The "Anomalous" Steric Course of Ring Opening Reactions of Indene Oxide. A Reexamination

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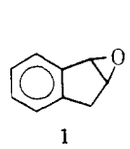
A reexamination of several reports on the apparently anomalous behavior of indene oxide in ring opening reactions has revealed some experimental deficiencies and dubious interpretations and shown that this epoxide behaves in the normal way expected for an aryloxirane, giving both cis and trans adduct in ratios which are dependent on the reagent and the solvent.

Back in 1928 Böeseken[1] reported on a rather awkward dependence of the steric course of the hydrolysis of indene oxide (1) on such factors as reaction time and temperature, type and concentration of the acid catalyst, etc. Some much more recent reports[2,3] confirmed several anomalies and implied that ring opening reactions of 1 may deviate considerably from the normal and by now thoroughly investigated behavior of aryl-substituted epoxides. A recent paper by Gagis, Fusco, and Benedict,[3] stating that 1 reacts with benzoic acid in chloroform to give exclusively anti opening products, induced us to reexamine this reaction, because of our long-standing interest in the reactions of aryloxiranes and because the authors took issue with some of the conclusions reached by our group in one of our early papers on this topic,[4] which were repeatedly confirmed by several later papers[5,6] that apparently escaped their attention; they conclude their paper by stating that on the basis of the exclusive formation of trans adducts in the ring opening of indene oxide in aprotic nonacidic solvents "the reaction mechanism is of an SN2 order, which is considered the normal course for ring openings of epoxides," a statement that may be true for purely aliphatic epoxides, but certainly not for aryloxiranes.[6]

The reaction of 1 with benzoic acid in chloroform was carried out as much as possible according to the described method (the amount of benzoic acid was not indicated in the experimental part of the paper). The crude reaction product was reduced with $LiAlH_4$, basic hydrolysis being avoided in order to prevent any change in configuration through displacement of the benzoyloxy group, or hydrolysis of any epoxide which could still be present. Glpc analysis showed that both the trans and cis diols 2 and 3 were present, in a ratio of 64:36. We think that in the previous work[3] the formation of 3 was overlooked because glpc was apparently not used, and the absence of 3 was deduced from the exclusive isolation of 2, but in an overall yield of only about 66%.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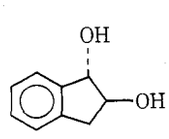
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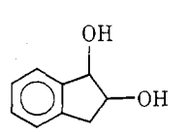
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We also investigated the reaction of 1 with trichloroacetic acid in several different solvents, since this acid usually gives higher amounts of cis adducts with aryloxiranes than weaker acids.[5a,7] The data in Table I show that the trans/cis ratio is really lower, ranging from 56:44 in carbon tetrachloride to 38.5:61.5 in methylene chloride. Such a solvent dependence has been observed before by us in other epoxide ring opening reactions, and was interpreted in terms of different solvation of the cationic intermediate.[5d,f,g]

It can therefore be concluded that the statement quoted above is not correct, and that indene oxide behaves in its ring opening reactions with carboxylic acids in aprotic solvents quite normally as an aryloxirane. These results can be compared, at least qualitatively, if not quantitatively, because of the different geometries and rigidities, to those obtained with styrene oxide.[5a] These reactions cannot be considered "of an SN2 order," but rather as ones that proceed, at least in part, through ion pairs (4) collapsing to cis adducts, with the amount of benzylic bond breaking in the transition state depending on the strength of the acid and on the type of solvent. It may also be mentioned that 1 has been found to give with hydrogen chloride in dioxane a 75:25 ratio of *trans*- to *cis*-1-chloro-2-indanol.[8]

