Benzene Oxide–Oxepin. Oxidation to Muconaldehyde

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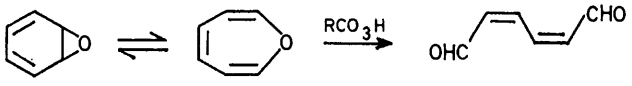
The benzene oxide–oxepin system is converted into muconaldehyde by oxidation with peroxy-acids or with *N*-bromosuccinimide in aqueous dimethyl sulphoxide. Comparative studies on indane 3a,7a-oxide and 2,7-dimethyloxepin lead to the conclusion that the oxidative ring opening involves the oxepin tautomer.

BENZENE OXIDE (1) is in rapid equilibrium with its valence tautomer, oxepin (2), the position of the equilibrium depending on the solvent and temperature.[1] Recently, arene oxides have been implicated in the metabolism of aromatic substrates,[2a] and most chemical studies have centred on the reactions of benzene oxide rather than of oxepin.[2b] Nucleophiles react with the benzene oxide tautomer in preference to the oxepin, causing opening of the epoxide ring.[3] Reactions with electrophiles have not been reported.

Benzene oxide–oxepin readily reacted with peroxy-acids at 0 °C to yield (*Z*,*Z*)-muconaldehyde (3). The dialdehyde (3) was thermally unstable and slowly isomerised first to (*E*,*Z*)-muconaldehyde and finally to the (*E*,*E*)-isomer. The isomerisation could be followed by the observation of the aldehydic proton signals in the n.m.r. spectrum.



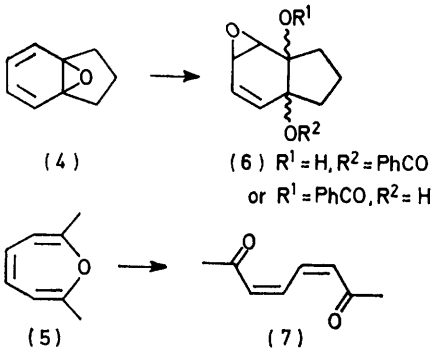
(1) (2) (3)

(*E*,*E*)-Muconaldehyde was also produced from benzene oxide–oxepin in 72% yield under conditions which normally lead to bromohydrin formation with olefins [*N*-bromosuccinimide (NBS) in aqueous dimethyl sulphoxide (DMSO)]. Also benzene oxide–oxepin kept at −3 °C in the presence of oxygen (air) and the absence of light underwent partial conversion (17%) into (*Z*,*Z*)-muconaldehyde.

The conversion of benzene oxide–oxepin into muconaldehyde appears to be a general reaction with mild oxidising agents. In order to gain further information indane 3a,7a-oxide (4) and 2,7-dimethyloxepin (5) were studied as model compounds.[1]

2,7-Dimethyloxepin reacted readily with perbenzoic acid to give a mixture of isomeric octa-3,5-diene-2,7-diones (7), and with NBS in aqueous DMSO to give the (*E*,*E*)-isomer. However indane 3a,7a-oxide reacted only slowly with perbenzoic acid, to produce a hydroxybenzoate (6) in which the indane ring system was intact.

By analogy, conversion of benzene oxide–oxepin into muconaldehyde is considered to involve the oxepin and not the benzene oxide form. This result can be rationalised in terms of electrophilic addition to the more electron-rich oxepin form. The mechanisms proposed

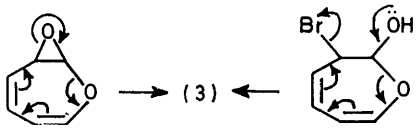


(4) (6) R^1 = H, R^2 = PhCO or R^1 = PhCO, R^2 = H

(5) (7)

are indicated; it is not intended to imply that they are necessarily concerted.

Two of the major metabolites of benzene in the rabbit are phenol and (*E*,*E*)-muconic acid.[4] Phenyl is believed to arise by aromatisation of benzene oxide,[5] whereas the pathway to (*E*,*E*)-muconic acid has not been fully elucidated. However the above reactions lend some chemical support to the suggestion that the metabolic



pathway involves (*Z*,*Z*)-muconaldehyde, which is converted into the (*E*,*E*)-isomer before oxidation to (*E*,*E*)-muconic acid.[6]

EXPERIMENTAL

Instruments were (i.r.) Perkin-Elmer 257 and (^{1}H n.m.r.) Perkin-Elmer R32 (90 MHz) and R14 (100 MHz) (Me_4Si as internal standard; solvent $CDCl_3$).

