386. *The Mechanism of Epoxide Reactions. Part I. The Reactions of 1 : 2-Epoxyethylbenzene, 1 : 2-Epoxy-3-phenylpropane, and 1 : 2-Epoxy-3-phenoxypropane with Some Secondary Amines.*

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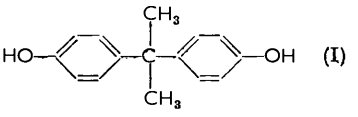
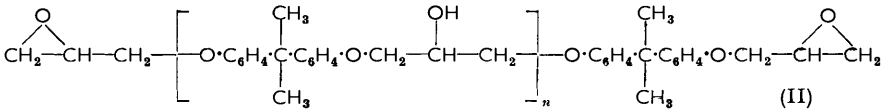
Arrhenius parameters have been determined for the reactions of 1 : 2-epoxyethylbenzene, 1 : 2-epoxy-3-phenylpropane, and 1 : 2-epoxy-3-phenoxypropane with some secondary amines in 99·8% ethanol. In selected cases product analyses have been carried out by infrared spectroscopy whence it is inferred that all the reactions studied give entirely, or almost entirely, " normal " products. The kinetic results therefore refer unambiguously to attack at one position of the epoxide ring. The mechanism of the reactions is discussed and the effect of substituents is analysed in terms of the Taft linear free-energy relation.

Epoxide resins are manufactured by the reaction of an epoxide, usually epichlorohydrin, with a dihydric phenol.[1] From the phenol (I), the resin would have an idealised structure (II). The resin is then cured (*i.e.*, cross-linked), usually by heating it with an amine. The curing process is known to involve reaction between amine molecules and the terminal epoxide groups in the resin. Primary, secondary, and tertiary amines are all used for curing, and especially polyamines (*e.g.*, 2 : 2′-diaminodiethylamine). The present paper



(I)



(II)

records a kinetic study of the reactions between simple epoxides related to the resin (II) and a series of amines. Of the epoxides chosen for study, 1 : 2-epoxy-3-phenoxypropane is clearly related closely to (II), while 1 : 2-epoxyethylbenzene and 1 : 2-epoxy-3-phenylpropane were included in order to determine the effect of structural variation in the epoxide molecule on the rate of the reaction. The amines piperidine, morpholine, and 2-, 3-, and 4-methylpiperidine were chosen in order to determine both the polar and the steric effects of substituents in the amine molecule on the rate. Diethanolamine was included because of its relation to morpholine and to 2 : 2′-diaminodiethylamine. Work is also being carried out with primary amines and this will be reported in a subsequent publication. Ethanol (99·8% w/w) was used as solvent because, in our experience, it is very suitable for the study of nucleophilic substitution, and, in particular, ion exchange with the solvent is usually unimportant.[2]

Previous kinetic work on the reactions of epoxides with amines [3] and with other nucleophiles [4] has usually been restricted to purely aliphatic epoxides. Very few kinetic measurements have been made, and no Arrhenius parameters determined, for the reactions

[1] Narracott, *Brit. Plastics*, 1953, **24**, 120.

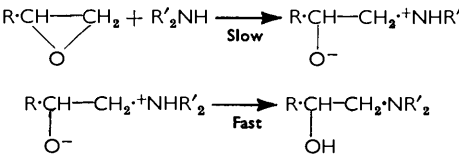
[2] Cavell and Chapman, *J.*, 1953, 3392; *Chem. and Ind.*, 1953, 1226.

[3] Smith, Mattsson, and Andersson, *Kgl. Fysiograf. Sallskap. Lund*, 1946, **42**, No. 7, p. 1; Hansson, *Svensk kem. Tidskr.*, 1948, **60**, 183; 1950, **62**, 185; 1954, **66**, 351; 1955, **67**, 246; Andersson, Thesis, Lund, 1955; Eastham *et al.*, *Canad. J. Chem.*, 1951, **29**, 575, 585; *J.*, 1952, 1936; Berbé, *Chimie et Industrie*, 1950, **63**, 3 bis, 492.