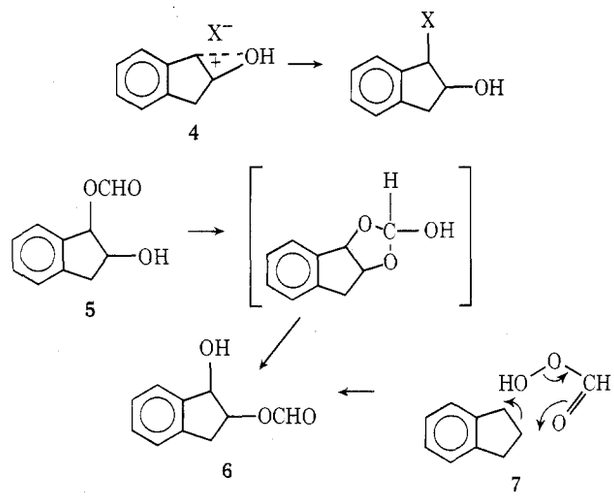
Table I
Ratios of Trans to Cis Adducts in the Ring Openings of Indene Oxide

Acid	Solvent	Trans/cis ratio
C_6H_5COOH	$CHCl_3$	64:36
CCl_3COOH	Cyclohexane	55:45
	CCl_4	56:44
	C_6H_6	48.5:51.5
	$CHCl_3$	47:53
	CH_2Cl_2	38.5:61.5
0.1 *N* H_2SO_4	H_2O	31:69
1 *N* H_2SO_4	H_2O	31:69
HCOOH	HCOOH	25:75

We also decided to check the literature reports on the very irregular behavior of indene oxide in its hydrolysis reactions. According to Böeseken[1] the diols 2 and 3 are obtained in amounts ranging all the way from the exclusive formation of the trans diol 2 (11 months in neutral water) to that of the cis diol 3 (45 min in *N*/60 acetic acid), intermediate ratios being obtained at different reaction times, temperatures, and acid concentrations. Partial support to these results was recently given through glc analysis,[2] when it was shown, for instance, that the ratio of 2 to 3 formed in the sulfuric acid catalyzed hydrolysis of 1 changed from 61.5:38.5 to 45:55 simply on passing from 1 to 0.1 *N* acid. Since such a relevant effect of the acid concentration had never been observed by us in other epoxide ring opening reactions, we repeated the hydrolysis of 1 in 0.1 and 1 *N* sulfuric acid at room temperature, and not at reflux as reported.[2] Under these conditions we found no dependence on acid normality, 2 and 3 being observed in a 31:69 ratio in both cases. The previously reported differences are therefore clearly not due to an influence of the pH of the medium on the primary hydrolysis reaction, but rather to secondary transformations of the glycols at the higher temperatures and reaction times. It has been known for a long time[9] that 2 and 3 equilibrate under acidic catalysis, and that the cis diol 3 is slowly converted into 2-indanone. We actually found that a 1-hr reflux of 2 and 3 in 1 *N* sulfuric acid in dioxane–water gave mixtures of 2 and 3 in ratios of

about 7:3 together with 2-indanone, the amount of which was higher when starting from **3** than from **2**, in accordance with the fact that only the cis diol is directly converted into the ketone, as would be expected for a concerted trans elimination, or, more likely, for a concerted 1,2 hydride shift. The latter results are also in contrast with the statement by Rosen, Dorfman, and Linfield[10] that 2-indanone is formed at the same rate from **2**, **3**, and from the corresponding 2-formyl esters. This was apparently deduced on the basis of very rough data that showed similar yields of ketone from all four substrates after 30-min reflux in 25% or more concentrated sulfuric acid, and taken as a proof that in all four cases the reaction proceeds through open carbonium ions. Beside the fact that under these conditions the formate esters were certainly hydrolyzed to the glycols much faster than they were rearranged, so that the substrates were actually two, and not four, the reaction conditions were so drastic that equilibration of **2** and **3** certainly took place before rearrangement. The more accurate older kinetic measurements,[9b] as well as our observations, clearly demonstrate that the rearrangement of **2** requires prior conversion into **3**, and that a free carbonium ion, which would be common to **2** and **3**, is not involved.

