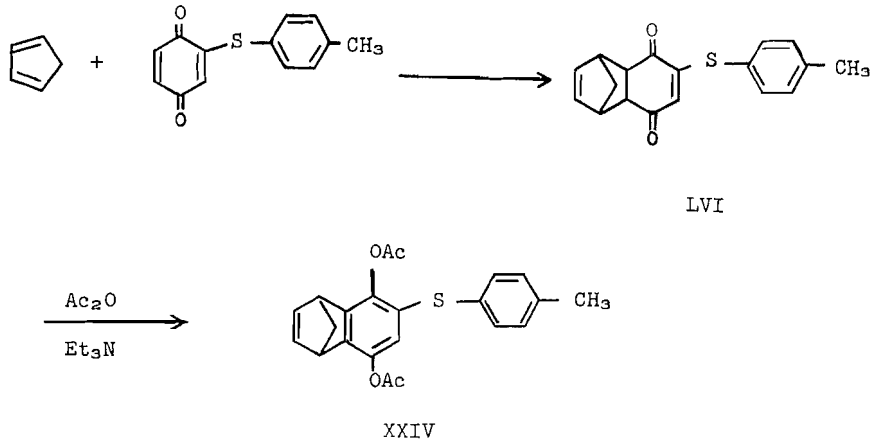
LIV XLVI

(VII) or *t*-butyl (VIII), no reaction was observed, even with the sodium mercaptides. In addition, the epoxides of the three isomeric dimethyl quinone – cyclopentadiene adducts were prepared (3). The 2,3-dimethyl epoxide LV did not react. This result is consistent with a S_N2 reaction mechanism.



LV

When nonheterocyclic mercaptans were used in this study, the enedione form could not be isolated and the hydroquinone derivatives were usually not stable; the presence of the latter was indicated by infrared spectra. These reaction products were usually isolated as their stable diacetates. The structure of one of these diacetates (XXIV) was confirmed by an alternate synthesis, as shown in eq. [4]. The conversion of LVI into XXIV was effected by a method of rearrangement used by Meinwald and Wiley (8).

[4] 

LVI

XXIV

EXPERIMENTAL

Unless otherwise specified, all chemicals were Eastman Kodak Company materials. The elemental analyses of all the new compounds reported in this paper were within the accepted tolerances.

1,4-Diphenyl-2-(1'-phenyl-5'-tetrazolylthio)-2-buten-1,4-dione (II)

Chalcone epoxide (9) was allowed to react at room temperature for 2 weeks with an alcoholic solution containing an equimolar amount of HPMT. The solvent was removed and the product was recrystallized from benzene–alcohol to give a 65% yield, m.p. 158–159° (decomp.).

1,4-Diacetoxy-5,8-dihydro-5,8-methano-2-(4'-toluenethio)-1,4-naphthohydroquinone (XXIV)

To a mixture of 1.4 g of 5,8-methano-4*a*,5,8,8*a*-tetrahydro-2-(4'-toluenethio)-1,4-naphthoquinone (LVI) in 25 ml of acetic anhydride was added 0.6 g of triethylamine. Tetrahydrofuran (1 ml) was then added to produce a clear solution. This solution was allowed to stand at room temperature for 3 days and was then

poured into 300 ml of cold water. Through continued stirring and trituration, the gummy material which separated solidified to give a red-brown solid. This material was collected and recrystallized from alcohol to give 1.4 g (73.7%) of an off-white powder, m.p. 145–147°. This material was identical in all respects with the sample of XXIV prepared as given in Table III.

5,8-Methano-1-(1'-phenyl-5'-tetrazolylthio)-5,6,7,8-tetrahydro-1,4-naphthohydroquinone (XLV)

To 5.0 g of 5,6,7,8-tetrahydro-5,8-methano-1,4-naphthoquinone (5) (LIV) was added 50 ml ethanol, followed by 5.1 g of HPMT. After the mixture had been refluxed for 3 h, the solvent was removed on a rotary evaporator and the residue was dissolved in chloroform. After 2 days, white crystals (2.83 g) were collected, m.p. 174–175° (decomp.). An additional 7.20 g of less-pure product was obtained. An infrared spectrum of this compound was identical with that of the sample prepared by another route, as shown in Table IV.

4'-Toluenethio-p-benzoquinone

To a chilled solution of 18.6 g of *p*-benzoquinone in 100 ml of methanol was added, with stirring, 10.7 g of *p*-toluenethiol in 50 ml of methanol during 30 min. Stirring was continued for 1 h while the reaction mixture warmed to room temperature. At the end of this time, the suspension was poured into 200 ml of ice water and the rust-colored precipitate was collected. The crude product, 19 g, m.p. 100–107°, was crystallized from ethanol to give 16 g of product, m.p. 108–110°.

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