Reaction of Benzene Oxide–Oxepin with N-Bromosuccinimide in Dimethyl Sulphoxide and Water.—Benzene oxide–oxepin [1] (1.5 g, 0.016 mol) in DMSO (80 ml) under nitrogen was treated with water (0.3 ml, 1.1 mol. equiv.) and cooled

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to 15 °C. With stirring, recrystallised NBS (3.13 g, 1.1 mol. equiv.) was added in one portion and stirring was continued for 1 h at 20 °C. The mixture was added to water (400 ml) and the product extracted with ether (12 × 50 ml). The extracts were dried ($MgSO_4$) and evaporated to yield a yellow solid (1.95 g), which was recrystallised twice from light petroleum (b.p. 40—60 °C)–ether (1 : 1) to afford pale yellow needles (1.26 g, 72%) of (*E,E*)-muconaldehyde, m.p. 120.5—121° (lit.,[7] 121°) (Found: C, 65.5; H, 5.6. Calc. for $C_6H_6O_2$: C, 65.4; H, 5.5%), $\lambda_{max.}$ (EtOH) 271 nm (ε 32 700) [lit.,[7] 270 nm (ε 32 400)]. The i.r. spectra ($CHCl_3$; Nujol) agree closely with the published spectrum.[7]

Reactions of Benzene Oxide–Oxepin with Perbenzoic Acid.—(a) *At* 80 °C *in benzene.* Benzene oxide–oxepin (0.8 g, 0.008 5 mol) in benzene (5 ml) was added to a solution of perbenzoic acid in benzene (12.2%; 11 ml, 1.1 mol. equiv.). After an induction period of *ca.* 2 min the solution turned dark red and the benzene boiled. When cool, the solution was shaken with solid calcium hydroxide for 10 min (to remove benzoic and perbenzoic acids), filtered, and evaporated to yield a red solid. T.l.c. showed the presence of a mixture of benzene oxide–oxepin and muconaldehyde. The i.r. spectrum of the crude material contained two carbonyl bands, $\nu_{max.}$ (Nujol) 1 730 and 1 680 cm^{-1}, and was similar to the published spectrum of (*E,Z*)-muconaldehyde.[7] The n.m.r. spectrum showed two doublets of equal intensity at τ ($CDCl_3$) −0.25 and 0.25. The dialdehyde was isolated by column chromatography [40 g of silica gel M60; light petroleum–ether (1 : 1)] to yield yellow crystals (250 mg, 32%). The product was recrystallised from light petroleum (b.p. 60—80 °C)–ether (1 : 1); m.p. 77—79 and 100—102° (mixture); $\lambda_{max.}$ 272 nm. Comparison of the i.r. spectrum with the published spectra [7] indicated the presence of a mixture of (*E,Z*)- and (*E,E*)-muconaldehyde. The n.m.r. spectrum confirmed the presence of a mixture of (*E,Z*)- (60%) and (*E,E*)- (40%) muconaldehyde: τ ($CDCl_3$) −0.25 (d, *J* 7 Hz), 0.23 (d, *J* 7 Hz), 0.25 (d, *J* 7 Hz), 1.9 (m), 2.7 (m), and 3.5 (m); ratio of doublets to multiplets 1 : 2.

(b) *At* 0 °C *in benzene.* Benzene oxide–oxepin (1.5 g, 0.016 mol), made up to 9.6 ml with benzene, was stirred at 0 °C during dropwise addition of a solution of perbenzoic acid in benzene (12.2%; 20.4 ml, 1.1 mol. equiv.) over 1 h. The reaction was followed by titration of samples (0.5 ml); 0.6 mol. equiv. had reacted after 2 h; 0.87 mol. equiv. after 5.5 h. After 5.5 h the mixture was worked up in the usual way and yielded a mixture (0.35 g) of muconaldehyde (0.16 g, 8.5%) and benzene oxide–oxepin (0.2 g, 13.5%). The n.m.r. spectrum ($CDCl_3$) contained a doublet at τ −0.25 (*J* 7 Hz) showing that the dialdehyde was (*Z,Z*)-muconaldehyde.