The same paper[10] also reported that the reaction of indene with peroxyformic acid gave almost exclusively cis adducts (**3** and the corresponding 2-formyl ester **6**) with less than 5% trans adducts. On the basis of this result it was proposed that the reaction takes place through a concerted attack by the peroxy acid, such as that shown in **7**, with formation of the 2-formate as a primary product, rather than by the primary formation of the epoxide **1**, followed by ring opening through attack by formate at the benzylic carbon to give **5** and by a 1,2-acyl shift, which should be very rapid in the acidic medium.[5,7b,11] The former hypothesis was preferred on the basis of the fact that the product composition of the indene–peroxyformic reaction was reported to be very different from that of the indene oxide–formic acid reaction. Since the latter composition was not specified, we also checked this point and found that the reaction of indene with peroxyformic acid, under the reported conditions,[10] gave after hydrolysis of the crude reaction mixture the diols **2** and **3** in a ratio of 15:85 (that is, much more of the trans isomer than reported), whereas the reaction of indene oxide with formic acid under conditions reproducing as much as possible those of the peroxyformic acid oxidation yielded the same two diols in a ratio of 25:75. Examination of the crude reaction mixtures from the two reactions by glc before hydrolysis revealed in both of them the presence of seven peaks, three of which were identified as due to the cis diol **3**, its 2-formate ester **6** (main product) and the trans diol **2**; the other four peaks were probably due to the other three possible monoformates and to the diformate, since only the two diols, traces of 2-indanone, and no other products were obtained after hydrolysis. The relative intensities of some of the peaks were a little different in the crudes from the two types of reactions, but the ratios of the cis 2-formate (**6**, the main product) to the cis diol were the same. Since a primary attack of formic acid at the nonbenzylic 2 position of the epoxide is extremely unlikely, the latter results indicate that the large amount of **6** in the reaction product from indene and peroxyformic acid can in no way be taken as a proof of the concerted mechanism **7**. The distribution of the diols and mono- and diformates rather appears to be due to a secondary equilibration in the formic acid–water medium, involving esterifications, hydrolyses, and acyl shifts, but not changes in relative configurations. The difference in the ratios of trans to cis adducts we have observed in the two types of reaction could imply for the peroxyformic acid oxidation a mechanism not involving the free epoxide as an intermediate, but we are rather inclined to assume, in view of the small size of this difference, that it stems from the difficulty in reproducing the exact experimental conditions in the two different types of reactions.



Experimental Section

Melting points were taken on a Kofler block. Gas–liquid chromatographic analyses were carried out on a Carlo Erba Fractovap Model G. V. equipped with a flame ionization detector and with 2-m glass columns. The mixtures of the diols **2** and **3**, 2-indanol, and 2-indanone were analyzed on a column of 5% DC-550 silicone oil on 80–100 mesh silanized Chromosorb W: injector block temperature 160°, column temperature 100°, nitrogen flow 35 ml/min; relative retention times of 2-indanone, 2-indanol, **3**, and **2**, 1:1.1:3.4:4.1. Petroleum ether refers to the fraction of bp 30–50°. $MgSO_4$ was always used as the drying agent in work-up procedures. Solvents used in the ring opening reactions were distilled from P_2O_5.

Starting and Reference Compounds. 1,2-Epoxyindan (**1**), mp 29–30° (from petroleum ether) (lit.[3] mp 30°), was obtained by cyclization of *trans*-2-bromo-1-indanol with base.[3] The latter compound was prepared by the following modification of the method of Suter and Milne.[9b] A solution of indene (20 g, 0.18 mol in 8:2 dioxane–water, v/v, 480 ml) was treated with *N*-bromoacetamide (26.2 g, 0.19 mol) in 1:1 dioxane–water (300 ml), heated for 10 min on a steam bath, and then poured onto ice to give the solid crude bromohydrin (32 g), after crystallization from ethanol, mp 127–128degr (lit.[9b] mp 126–127°).

