

Solvent Dependence of the Reaction of 1,2-Epoxy-1-(*p*-nitrophenyl)cyclohexane with Boron Trifluoride–Diethyl Ether Complex

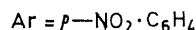
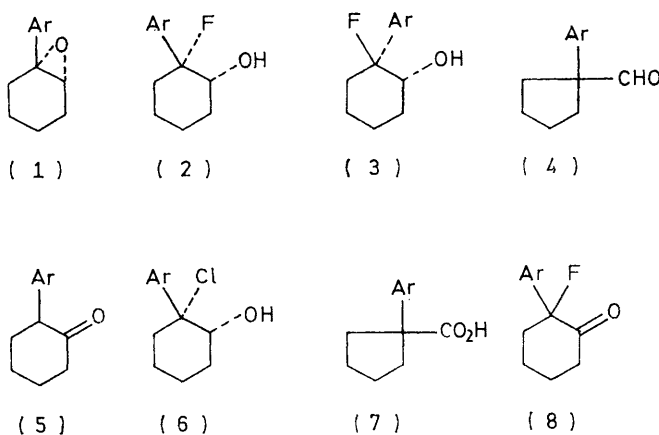
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The reaction of 1,2-epoxy-1-(*p*-nitrophenyl)cyclohexane with boron trifluoride–diethyl ether exhibits a pronounced solvent dependence: in benzene it gives a 9:1 ratio of *cis*-2-fluoro-2-(*p*-nitrophenyl)cyclohexanol to 1-(*p*-nitrophenyl)cyclopentanecarbaldehyde, which does not change with reaction time; in dichloromethane the *cis*-fluorohydrin is again the main primary product, but is rapidly converted into the aldehyde in the reaction medium; and in ether about equimolar amounts of *cis*- and *trans*-2-fluoro-2-(*p*-nitrophenyl)cyclohexanol are formed. The presence of small amounts of water in the dichloromethane solvent causes the formation of a *ca.* 6:4 mixture of *cis*-fluorohydrin and aldehyde, the composition of which changes little with reaction time. This solvent dependence of the reaction can be useful for preparative purposes. A reaction mechanism is suggested.

EPOXIDES are converted by boron trifluoride–diethyl ether complex ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) into several different types of rearrangement products. Aldehydes, ketones, unsaturated alcohols, dienes, *etc.* may be obtained, and in some cases also fluorohydrins, formed through simple addition of the elements of hydrogen fluoride.¹ The preparative usefulness of these reactions would be greatly increased by an understanding of the factors influencing the various pathways, with a view to modifying the product composition by an appropriate choice of reaction conditions. We have previously shown that the reactions of 1,2-epoxy-1-phenylcyclohexane² and its 4-*t*-butyl derivatives³ with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ can be interpreted on the basis of the preferential breaking of the benzylic C–O bond and subsequent transformations involving carbenium ions. We have now extended this work to 1,2-epoxy-1-(*p*-nitrophenyl)cyclohexane (1), which is particularly sensitive to the reaction conditions because of the presence of the electron-withdrawing nitro-group, which decreases the carbocationic character of the transition state and places the epoxide (1) on the borderline between aryl-substituted epoxides, which preferentially open in a *syn* fashion, and alkyl-substituted epoxides, for which the mode of opening is *anti*; for instance, in the reaction of the epoxide (1) with hydrogen chloride the ratio of *anti* to *syn* opening (*trans*- to *cis*-chlorohydrin) changes from 92:8 to 5:95 simply on changing the solvent from carbon tetrachloride to chloroform.⁴

The Table shows that the course of the reaction of the epoxide (1) with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is also highly dependent on the solvent. In benzene and in dry dichloromethane the reaction is fast and gives after a short time the *cis*-fluorohydrin (2) as the main product, together with minor

amounts of the aldehyde (4). A little of the ketone (5) is also formed in dichloromethane, but not in benzene.



Product composition in the reactions of the epoxide (1) with $\text{BF}_3 \cdot \text{Et}_2\text{O}$

Solvent	Reaction time	Products %			
		(2)	(3)	(4)	(5)
C_6H_6	2 min	92		8	
C_6H_6	20 min	92		8	
CH_2Cl_2	2 min	85		14	1
CH_2Cl_2	7 min	37		61	2
CH_2Cl_2	1 h			97	3
CH_2Cl_2	3 h			97	3
CH_2Cl_2 (H_2O -satd.)	2 min	58		42	
CH_2Cl_2 (H_2O -satd.)	20 min	56		44	
Et_2O	48 h	51	44	5	

Furthermore, whereas the product composition remains constant with time in benzene, it changes rapidly in dichloromethane, with a decrease in *cis*-fluorohydrin (2)

¹ P. L. Barili, G. Berti, B. Macchia, F. Macchia, and L. Monti, *J. Chem. Soc. (C)*, 1970, 1168.

