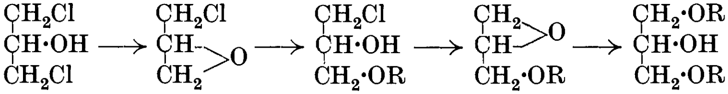
266. *The Partial Esterification of Polyhydric Alcohols. Part XII. The Function of Ethylene-oxide Rings.*

By Arthur Fairbourne, George Philip Gibson, and David William Stephens.

Ethylene-oxide rings are formed during apparently simple reactions, and cause changes in molecular structure that are often unsuspected, or believed due to a migration of radicals.

The intermediate formation of ethylene oxide itself from ethylene glycol cannot produce isomeric change, and for this reason propylene glycol and glycerol (compare Part VII; J., 1929, 129) offer probably the least complicated opportunities for study.

The preparation of glycerol di-ethers by the action of sodium hydroxide upon alcoholic dichlorohydrin has a special interest in this connexion, since it is now found to take place in four stages, which involve the formation and destruction of *two* ethylene-oxide rings consecutively.

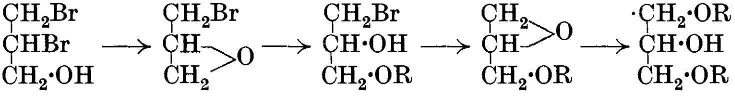


$$\begin{array}{l}CH_2Cl\\CH{\cdot}OH\\CH_2Cl\end{array}\longrightarrow\begin{array}{l}CH_2Cl\\CH\\CH_2\end{array}\!\!>\!O\longrightarrow\begin{array}{l}CH_2Cl\\CH{\cdot}OH\\CH_2{\cdot}OR\end{array}\longrightarrow\begin{array}{l}CH_2\\CH\\CH_2{\cdot}OR\end{array}\!\!>\!O\longrightarrow\begin{array}{l}CH_2{\cdot}OR\\CH{\cdot}OH\\CH_2{\cdot}OR\end{array}$$

[R = Me or Et or Ph]

Conditions which govern these four separate reactions have been investigated and modified to enable the process to be stopped at any stage, and each of the intermediate compounds to be isolated in good yield: the rings are produced by alkali, and are re-opened by further alkali or by acid, although they remain stable in neutral solution.

The mechanism is thus analogous with that indirectly deduced by Abderhalden and Eichwald to explain their unexpected conversion of an active αβ-dibromohydrin into a non-rotating αγ-diamine (*Ber.*, 1915, **48**, 1848). It also explains the unexpected preparations of glycerol αγ-diphenyl and dimethyl ethers from αβ-dibromohydrin described by Boyd and by Gilchrist and Purves (J., 1901, **79**, 1221; 1925, **127**, 2735; Part VIII, J., 1929, 1151).