Stability of Benzene Oxide–Oxepin in the Presence of Air.—Benzene oxide–oxepin (0.05 g) was kept in the presence of air and in the dark at −3 °C for 36 days. T.l.c. showed the presence of a mixture of benzene oxide–oxepin and muconaldehyde. The n.m.r. spectrum ($CDCl_3$) showed signals for benzene oxide–oxepin (τ 3.75, 4.1, and 4.9) and (*Z,Z*)-muconaldehyde (17%) [τ −0.26 (2 H, d, *J* 7 Hz, CHO), 2.2 (2 H, m, H-2 and -5); the H-3 and -4 signal was hidden by the benzene oxide–oxepin resonance at τ 3.75].

Reaction of 2,7-Dimethyloxepin with N-Bromosuccinimide in Dimethyl Sulphoxide and Water.—2,7-Dimethyloxepin [8] (0.4 g, 0.003 3 mol) in DMSO (15 ml) and water (1 drop) was stirred under nitrogen during addition of recrystallised NBS (0.63 g, 1.1 mol. equiv.) in one portion. The mixture was stirred at 20 °C for 1 h before work-up in the usual way. The reaction yielded a pale yellow solid which was recrystallised twice from light petroleum–ether (1 : 1) to give pale yellow crystals of (*E,E*)-octa-3,5-diene-2,7-dione (0.37 g, 84%), m.p. 124—125° (lit.,[9] 124°) (Found: C, 69.3; H, 7.0. Calc. for $C_8H_{10}O_2$: C, 69.5; H, 7.3%), $\lambda_{max.}$ (EtOH) 276 nm (ε 34 200) [lit.,[9] 276 nm (ε 34 500)].

Reaction of 2,7-Dimethyloxepin with Perbenzoic Acid.—2,7-Dimethyloxepin (0.61 g, 0.005 mol) dissolved in benzene (20 ml) was stirred overnight at 20 °C with perbenzoic acid solution (15.4%; 5 ml; 1.1 mol. equiv.). After 14 h estimation of the peroxy-acid content indicated that *ca.* 1 mol. equiv. had reacted. The mixture was shaken for 10 min with solid calcium hydroxide, filtered, and evaporated to yield an orange crystalline solid (0.5 g). Recrystallisation from light petroleum–ether (1 : 1) first yielded orange crystals (0.05 g), and then pale yellow crystals, m.p. 125—126°, identical with (*E,E*)-octa-3,5-diene-2,7-dione (see above).

The n.m.r. spectrum (CCl_4) of the orange crystals showed multiplets at τ 2.5, 2.9, and 3.7 (4 H) and singlets at τ 7.72 and 7.79 (6 H, indicating a mixture of octa-3,5-diene-2,7-diones). After a few minutes the carbon tetrachloride solution became pale yellow owing to formation of (*E,E*)-octa-3,5-diene-2,7-dione.

Reaction of Indane 3a,7a-*Oxide with Perbenzoic Acid.*—Indane oxide (0.67 g, 0.005 mol) diluted to 20 ml with benzene was stirred overnight at 20 °C with perbenzoic acid solution (15.4%; 5 ml, 1.1 mol. equiv.). Estimation of the peroxy-acid after 14 h showed that 74% had reacted. The mixture was shaken with solid calcium hydroxide for 10 min, filtered, and evaporated at 20 °C under reduced pressure to yield an oil (0.9 g), which solidified. The crude material was recrystallised twice from methanol to yield needles of a hydroxy-benzoate (6) (0.8 g), m.p. 124—125° (Found: C, 70.4; H, 5.9. Calc. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9%), $\nu_{max.}$ (Nujol) 2 860br,s (OH), 1 695s (C=O of ester), 1 605m (aryl-H), 1 340s (O–H bend), 1 280s (ester C–O stretch), 1 260m (epoxide), 1 070s (ester C–O stretch), 820m (epoxide), 710s (aromatic ring), and 690s cm^{-1} (=CH), τ ($CDCl_3$) 2.00 (2 H, m, *ortho*-aryl-H), 2.55 (3 H, m, *meta* and *para* aryl-H), 4.41 (2 H, s, vinyl-H), 6.50 (2 H, s, H α to oxygen), 7.4br (1 H, s, OH, D_2O exch.), and 7.5—8.5 (6 H, m, $[CH_2]_3$), τ (pyridine) 4.05 (1 H, d, *J* 7 Hz), 4.29 (1 H, dt), 6.25 (1 H, dd), and 6.35 (1 H, dt), τ $[(CD_3)_2SO]$ 4.5 (sharp) (s, OH).

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