trans-1,2-Indandiol (**2**) was prepared by 5-hr reflux of the epoxide **1** (2.0 g) in 2 *N* aqueous KOH (200 ml), followed by saturation with NaCl, extraction with ether, and crystallization from toluene, mp 158–160° (lit.[3,10] mp 157–159°).

cis-2-Formyloxy-1-indanol (**6**), mp 125–127° (lit.[10] mp 132–134°), was prepared according to Rosen, Dorfman, and Linfield[10] and converted into *cis*-1,2-indandiol (**3**), mp 98–100° (lit.[10] mp 99–101°).

2-Indanone, mp 50–52° (lit.[12] mp 57–58°), was obtained from **1** (0.50 g) in dry benzene (25 ml) through treatment with boron trifluoride–ethyl ether complex (0.58 ml) for 5 min, washing with aqueous $NaHCO_3$, evaporation, and crystallization from petroleum ether.

2-Indanol, mp 67–68° (lit.[13] mp 69°), was obtained by lithium aluminum hydride reduction of a solution of 2-indanone in ether, followed by decomposition of the excess of hydride with the minimum amount of water and 2 *N* NaOH.

Reaction of 1 with Benzoic Acid. A solution of **1** (0.250 g, 1.9 mmol) and benzoic acid (0.250 g, 2.0 mmol) in neutral, dry $CHCl_3$ (3 ml) was allowed to stand for 3 days at room temperature and then diluted with more $CHCl_3$ (10 ml) and washed with saturated aqueous $NaHCO_3$ (3 ml). The washing was extracted with three 10-ml portions of $CHCl_3$ and the combined organic layers were dried and evaporated to give a residue of benzoic esters (0.41 g). $LiAlH_4$ (0.4 g) was added in small portions to a solution of this residue in dry tetrahydrofuran (15 ml). After a 30-min reflux the excess of hydride was decomposed with the minimum amount of water and 2 *N* NaOH, the slurry was filtered, and the solid residue

was washed four times with portions of 25 ml of warm tetrahydrofuran. The combined organic solutions were dried and evaporated under reduced pressure. The residue was analyzed by glc and shown to contain the glycols **2** and **3** in a ratio of 64:36. This ratio did not change when a similar reaction mixture was left at room temperature for 80 days and then worked up as above. When the reaction was conducted in a more dilute solution (1.13 mmol of **1** and 1.24 mmol of benzoic acid in 15 ml of $CHCl_3$ for 20 days at room temperature) the ratio of **2** to **3** was 71:29. In all cases glc revealed the presence of some 2-indanol (5–10%), which could derive either from some unreacted epoxide or from some 2-indanone in the primary reaction products.

Reactions of 1 with Trichloroacetic Acid. These reactions were carried out in carefully dried vessels and solvents in the following way. A solution of **1** (0.53 mmol) in the appropriate solvent (7 ml) was treated with trichloroacetic acid (0.58 mmol) as a *ca.* 1 *M* solution in the same solvent, left at room temperature for 24 hr, and then evaporated *in vacuo*.[14] The residue was taken up in dry tetrahydrofuran (15 ml), treated with lithium aluminum hydride (0.300 g), and refluxed for 30 min. Work-up was carried out as in the case of the benzoic acid reaction. The ratios of **2** to **3** obtained by glc are shown in Table I. Amounts of 2-indanone (revealed as 2-indanol), ranging from 13 to 20%, were also found.

Hydrolysis of 1. A suspension of **1** (0.100 g) in 0.1 or 1 *N* aqueous H_2SO_4 (10 ml) was stirred for 24 hr at room temperature and then made alkaline with $NaHCO_3$, saturated with NaCl, and extracted with five 25-ml portions of ether. The residue obtained after evaporation of the dried extract was analyzed by glc; see Table I. The diols **2** and **3** were found to be stable under the reaction conditions. Small amounts of 2-indanone (1 and 4% in the reactions carried out in 0.1 and 1 *N* H_2SO_4, respectively) were found.