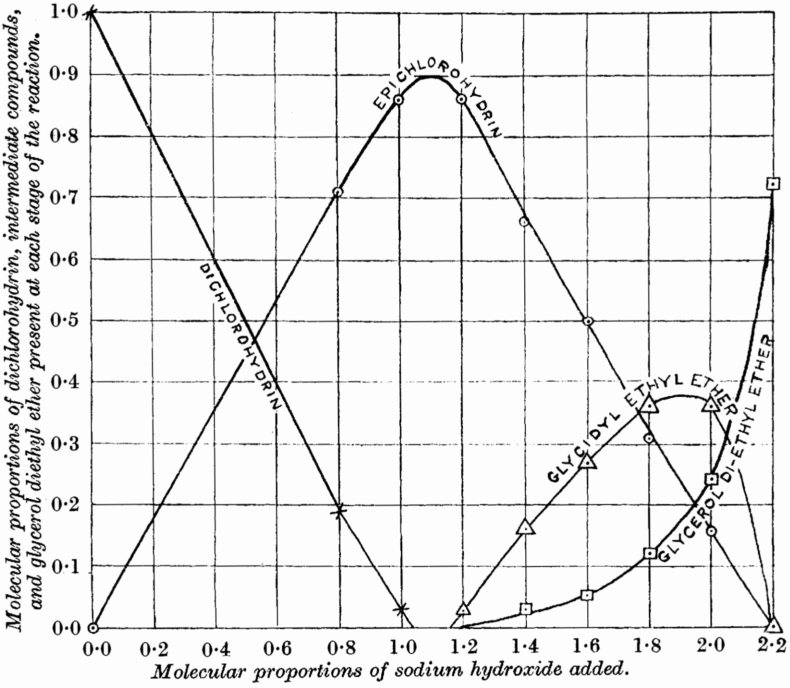


$$\begin{array}{l}CH_2Br\\CHBr\\CH_2{\cdot}OH\end{array}\longrightarrow\begin{array}{l}CH_2Br\\CH\\CH_2\end{array}\!\!>\!O\longrightarrow\begin{array}{l}CH_2Br\\CH{\cdot}OH\\CH_2{\cdot}OR\end{array}\longrightarrow\begin{array}{l}CH_2\\CH\\CH_2{\cdot}OR\end{array}\!\!>\!O\longrightarrow\begin{array}{l}CH_2{\cdot}OR\\CH{\cdot}OH\\CH_2{\cdot}OR\end{array}$$

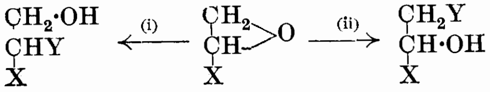
[R = Me or Ph]

Although glycerol β-ethers (Part XI; J., 1931, 445) and β-amines (Abderhalden and Eichwald, *Ber.*, 1916, **49**, 2095) can be prepared and are stable, a glycerol ether or amine which results from this type of reaction may apparently be relied upon *always to possess the α-constitution*, whatever the structure of the initial mono- or di-halogenohydrin, and whatever the nature of the alcohol or amine employed (for references, see J., 1929, 129; 1931, 445; also Melikow, *Ber.*, 1879, **12**, 2227; Hess and Fink, *Ber.*, 1915, **48**, 1990; Smith, *Z. physikal. Chem.*, 1919, **93**, 59; Lespieau, *Bull. Soc. chim.*, 1923, **33**, 725; Fourneau and Ribas, *ibid.*, 1927, **41**, 1053; Naoúm, "Nitroglycerine and Nitroglycerine Explosives," London, 1928, 172; Krasuski and Pilingen, *Ukraine Chem. J.*, 1930, **5**, 135, 237, 349).

The Conversion of Alcoholic Dichlorohydrin into Glycerol Diethyl Ether by the Gradual Addition of Sodium Hydroxide.



Clearly these glycidic rings must therefore be capable of rupturing according to the second of the following alternative reactions preferentially or exclusively, a conclusion which has also now been reached by Blanchard (*Bull. Soc. chim.*, 1931, **49**, 283; compare Nef, *Annalen*, 1904, **335**, 191):



$$\begin{array}{l}CH_2\cdot OH\\ CHY\\ X\end{array} \xleftarrow{(i)} \begin{array}{l}CH_2\\ CH\end{array}\!\!>O\ \ (\text{with } X \text{ on } CH) \xrightarrow{(ii)} \begin{array}{l}CH_2Y\\ CH\cdot OH\\ X\end{array}$$

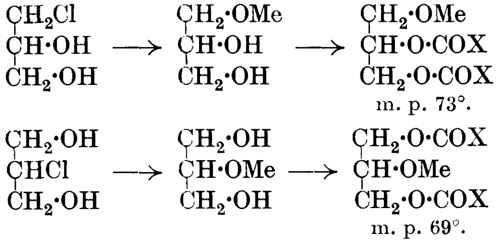
[X = $CH_2{\cdot}OMe$, $CH_2{\cdot}OPh$, $CH_2{\cdot}NH_2$,$CH_2{\cdot}NEt_2$, $CH_2{\cdot}NC_4H_4$, CH_3, $CH_2{\cdot}OH$, CH_2Cl, $CH_2{\cdot}NO_2$, or CO_2H.
Y = OMe, OEt, OPh, NH_2, NHC_5H_{11}, $NH{\cdot}CH_2Ph$, NC_4H_8NH, $N(CO)_2C_6H_4$, OH, Cl or $O{\cdot}CO{\cdot}C_3H_7$]

When acyl radicals are introduced in this way, however, there exists the further complication that they may afterwards migrate (Part X; J., 1930, 369), particularly, as Bergmann and Carter have shown (*Z. physiol. Chem.*, 1930, **191**, 211), when alkaline conditions are not avoided.