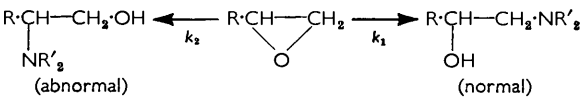
[4] Brönsted, Kilpatrick, and Kilpatrick, *J. Amer. Chem. Soc.*, 1929, **51**, 428; Lichtenstein and Twigg, *Trans. Faraday Soc.*, 1948, **44**, 905; Smith, Wode, and Widhe, *Z. phys. Chem.*, 1927, *A*, **130**, 154; Eastham and Latremouille, *Canad. J. Chem.*, 1952, **30**, 169; Nichols and Ingram, *J. Amer. Chem. Soc.*, 1955, **77**, 6547; Petty and Nichols, *ibid.*, 1954, **76**, 4385.

of epoxides containing aryl residues. The reactions of epoxides with nucleophiles have usually been followed either by physical methods (*e.g.*, dilatometry or polarimetry) [5] or by adding a known excess of a reagent for epoxide (*e.g.*, hydrogen chloride or sodium thiosulphate) and determining the excess of this reagent. We have found none of these methods to be entirely satisfactory and we have developed a method for determining the *tertiary* amine produced, namely, by potentiometric titration with perchloric acid in a non-aqueous medium after acetylation of all the secondary amine (see Experimental section). This appears to be the first time these reactions have been followed by direct determination of the product.

The mechanism of epoxide–amine reactions has been shown by previous work often to be a simple S_N2 displacement of oxygen by amine, followed by a rapid proton-transfer (no doubt *via* the hydroxylic solvent):



This simple kinetic picture is, however, complicated by two factors. First, the amine may attack either of the two epoxide-ring carbon atoms to give an amino secondary alcohol or an amino primary alcohol. These two routes are usually referred to as " normal " and " abnormal " ring-opening, respectively:



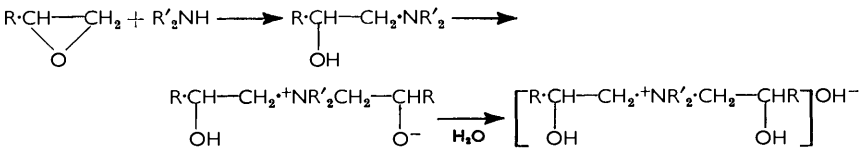
Most of the reactions between epoxides and nucleophiles under basic or neutral conditions give entirely or predominantly the normal isomer. However, there are many cases where no product analysis has been carried out and, even where this has been done, the methods used often leave much to be desired. It is, therefore, not surprising that the position is confused and that there are conflicting reports in the literature.[6] If both reactions occur, the observed second-order rate constant will be the sum of the individual rate constants k_1 and k_2, and the ratio of k_1 to k_2 will be determined by the product ratio. We have investigated the product ratio in three cases (piperidine with each of the three epoxides) by comparing the infrared spectrum of the product with that of each pure isomer. For this purpose the products obtained at 60° (the highest temperature used in the kinetic work) were chosen since it is likely that formation of the abnormal products will be more significant at higher temperatures. (The energy of activation will probably be higher for the formation of the abnormal isomers because of increased steric compression in the transition state.) With 1 : 2-epoxyethylbenzene each product was synthesised by an unambiguous route. With the other two epoxides the abnormal product was synthesised unambiguously, and the normal product by the reaction of the epoxide with piperidine, followed by crystallisation to constant melting point. In the cases of 1 : 2-epoxy-3-phenylpropane and 1 : 2-epoxy-3-phenoxypropane the spectrum of the product was identical with that of the normal isomer. In the case of 1 : 2-epoxyethylbenzene it is just possible to discern the " abnormal " peaks at 945 and 1022 cm.$^{-1}$ in the spectrum of the product; we estimate that these correspond to about 4% of abnormal isomer; since this is such a small amount and is likely to be even less at lower temperatures we have ignored it in kinetic calculations.