² G. Bellucci, G. Berti, B. Macchia, and F. Macchia, *Gazzetta*, 1973, 103, 345.

¹ A. Rosowski, in 'Heterocyclic Compounds with Three- and Four-Membered Rings,' ed. A. Weissberger, Interscience, New York, 1964, p. 231.

² G. Berti, B. Macchia, F. Macchia, and L. Monti, *J. Chem. Soc. (C)*, 1971, 3371.

and a parallel increase in the rearrangement products (4) and (5), so that after 1 h the fluorohydrin has completely disappeared. The use of water-saturated dichloromethane produces a 58 : 42 ratio of fluorohydrin (2) to aldehyde (4), which changes little with time. In diethyl ether the reaction is much slower, and a substantial amount of the *trans*-fluorohydrin (3) is formed as well as the *cis*-isomer (2) and the aldehyde (4).

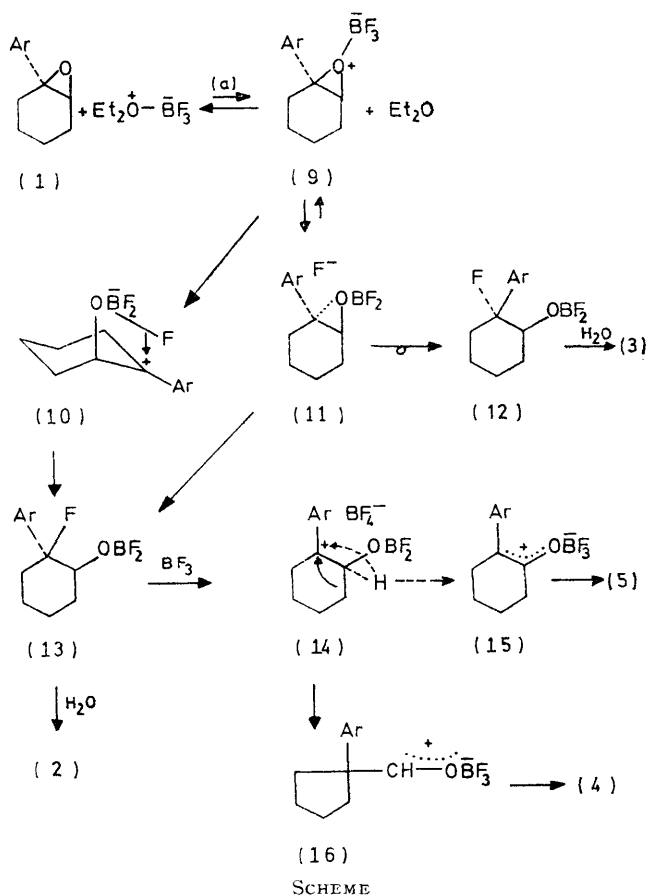
Compounds (2) and (4) were obtained pure simply through crystallization of the products of the reactions conducted in benzene and dichloromethane, respectively; compound (3) was obtained by preparative t.l.c. of the product of reaction in ether. The ketone (5) was isolated by fractional crystallization of the 7 : 3 mixture of (5) and (4) formed in the reaction of the chlorohydrin (6) with silver oxide in hexane; the preferential formation of (5) is in agreement with previous results with analogous chlorohydrins.³⁻⁵

The oxidation of the aldehyde (4) to the acid (7) confirmed its structure. The diastereoisomeric nature of (2) and (3) was proven by their oxidative conversion into the same fluoro-ketone (8); their relative configurations were deduced from n.m.r. and i.r. spectra. In the case of the *cis*-fluorohydrin (2) the *CH*·OH signal appeared as two broad multiplets ($W_{\frac{1}{2}}$ 20 Hz) centred at δ 3.84 and separated by 25 Hz ($^3J_{\text{HF}}$), whereas in the *trans*-isomer (3) the same proton gave a much narrower single multiplet at δ 3.82 ($W_{\frac{1}{2}}$ 9 Hz). Although the values of vicinal H,F coupling constants are markedly affected by structural factors and particularly by substituent electronegativities,⁶ in all known cases $^3J_{\text{HF}}$ is much larger for the anticoplanar than for the gauche disposition of the two atoms. A value of 25 Hz has been found previously for $^3J_{\text{HF}}$ of the analogue of (2) without the *p*-nitro-group.² The assigned configurations and conformations were also confirmed by i.r. spectra of dilute solutions in carbon tetrachloride: the OH stretching band occurs at 3605 for (2) and at 3626 cm^{-1} for (3), in agreement with the possibility of intramolecular OH...F bonding in the former, but not in the latter.^{7,8}