Grün and Limpächer (*Ber.*, 1926, **59**, 690) were of opinion that, although glycidol was formed during certain corresponding reactions of monoiodohydrin when a silver soap was used, its formation was at the most only subordinate when a potassium soap was substituted. More probably, however, these silver and potassium soaps both produce glycidol in quantity and the alkaline nature of the potassium soap causes the ring to re-open immediately, thus effecting the esterification.

This view receives support from the fact that the direct replacement of halogens in the glycerol molecule is a process of considerable difficulty (Part X; J., 1930, 382), whereas ethylene-oxide rings are formed and re-opened with ease. Moreover, Abderhalden and Eichwald used virtually the same reaction, successfully dividing it into its two stages and isolating the intermediate glycidol, in their synthesis of optically active α-monobutyrin (*Ber.*, 1915, **48**, 1847).

Suzuki and Inoue (*Proc. Imp. Acad., Tokyo*, 1930, **6**, 71) assume the absence of such glycidic intermediates in their recent preparations of supposed di-*p*-nitrobenzoates of glycerol α- and β-monomethyl ethers from the corresponding α- and β-monochlorohydrins,



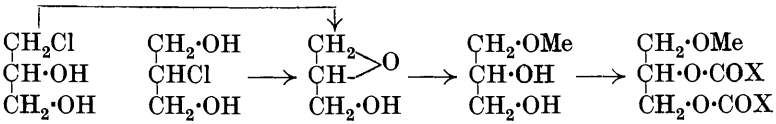
$$\begin{array}{l}CH_2Cl\\ CH{\cdot}OH\\ CH_2{\cdot}OH\end{array} \longrightarrow \begin{array}{l}CH_2{\cdot}OMe\\ CH{\cdot}OH\\ CH_2{\cdot}OH\end{array} \longrightarrow \begin{array}{l}CH_2{\cdot}OMe\\ CH{\cdot}O{\cdot}COX\\ CH_2{\cdot}O{\cdot}COX\\ \text{m. p. } 73^\circ.\end{array}$$

$$\begin{array}{l}CH_2{\cdot}OH\\ CHCl\\ CH_2{\cdot}OH\end{array} \longrightarrow \begin{array}{l}CH_2{\cdot}OH\\ CH{\cdot}OMe\\ CH_2{\cdot}OH\end{array} \longrightarrow \begin{array}{l}CH_2{\cdot}O{\cdot}COX\\ CH{\cdot}OMe\\ CH_2{\cdot}O{\cdot}COX\\ \text{m. p. } 69^\circ.\end{array}$$

[X = $p\text{-}NO_2{\cdot}C_6H_4{\cdot}$]

and believe that they have confirmed the structures of their compounds by an independent synthesis of the isomeride melting at 69°.

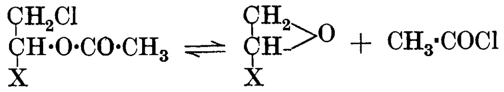
These conclusions, if they were justified, would be seriously contradictory to the views now being advocated, which undoubtedly require both chlorohydrins to yield the same product.



$$\begin{array}{l}CH_2Cl\\CH\cdot OH\\CH_2\cdot OH\end{array}\qquad\begin{array}{l}CH_2\cdot OH\\CHCl\\CH_2\cdot OH\end{array}\longrightarrow\begin{array}{l}\left.\begin{array}{l}CH_2\\CH\end{array}\right>O\\CH_2\cdot OH\end{array}\longrightarrow\begin{array}{l}CH_2\cdot OMe\\CH\cdot OH\\CH_2\cdot OH\end{array}\longrightarrow\begin{array}{l}CH_2\cdot OMe\\CH\cdot O\cdot COX\\CH_2\cdot O\cdot COX\end{array}$$

It is therefore specially noteworthy that the structure of their initial "β"-monochlorohydrin is unproven (Thieme, *Ber.*, 1913, **46**, 1653; Part V, J., 1926, 3148; Brash, *J. Soc. Chem. Ind.*, 1927, **46**, 481T; Part X, J., 1930, 370; Smith and Lindberg, *Ber.*, 1931, **64**, 505; Glattfeld, Leavell, Spieth, and Hutton, *J. Amer. Chem. Soc.*, 1931, **53**, 3169), and also that their final products cannot be the compounds they suppose, since the true di-*p*-nitrobenzoates of glycerol α- and β-monomethyl ethers melt at 108° and 155°, instead of at 73° and 69° respectively (Part XI, *loc. cit.*).