As the proportion of abnormal isomer will almost certainly decrease as the steric

[5] Andersson *et al.*, ref. 3.
[6] Swern, Billen, and Knight, *J. Amer. Chem. Soc.*, 1949, **71**, 1152; Hayes, *ibid.*, 1950, **72**, 3321.

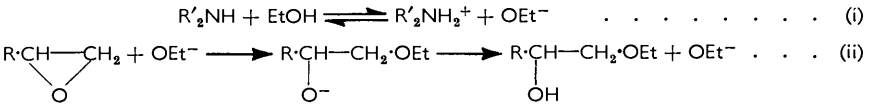
requirements of the reagent increase, and as our other reagents are at least as bulky as piperidine, we assume that all our reactions give entirely, or almost entirely, normal product. It is noteworthy that we could not separate the isomeric piperidino-compounds related to 1 : 2-epoxyethylbenzene either by gas-chromatography (using Silicone grease on Celite) or by paper chromatography (using several different solvent mixtures for development).

The second complication is due to the possibility of consecutive reactions. This is because the product of the reaction of a secondary amine with an epoxide contains a tertiary amino-group and may, therefore, react with further epoxide:



Since our method of analysis does not distinguish between a tertiary amine and a quaternary ammonium hydroxide, we have investigated this possibility in the following manner: 1 : 2-epoxyethylbenzene was allowed to react with an excess of piperidine, and a titration at " infinite " time (at least thirty times the half-life) carried out. This must correspond to the amount of tertiary (and quaternary) base present and, if no quaternary ammonium hydroxide is formed, also to the amount of epoxide present initially. If, however, quaternary hydroxide was formed, more than one mole of epoxide would be consumed per mole of titratable base (tertiary plus quaternary) formed and the " infinity " titration would correspond to less than the initial number of moles of epoxide. In fact, we found no quaternary hydroxide to be formed.

A final complication in our system is the possibility of ethanolysis of the amines, followed by reaction of the ethoxide ion formed with the epoxide:



The incursion of this reaction will be greatest with amines which are strong enough bases to produce ethoxide ions by reaction (i), but which are sufficiently sterically encumbered for their direct reaction with epoxide to be slow. In our system the amine most likely to produce this effect is 2-methylpiperidine. We have therefore examined the product from the reaction of 2-methylpiperidine and 1 : 2-epoxyethylbenzene by gas chromatography, but can find no evidence of 2-ethoxy-1-phenylethanol (less than 1% of the total product). Since this ether is absent in this case it is reasonable to assume it to be absent in the other cases also, and hence that reactions (i) and (ii) are probably unimportant in the systems we have studied. The reaction with ethoxide ion cannot be appreciable because it would be a first-order reaction (not consuming amine or ethoxide) and would be incompatible with our observed second-order kinetics.

Experimental

Materials.—1 : 2-Epoxyethylbenzene and 1 : 2-epoxy-3-phenoxypropane (from Eastman Kodak Ltd.) were fractionated to constant refractive index through a 60 × 1·5 cm. column packed with Fenske helices, in nitrogen. The pure materials had b. p. 79·5—80°/18 mm., n_D^{25} 1·5334, and b. p. 78°/0·9 mm., n_D^{15} 1·5336, respectively. 1 : 2-Epoxy-3-phenylpropane was prepared by the method of Fourneau and Tiffeneau [7] and, when fractionated to constant refractive index as above, had b. p. 92—93°/10 mm., n_D^{20} 1·5262.

Piperidine (from Robinson Bros., Ltd., free from pyridine and tetrahydropyridine), morpholine, and 2-methylpiperidine (from Hopkin and Williams, Ltd.) were dried (NaOH, and then

[7] Fourneau and Tiffeneau, *Bull. Soc. chim. France*, 1907, **1**, 1226.