A comparison of the present data with those obtained in the analogous reactions of 1,2-epoxy-1-phenylcyclohexane (1; Ar = Ph) shows that the introduction of the *p*-nitro-group affects considerably the behaviour with $\text{BF}_3, \text{Et}_2\text{O}$, the main differences being that (1; Ar = Ph) gives the fluorohydrin only in ether, but none in benzene, and that no *trans*-fluorohydrin is formed in any case from (1; Ar = Ph). From the as yet limited data available in the literature it appears that fluorohydrins may be the normal primary reaction products under conditions that are not favourable for the formation of carbocationic intermediates, *i.e.* low acidity (low concentration of boron trifluoride in a basic solvent), absence of electron-

donating and presence of electron-withdrawing substituents.^{1,9,10} That this reaction has not been noticed more often may be explained by the fact that in the presence of an excess of the Lewis acid and in non-basic solvents rapid secondary rearrangements can convert the intermediate fluorohydrins completely into carbonylic rearrangement products. It is however likely^{2,9} that the fluorohydrin derivatives are not necessary intermediates between epoxide and carbonyl compound; alternative direct rearrangement pathways are probably available when the conditions are such as to favour the formation of carbenium ions.

In the case of the epoxide (1) the electron-attracting properties of the *p*-nitro-group favour the formation of the fluorohydrin even in non-basic solvents, although the C-O cleavage occurs only at the benzylic carbon atom. The Scheme provides a possible interpretation



⁵ D. Y. Curtin and R. J. Harder, *J. Amer. Chem. Soc.*, 1960, **82**, 2357.

⁶ K. L. Williamson, Y.-F. Li Hsu, F. H. Hall, S. Swager, and M. S. Coulter, *J. Amer. Chem. Soc.*, 1968, **90**, 6717.

⁷ M. Tichý, in 'Advances in Organic Chemistry: Methods and Results,' eds. R. A. Raphael, E. C. Taylor, and H. Wynberg, Interscience, New York, 1965, vol. 5, p. 115.

⁸ B. Macchia, F. Macchia, and L. Monti, *Gazzetta*, 1970, **100**, 35.

⁹ D. J. Goldsmith, *J. Amer. Chem. Soc.*, 1962, **84**, 3913.

¹⁰ I. G. Guest and B. A. Marples, *J.C.S. Perkin I*, 1973, 900.

¹¹ S. Searles, M. Tamres, and E. R. Lippincott, *J. Amer. Chem. Soc.*, 1953, **75**, 2775.

the use of a large excess of ether further decreases the concentration of (9). This can explain the decrease in rate observed in this solvent.

The complex (9) could be converted into the fluorohydrin either through 'axial cleavage'¹² to give the dipolar ion (10), followed by intramolecular transfer of fluorine, which should give the *cis*-adduct (13), or through heterolysis of one of the B-F bonds to give an ion pair such as (11), in which the positive charge may be in part transferred from oxygen to carbon; the collapse of (11) could give both the *cis*- and *trans*-adducts (13) and (12), converted into the fluorohydrins (2) and (3) on treatment with water. The observed steric course of fluorohydrin formation indicates that either mechanism may be involved, depending on the solvent. Purely aliphatic or cycloaliphatic epoxides give exclusively *trans*-fluorohydrins with BF₃·Et₂O,^{10,13} whereas aryl-substituted epoxides produce, in all cases so far reported, only the *cis*-fluorohydrins.^{2,14} This is the usual trend for the ring opening of epoxides, in which electron-donating substituents favour the formation of *syn* adducts. As already pointed out, the epoxide (1) exhibits behaviour intermediate between those of alkyl- and aryl-substituted oxirans; this is well illustrated in the present reaction, where a change to a more basic solvent is enough to modify the steric course from pure *syn* to a substantial amount of *anti* opening.