The transitory formation of ethylene-oxide rings need not be confined to molecules which contain a free hydroxyl group; there is already some evidence that reactions of the following type occur:



$$\begin{array}{l}CH_2Cl\\CH\cdot O\cdot CO\cdot CH_3\\X\end{array}\rightleftharpoons\begin{array}{l}\left.\begin{array}{l}CH_2\\CH\end{array}\right>O\\X\end{array}+CH_3\cdot COCl$$

EXPERIMENTAL.

The Reaction αγ-Dichlorohydrin ⟶ Glycerol αγ-Diethyl Ether.

(I) *Epichlorohydrin.*—This compound is noticeable during the preparation of glycerol di-ethers by the action of sodium hydroxide upon dichlorohydrin and alcohols; its entire substitution for the dichlorohydrin has already been shown (Parts VIII and XI; J., 1929, 1151; 1931, 450) not to affect the nature of the product. It is now found that, if the alkali is added *gradually and in one molecular proportion only*, the reaction proceeds to an almost quantitative formation of epichlorohydrin, but no further. A similar result is achieved if water is employed instead of alcohol, and probably this process then constitutes the most convenient preparation of epichlorohydrin.

345 G. of 46% aqueous sodium hydroxide were gradually added with vigorous stirring during 1 hour to 516 g. of dichlorohydrin at 75—80°; crude epichlorohydrin separated from the salt and water as an immiscible layer. Distillation of the layer yielded a constant-boiling mixture at 88°, and pure epichlorohydrin at 115—116° or 60—61°/100 mm., $d_{4^\circ}^{20^\circ}$ 1·181, $n_D^{20^\circ}$ 1·438; yield, 70% (Found : Cl, 38·5. Calc. for C_3H_5OCl : Cl, 38·4%). A further yield, making a total of 85%, was similarly obtainable from the lower fractions,

including this constant-boiling mixture, which consisted of 75% of epichlorohydrin and 25% of water and separated at 25° into layers containing 98% of epichlorohydrin and 93% of water respectively.

The following figures, which are plotted in the diagram, indicate the extent to which epichlorohydrin was both formed and destroyed when various molecular proportions of powdered sodium hydroxide were gradually added with stirring to 22% alcoholic solutions of dichlorohydrin under identical conditions :

Mols. NaOH added ...	0·8	1·0	1·2	1·4	1·6	1·8	2·0	2·2
Mol. resulting epichlorohydrin	0·71	0·86	0·86	0·66	0·50	0·31	0·16	0·00
Mol. unchanged dichlorohydrin	0·19	0·03	—	—	—	—	—	—

In each of these experiments the temperature was allowed to rise to 50°, cooling being applied to prevent volatilisation during the addition of the sodium hydroxide; the mixture was then refluxed for an hour, cooled, separated from salt by filtration and washing with alcohol, neutralised if alkaline, and distilled through a column with a final bath temperature of 150°. The epichlorohydrin was estimated in the distillate, and unchanged dichlorohydrin in the residue, by alkaline hydrolysis.

(II) *α-Monochlorohydrin γ-Ethyl Ether*, $CH_2Cl\cdot CH(OH)\cdot CH_2\cdot OEt$. —The detection of this ether during the preparation of glycerol diethyl ether from dichlorohydrin is difficult, owing to its immediate destruction by alcoholic alkali at a speed comparable with that of its formation. By increasing the hydrion concentration, however, it is possible to prevent this destruction. Sulphuric acid proved very convenient for the purpose, but hydrochloric acid was unsuitable owing to its combining with the epichlorohydrin to regenerate dichlorohydrin.