Na) and fractionated to constant refractive index. The pure materials had b. p. 105·5—105·6°/760 mm., n_D^{20} 1·4527; b. p. 129·0—129·5°/775 mm., n_D^{25} 1·4525; and b. p. 118°/750 mm., $n_D^{18·5}$ 1·4480, respectively. Diethanolamine (from British Drug Houses, Ltd.) was fractionated twice, the middle fraction being collected each time, and finally fractionally frozen, giving a product of m. p. 28° (lit.,[8] 28°). 3- and 4-Methylpiperidine (from Hopkin and Williams, Ltd.) were purified through their hydrochlorides which had m. p. 172° (lit.,[9] 171—172°) and 189° (lit.,[10] 186—189·5°) respectively. The free bases were then fractionated and had b. p. 125°/763 mm., n_D^{25} 1·4448, and b. p. 124·5°/755 mm., n_D^{25} 1·4430, respectively.

Ethanol was dried by Lund and Bjerrum's method.[11] The water content was determined by Karl Fischer titration to a conductimetric end-point, and adjusted to 0·20% w/w by addition of distilled water.

Rate Measurements.—Epoxide (~0·01 mole) was weighed into a 100 ml. graduated flask, and about 70 ml. of 99·8% ethanol were added. The flask was placed in the thermostat and at zero time the amine, in approximately equivalent amount and previously weighed into a narrow-necked flask, was added together with 99·8% ethanol to bring the volume to the mark. Aliquot parts (5 ml.) were run at appropriate intervals into a mixture of acetic anhydride (15 ml.) and acetic acid (5 ml.). The mixture was usually set aside for 2 hr. (at least 4 hr. in the case of 2-methylpiperidine): the reaction was immediately quenched thereby and the secondary amine quantitatively acetylated after 2 or 4 hr. The tertiary amine produced in the reaction, unaffected by the above treatment, was then determined by titration against perchloric acid in glacial acetic acid to a potentiometric end-point. The acetylated secondary amine is too feebly basic to affect the titration. For greater speed and accuracy the E.M.F. of the titration cell, containing silver–silver chloride and glass electrodes, was amplified by means of a valve voltmeter and read directly on a sensitive galvanometer. The end-point is then given by the single drop of perchloric acid added which causes the greatest deflection on the galvanometer. In this way a titration can be accomplished in 2—3 min., with an accuracy of 0·01 ml. of reagent added.

Synthesis of Products.—*1-Phenyl-2-piperidinoethanol.* 1-Phenyl-2-piperidinoethanol, $C_5H_{10}N·CH_2·CHPh·OH$, previously prepared from phenacylpiperidine, $C_5H_{10}N·CH_2·COPh$, by reduction with sodium and ethanol,[12] has been prepared by us by heating phenacylpiperidine (8 g., 0·04 mole) in propan-2-ol (30 g.) containing aluminium *iso*propoxide (15·5 g., 0·08 mole) for 4 hr., allowing the acetone formed to distil off. The excess of propan-2-ol was removed *in vacuo* and the base extracted with ether. 1-Phenyl-2-piperidinoethanol was obtained from the ether as prisms, m. p. 68° (lit.,[13] 68·5—69·5°) (Found: C, 76·2; H, 9·3; N, 6·5. Calc. for $C_{13}H_{19}ON$: C, 76·0; H, 9·3; N, 6·8%) [picrate, m. p. 137° (lit.,[13] 137·5°); methiodide, m. p. 137° (lit.,[12] 136—137°)]. It was identical with that prepared by heating 1 : 2-epoxyethylbenzene (10 g., 0·084 mole) with piperidine (8·8 g., 0·1 mole) in ethanol at 50° for 48 hr. After removal of solvent and excess of piperidine *in vacuo*, the product was crystallised from ethanol until it melted sharply at 69·5° (mixed m. p. 69°).