One possible explanation of the general ability of ether to facilitate the formation of fluorohydrins, and in the particular case of the epoxide (1) to induce *anti* opening of the ring, can be found in the favourable effect of this donor solvent on the ionization of the B-F bond, through solvation of the electron-deficient boron atom in the intermediate (11).

The secondary conversion of the adduct (13) into the aldehyde (4) probably involves abstraction of the benzylic fluorine atom by boron trifluoride, followed by rearrangement of the carbenium ion (14) to (16), a small amount of the ketone (5) being concurrently formed through (15). The direct conversion of (10) into (16) is in this case only of minor importance. The absence of these secondary reactions when benzene or ether is used as solvent must be due to a decreased tendency to form the cation (14), because of the lower Lewis acidity of boron trifluoride in these donor solvents.

The change in product composition caused by the presence of small amounts of water in dichloromethane may be connected with the formation of protic acidic species such as H⁺[BF₃OH]⁻, [H₃O]⁺[BF₃OH]⁻, or HF,¹⁵ which could modify the reaction course and favour the primary formation of the aldehyde (4). This is supported by the much slower conversion of (13) into (4) in this medium, because of the non-availability of the Lewis acid necessary for the conversion of (13) into (14).

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were taken for Nujol mulls on a Perkin-Elmer Infracord 137 instrument; spectra of dilute solutions (<5 × 10⁻³M) in dried (P₂O₅) carbon tetrachloride were obtained with a Perkin-Elmer 257 double-beam grating spectrophotometer (indene band at 3110 cm⁻¹ as calibration standard; quartz cell of 2 cm optical length). N.m.r. spectra were determined for *ca.* 10% solutions in [²H]chloroform with a JEOL C-60-HL spectrometer (Me₄Si as internal standard). G.l.c. analyses of the mixtures of the fluorohydrins (2) and (3) (as their trimethylsilyl ethers) and of the carbonyl compounds (4) and (5) were run on a Carlo Erba Fractovap GV apparatus with a flame ionization detector [dual glass columns (2.5 mm × 1.5 m) packed with 1% neopentylglycol succinate on 80–100 mesh silanized Chromosorb W; programmed from 170 to 215° (1° min⁻¹); evaporator 210°; detectors 210°; nitrogen flow 45 ml min⁻¹]. The order of retention times was: (3) < (2) < (4) < (5). Magnesium sulphate was used as drying agent. Evaporations were carried out *in vacuo* (rotary evaporator). Benzene was washed with concentrated sulphuric acid, refluxed over sodium, and rectified. Dichloromethane was refluxed over phosphoric oxide and rectified. Diethyl ether was refluxed over sodium and distilled. The BF₃·Et₂O complex was purified by the method of Zweifel and Brown.¹⁶

cis-2-Fluoro-2-(*p*-nitrophenyl)cyclohexanol (2).—A solution of the epoxide (1) (0.70 g, 3.20 mmol) in dry benzene (70 ml) was treated with BF₃·Et₂O (0.40 ml, 3.24 mmol) and left for 20 min at room temperature. The mixture was then washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated. Crystallization of the crude residue from light petroleum (b.p. 80–100°) yielded pure *fluorohydrin* (2) (0.35 g), which crystallized in two polymorphic forms, one melting at 94–95°, the other at 106–108° (Found: C, 59.95; H, 6.0; F, 7.8. C₁₂H₁₄FNO₃ requires C, 60.25; H, 5.9; F, 7.95%).

trans-2-Fluoro-2-(*p*-nitrophenyl)cyclohexanol (3).—BF₃·Et₂O (0.18 ml, 1.46 mmol) was added to a solution of the epoxide (1) (0.30 g, 1.37 mmol) in anhydrous diethyl ether (30 ml). The mixture was left for 48 h at room temperature, then washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated. The solid residue, consisting of (2) and (3), was subjected to preparative t.l.c. (97:3 benzene-ether as eluant; two elutions). Extraction of the two bands [the faster moving band contained (3)] with ether yielded the *cis*-isomer (2) (0.16 g) and the *trans*-*fluorohydrin* (3) (0.12 g), m.p. 125–126° [from light petroleum (b.p. 60–80°)] (Found: C, 59.95; H, 6.0; F, 8.25. C₁₂H₁₄FNO₃ requires C, 60.25; H, 5.9; F, 7.95%).