370 G. of epichlorohydrin were boiled with 1,840 g. of alcohol containing 20 g. of sulphuric acid for 6 hours, cooled, neutralised to phenolphthalein, concentrated, and distilled. 423 G. of the ether (II) were obtained, b. p. 104—106°/60 mm., $d_{4^\circ}^{25^\circ}$ 1·107, $n_D^{25^\circ}$ 1·442 (Found : Cl, by hydrolysis, 25·3. Calc. for $C_5H_{11}O_2Cl$: Cl, 25·6%).

A small amount of glycidyl ethyl ether (III) may be formed from sodium ethoxide and epichlorohydrin without passing through this intermediate α-monochlorohydrin γ-ethyl ether (II), but such a direct replacement of halogen is extremely slow (compare Part X; J., 1930, 369), relative to the opening and closing of the glycidic rings caused in hot alcohol by the addition of alkali, and its extent must consequently be negligible.

α-Monochlorohydrin γ-ethyl ether never accumulated to a sufficient extent to be measured when sodium hydroxide was added to 22% alcoholic solutions of dichlorohydrin, and it is therefore not represented in the diagram.

(III) *Glycidyl Ethyl Ether,*  $\overset{O}{CH_2—CH}\cdot CH_2\cdot OEt$.—This ether, previously detected in the preparation of glycerol diethyl ether (Part XI; J., 1931, 455), has now been obtained in good yield by treating α-monochlorohydrin γ-ethyl ether (II), *gradually and without final excess,* with aqueous sodium hydroxide at 80—100°. 521 G. of 27% sodium hydroxide solution were introduced with stirring into 487 g. of the monochlorohydrin ether sufficiently slowly to avoid the coloration of phenolphthalein. Separation of sodium chloride and two liquid layers occurred. The lighter layer gave on distillation a constant-boiling mixture at 90—91° and the required glycidic ether at 124—126°; $d_{4°}^{25°}$ 0·94, $n_D^{25°}$ 1·406 (compare Part XI; *loc. cit.*). The yield was increased to 78% by addition of salt to the lower-boiling fractions including the constant-boiling mixture, removal of an aqueous layer which separated, and refractionation.

When made in alcohol, glycidyl ethyl ether is difficult to separate by distillation, but may readily be converted into glycerol diethyl ether by the catalytic action of a slight excess of the alkali (or by acid).

The following figures, which are plotted in the diagram, indicate the extent to which glycidyl ethyl ether was both formed and destroyed under the conditions already defined for epichlorohydrin :

Mols. NaOH added ...	0·8	1·0	1·2	1·4	1·6	1·8	2·0	2·2
Mol. resulting glycidyl ethyl ether	—	—	0·03	0·16	0·27	0·36	0·36	0·00

Each of these experiments was carried out as described on p. 1969. The distillation yielded an alcoholic mixture of glycidyl ethyl ether and epichlorohydrin, which were converted by treatment with acid into glycerol diethyl ether (IV) (75% yield; see below) and monochlorohydrin ethyl ether (II), respectively. The amounts of these two ethers were then determined by alkaline hydrolysis.

(IV) *Glycerol Diethyl Ether,* $EtO\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot OEt$. Glycidyl ethyl ether (III) was converted into the diethyl ether in 75% yield when it was boiled in excess of alcohol containing 1% of sulphuric acid during 6 hours, cooled, neutralised to phenolphthalein, concentrated, and distilled (Found : OH, 11·9. Calc. for $C_7H_{16}O_3$: OH, 11·5%).

A more convenient preparation, however, notwithstanding the number of reactions involved, has been from dichlorohydrin : the following figures (see diagram also) indicate the extent to which the ether was so produced under the conditions defined for epichlorohydrin :

Mols. NaOH added ...	0·8	1·0	1·2	1·4	1·6	1·8	2·0	2·2
Mol. glycerol diethyl ether produced	—	—	—	0·03	0·05	0·12	0·24	0·72

These experiments were carried out as described on p. 1969, the ether being obtained by fractionation at 108—111°/60 mm.; $d_{4^\circ}^{25^\circ}$ 0·953, $n_D^{25^\circ}$ 1·420 (Found: OH, 11·8. Calc. for $C_7H_{16}O_3$: OH, 11·5%).