2-Phenyl-2-piperidinoethanol. Methyl piperidinophenylacetate, $C_5H_{10}N·CHPh·CO_2Me$, prepared by Klosa's method,[14] gave a *methiodide* (needles from ethanol), m. p. 151·5° (Found: C, 48·2; H, 6·0; I, 33·4. $C_{15}H_{22}O_2NI$ requires C, 48·0; H, 5·9; I, 33·8%). The ester-amine (13·2 g., 0·053 mole) was added in dry ether (20 ml.) during 1 hr. to a slurry of lithium aluminium hydride (3·4 g., 0·09 mole) in boiling ether (500 ml.). The solution was heated under reflux for a further 4 hr., after which water (100 ml.) was added. After filtration the ethereal layer was separated and dried (Na_2SO_4) and the ether removed. Distillation *in vacuo* of the residue gave *2-phenyl-2-piperidinoethanol*, b. p. 102—104°/0·002 mm., n_D^{25} 1·5434 (9·5 g., 82%) (Found: C, 76·5; H, 9·4. $C_{13}H_{19}ON$ requires: C, 76·0; H, 9·3%) [*picrate*, m. p. 140° (from slightly ethanolic water) (Found: C, 53·1; H, 5·2. $C_{19}H_{22}O_3N_4$ requires C, 52·5; H, 5·1%)]. Although this has been mentioned before [15] no method of preparation or physical constants were given.

[8] Knorr, *Ber.*, 1897, **30**, 915.
[9] Franke and Kohn, *Monatsh.*, 1902, **23**, 877.
[10] Paden and Adkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2495.
[11] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.
[12] Rabe and Scheider, *Annalen*, 1909, **365**, 380.
[13] Krönke, *Ber.*, 1934, **67**, 660.
[14] Klosa, *Arch. Pharm.*, 1952, **285**, 332.
[15] Thomson, Walker, and Dunn, *J. Amer. Pharm. Soc.*, 1953, **42**, 647.

1-*Phenyl*-3-*piperidinopropan*-2-*ol*. This compound, $C_5H_{10}N{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2Ph$, prepared from 1 : 2-epoxy-3-phenylpropane by the method of Fourneau, Tréfouel, and Tréfouel,[16] crystallised from ethanol to m. p. 44·5° (Found: C, 76·5; H, 9·3. Calc. for $C_{14}H_{21}ON$: C, 76·7; H, 9·6%).

3-*Phenyl*-2-*piperidinopropan*-1-*ol*. α-Bromo-β-phenylpropionic acid,[17] b. p. 128—130°/0·1 mm., crystallised in colourless needles. It (23 g., 0·1 mole) was added to piperidine (60 g., 0·7 mole) in water (100 ml.); the solution was kept at room temperature for 1 hr., then evaporated at 60°/12 mm. The white solid was repeatedly extracted with boiling absolute ethanol until the residue no longer contained bromide ion. The residue, recrystallised from 10% aqueous ethanol, gave **β-*phenyl*-α-*piperidinopropionic acid*** (12·5 g., 61%), m. p. 213—213·5° (Found: C, 71·8; H, 8·0; N, 5·7. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·1; N, 6·0%). The *hydrochloride* obtained by the action of ethanolic hydrogen chloride had m. p. 203° (Found: C, 62·3; H, 7·4; N, 5·5. $C_{14}H_{20}O_2NCl$ requires C, 62·3; H, 7·4; N, 5·2%).

By the Fischer method, this acid (10 g., 0·043 mole; dried at 100°/12 mm.), gave a glass which consisted of the hydrochlorides of the acid and its ethyl ester. The glass was dissolved in water and cooled to $<10°$, and ether added. 0·1N-Sodium hydroxide was slowly added until the solution was just alkaline. The ethereal layer was removed and the aqueous solution shaken twice more with ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated at 50°/12 mm.; there remained only ethyl β-phenyl-α-piperidinopropionate whose methiodide formed prisms (from ethanol), m. p. 150°. Unchanged amino-acid was recovered from the aqueous solution remaining after ether-extraction and recycled.