Equilibration and Rearrangement of 2 and 3. Solutions of each of the diols (50 mg) in 1 *N* H_2SO_4 in 75:25 dioxane–water (v/v, 5 ml) were refluxed for 1 hr and then worked up as above. Glc analysis gave the following results: from the trans diol **2**, 7% 2-indanone, 93% **2** + **3** (ratio 67:33); from the cis diol **3**, 18% 2-indanone, 82% **2** + **3** (ratio 69:31).

Comparison between the Reactions of Indene with Peroxyformic Acid and of 1 with Formic Acid. A. A mixture of 90% formic acid (7 ml), water (0.36 ml), and 35% hydrogen peroxide (1.2 ml) was heated at 35° for 15 min. Indene (1.16 g, 10 mmol) was then slowly added under stirring, while the temperature was kept at 35–40°. Stirring was continued for 1 hr at 35°, then at room temperature for 1 night. NaOH (6 *N*, 25 ml) was added; the mixture was heated at 90° for 3 hr, cooled, saturated with NaCl, and extracted with six 30-ml portions of ether. The dried extract was evaporated; glc analysis of the residue revealed the presence of **2** and **3** in a ratio of 15:85.

In a second run, with the same amounts of reagents and reaction conditions, the reaction product was not treated with base, but instead diluted with water (10 ml), saturated with NaCl, and extracted with five 30-ml portions of ether. The ether extracts were washed with water (2 × 25 ml), saturated $NaHCO_3$ (6 × 10 ml), and water (5 ml). The combined washings were extracted again with three 20-ml portions of ether, all the ether solutions were combined and evaporated, and the residue was examined by glc. The results are discussed in the introductory part.

B. The reactions were repeated under exactly the same conditions as in A, except for the reagents, that were 90% formic acid (7 ml), water (1.33 ml), 35% hydrogen peroxide (0.22 ml), and 1,2-epoxyindane (1.32 g, 10 mmol). In the hydrolyzed crude product **2** and **3** were present in a ratio of 25:75.

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Registry No.—**1**, 768-22-9; **2**, 4647-43-2; **3**, 4647-42-1; **6**, 19597-99-0; *trans*-2-bromo-1-indanol, 10368-44-2; 2-indanone, 615-13-4; 2-indanol, 4254-29-9.

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Ring Closure Reactions. III.[1] Synthesis of Some Medium-Sized Cyclic Aromatic Ethers from *o*-(ω-Bromoalkyl)phenols

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A synthesis of cyclic ethers of ring size n = 8, 9, and 10 as an alternative, convenient route to Ziegler's high-dilution technique is described. It is based on the highly favorable cyclization of *o*-(ω-bromoalkyl)phenate ions (**2**) in DMSO solution to yield 3,4,5,6-tetrahydro-2*H*-1-benzoxocin (**4**, n = 8), 2,3,4,5,6,7-hexahydro-2*H*-1-benzoxonin (**4**, n = 9), and 3,4,5,6,7,8-hexahydro-2*H*-1-benzoxecin (**4**, n = 10). The formation of varying amounts of isomeric alkenylphenols as by-products is recorded and discussed. Two alternative routes to the open-chain precursors from ω-X-alkyl *o*-anisyl ketones (**6** and **12**) are compared. In one of them the interesting competitive cyclization of 5-bromopentyl *o*-hydroxyphenyl ketone to cyclopentyl *o*-hydroxyphenyl ketone (**9**) is observed.

In the course of our investigation on the kinetics of ring closure of the anions derived from ω-bromoalkoxy- and ω-bromoalkylphenols, **1** and **2**, to the cyclic diethers[1] and monoethers,[2] **3** and **4**, respectively, cyclization on a preparative scale of compounds **2**, n = 8, 9, and 10, to the corresponding new macrocyclic monoethers[3] **4** was re-