When the reaction was carried out under the same conditions but for only 15 h, much unchanged epoxide (1) was still present.

2-Fluoro-2-(*p*-nitrophenyl)cyclohexanone (8).—Jones reagent (0.25 ml) was added to a solution of the fluorohydrin (2) (0.050 g, 0.21 mmol) in acetone (10 ml). After 12 h at room temperature the mixture was poured into water and extracted with ether. The organic layer was washed (water, saturated sodium hydrogen carbonate solution, and water), dried, and evaporated to give a solid residue which

¹² M. P. Hartshorn and D. N. Kirk, *Tetrahedron*, 1965, **21**, 1547.

¹³ H. B. Henbest and T. J. Wrigley, *J. Chem. Soc.*, 1957, 4596, 4765; J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1965, **21**, 559.

¹⁴ H. O. House, *J. Org. Chem.*, 1956, **21**, 1306.

¹⁵ C. A. Wamser, *J. Amer. Chem. Soc.*, 1951, **73**, 409.

¹⁶ G. Zweifel and H. C. Brown, *Org. Reactions*, 1963, **13**, 28.

on crystallization from light petroleum (b.p. 30–50°) afforded pure *ketone* (8) (0.035 g), m.p. 53–55°, λ_{\max} 5.79 μm (CO) (Found: C, 60.85; H, 5.25. $\text{C}_{12}\text{H}_{12}\text{FNO}_3$ requires C, 60.75; H, 5.1%).

Similar oxidation of (3) afforded pure (8).

1-(*p*-Nitrophenyl)cyclopentanecarbaldehyde (4).—A solution of the epoxide (1) (3.0 g, 13.7 mmol) in dry dichloromethane (300 ml) was treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.7 ml, 13.7 mmol) and after 20 min at room temperature was washed with saturated sodium hydrogen carbonate solution and dried. Evaporation and crystallization from propan-2-ol gave pure *aldehyde* (4) (1.5 g), m.p. 58–60°, λ_{\max} 5.78 μm (CO) (Found: C, 65.65; H, 5.9. $\text{C}_{12}\text{H}_{13}\text{NO}_3$ requires C, 65.75; H, 6.0%).

1-(*p*-Nitrophenyl)cyclopentanecarboxylic Acid (7).—A solution of the aldehyde (4) (0.040 g, 0.18 mmol) in acetone (6 ml) was treated with Jones reagent (0.1 ml) and left for 30 min at room temperature. Dilution with water yielded a solid product which on crystallization from benzene gave the pure *acid* (7) (0.030 g), m.p. 172–174° (Found: C, 61.3; H, 5.5. $\text{C}_{12}\text{H}_{13}\text{NO}_4$ requires C, 61.25; H, 5.55%).

Reaction of *cis*-2-Chloro-2-(*p*-nitrophenyl)cyclohexanol (6) with Silver Oxide.—A solution of the chlorohydrin (6)⁴ (0.24 g, 0.94 mmol) in hexane (60 ml) was stirred for 10 min

at 73° under nitrogen with freshly prepared silver oxide⁵ (1.6 g). Filtration and evaporation yielded a residue (0.19 g), consisting of a mixture of (5) and (4) in the ratio 70 : 30 (g.l.c.), which after two crystallizations from hexane yielded pure 2-(*p*-nitrophenyl)cyclohexanone (5), m.p. 87–88°, λ_{\max} 5.85 μm (CO) (Found: C, 65.9; H, 5.95. $\text{C}_{12}\text{H}_{13}\text{NO}_3$ requires C, 65.75; H, 6.0%).

Reactions of the Epoxide (1) with Boron Trifluoride–Ether Complex.—The reactions in benzene, dichloromethane, and diethyl ether were carried out in carefully dried apparatus in the following way. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.115 ml, 0.91 mmol) was added to a solution of the epoxide (1) (0.20 g, 0.91 mmol) in the appropriate solvent (20 ml) and the resulting mixture was left at room temperature. After the times reported in the Table, portions (4 ml) of the mixture were poured into saturated sodium hydrogen carbonate solution (10 ml) and extracted with the same organic solvent. The extracts were washed with water, dried, and evaporated to dryness, and the crude residue was analysed by g.l.c. (see Table).

We thank the Consiglio Nazionale delle Ricerche for financial support, Dr. V. Nuti for the elemental analyses, and Dr. M. Ferretti for the g.l.c. determinations.

[3/1595 Received, 30th July, 1973]