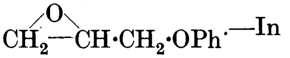
The Reaction αγ-Dichlorohydrin ⟶ *Glycerol αγ-Diphenyl Ether.*

(V) Epichlorohydrin was more noticeable during the early part of this reaction than in the corresponding preparations of glycerol dimethyl and diethyl ethers, and was easily isolated by distillation.

(VI) *α-Monochlorohydrin γ-Phenyl Ether*, $CH_2Cl{\cdot}CH(OH){\cdot}CH_2{\cdot}OPh$. —When epichlorohydrin was heated with sodium phenoxide, glycerol diphenyl ether resulted, but when phenol was substituted for the sodium phenoxide the reaction proceeded to α-monochlorohydrin γ-phenyl ether and no further. This result is analogous to that obtained by the use of sulphuric acid in the case of the corresponding ethyl ether (p. 1969), and is presumably due to the acidic nature of the phenol.

463 G. (1 mol.) of epichlorohydrin and 940 g. (2 mols.) of phenol were heated at 110° for 10 hours, and fractionated through a long column. After recovery of unchanged epichlorohydrin and phenol, 80 g. of the ether were obtained, b. p. 125—126°/2 mm., $d_{4^\circ}^{25^\circ}$ 1·209, $n_D^{25^\circ}$ 1·540 (Found : Cl, 19·0. Calc. for $C_9H_{11}O_2Cl$: Cl, 19·0%).

(VII) *Glycidyl Phenyl Ether*,



$\overset{\diagup O \diagdown}{CH_2{-}CH}{\cdot}CH_2{\cdot}OPh$

.—In contrast with what occurred when ethyl alcohol was used, and probably owing to the less alkaline nature of sodium phenoxide than that possessed by sodium ethoxide, it is possible, as the foregoing experiments would lead one to expect, to stop the reaction with epichlorohydrin at this stage, and thus to obtain glycidyl phenyl ether without isolating the intermediate chlorohydrin ether (VI). So readily indeed does this happen that glycidyl phenyl ether has been mistaken for the diphenyl ether (VIII) and has caused confusion in the literature (Boyd and Marle, J., 1908, **93**, 838; 1909, **95**, 1807).

A repetition of Boyd and Marle's preparation (*loc. cit.*, 1908) from epichlorohydrin resulted in a yield of 40%.

The following method, based on the theoretical considerations developed in this paper, gave 63%. 593 G. of 27% sodium hydroxide solution were introduced with stirring at 70—80° into a mixture of 188 g. of phenol and 258 g. of dichlorohydrin sufficiently slowly

(2 hrs.) to avoid the coloration of phenolphthalein. After the whole had been kept at 100° for a further hour, and cooled, separation of sodium chloride and two liquid layers occurred. The lighter layer gave on fractionation 190 g. of the ether, b. p. 115—116°/3—4 mm., $d_{4^\circ}^{25^\circ}$ 1·10 (Found : C, 72·4 ; H, 6·9. Calc. for $C_9H_{10}O_2$: C, 72·0 ; H, 6·7%).

A similar preparation carried out with the isolated intermediate monochlorohydrin phenyl ether (VI) and 1 mol. of the sodium hydroxide solution gave 65% yield after extraction in ether and fractionation; b. p. 115—116°/3—4 mm., $d_{4^\circ}^{25^\circ}$ 1·10, $n_D^{25^\circ}$ 1·53.

(VIII) *Glycerol Diphenyl Ether*, $PhO{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}OPh$.—The conversion of glycidyl phenyl ether into glycerol diphenyl ether has been effected by treatment with the theoretical quantity of phenol in both alkaline and acidic conditions, the yield being better in the former case : the amount of alkali employed should be very small, as otherwise high-boiling residues are produced.

The ether was most conveniently prepared by the gradual addition with stirring during 1 hour at 90—100° of 129 g. of dichlorohydrin (1 mol.) to a mixture which had previously been made at 120° from 188 g. of phenol (2 mols.) and 85 g. of sodium hydroxide (2·1 mols.). Heating was continued for a further hour at 120°; the product was washed with hot water, distilled in super-heated steam at 250°, and recrystallised from alcohol; m. p. 80—81°, yield 80%.

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RESEARCH LABORATORIES,
PORT SUNLIGHT.

KING'S COLLEGE, LONDON, W.C. 2.

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