The ester (4 g., 0·015 mole), in dry tetrahydrofuran (20 ml.), was added during 2 hr. to a stirred slurry of lithium aluminium hydride (1·25 g., 0·03 mole) in tetrahydrofuran (50 ml.) at room temperature, and the mixture heated to 40° and stirred for a further hour. Water (50 ml.) was added, followed by ether (100 ml.). The liquid was filtered and the ethereal layer separated, dried (Na_2SO_4), and evaporated at 40°/12 mm. Crystallisation of the residue from light petroleum (b. p. 40—60°) yielded **3-*phenyl*-2-*piperidinopropan*-1-*ol*** as prisms, m. p. 48—48·5° (Found: C, 76·8; H, 9·6; N, 6·2. $C_{14}H_{21}ON$ requires C, 76·8; H, 9·6; N, 6·4%) [*methiodide* (from ethanol), m. p. 153—153·5° (Found: C, 50·2; H, 6·7; I, 35·2. $C_{15}H_{24}ONI$ requires C, 49·8; H, 6·7; I, 35·1%); 2 : 4 : 6-*trinitrobenzenesulphonate*, needles (from ethanol), m. p. 117° (Found: C, 46·2; H, 4·8; N, 10·5. $C_{20}H_{24}O_{10}N_4S$ requires C, 46·8; H, 4·7; N, 10·9%)].

1-*Phenoxy*-3-*piperidinopropan*-2-*ol*. This compound, $C_5H_{10}N{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}OPh$, prepared by heating 1 : 2-epoxy-3-phenoxypropane and piperidine in ethanol at 50° (cf. Bradley, Forrest, and Stephenson [18]), formed needles (from ethanol), m. p. 54° (Found: C, 70·7; H, 9·0; N, 6·0. Calc. for $C_{14}H_{21}O_2N$: C, 71·4; H, 9·0; N, 6·0%).

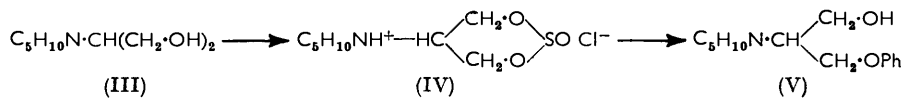
3-*Phenoxy*-2-*piperidinopropan*-1-*ol*. Diethyl piperidinomalonate, $C_5H_{10}N{\cdot}CH(CO_2Et)_2$, prepared according to Jones and Wilson's method [19] for diethyl dimethylaminomalonate, had b. p. 121—122°/0·25 mm., n_D^{19} 1·4570, and gave a 2 : 4 : 6-*trinitrobenzenesulphonate*, m. p. 154—155° (Found: C, 41·1; H, 4·6. $C_{18}H_{24}O_{13}N_4S$ requires C, 40·3; H, 4·5%). The ester (24·3 g., 0·1 mole) in ether (30 ml.) was added during 1 hr. to lithium aluminium hydride (7·6 g., 0·2 mole) in boiling ether (100 ml.). The mixture was boiled for a further 6 hr., treated with water (50 ml.), and filtered. The ethereal layer was separated and the aqueous layer shaken with two further portions of ether. The combined ethereal extracts were dried (Na_2SO_4), the ether was removed, and the residue distilled; 2-piperidinopropane-1 : 3-diol (III) (4·5 g., 30%) had b. p. 156—160°/13 mm.; its 2 : 4 : 6-*trinitrobenzenesulphonate* formed prisms (from water), m. p. 184·5° (Found: C, 37·2; H, 4·2. $C_{14}H_{20}O_{11}N_4S$ requires C, 37·2; H, 4·4%).

The diol (4 g., 0·025 mole) was treated in benzene (30 ml.) with thionyl chloride (3 g., 0·025 mole) dropwise. The precipitate crystallised when the solution was boiled for 30 min. and recrystallised from 10% aqueous ethanol as plates of *dihydro*-5-*piperidino*-1 : 3 : 2-*dioxathiin*-2-*oxide hydrochloride* (IV), m. p. 148° (Found: C, 40·0; H, 6·5; Cl, 15·0. $C_8H_{16}O_3NClS$ requires: C, 39·8; H, 6·6; Cl, 14·7%).

Sodium (1·58 g., 0·025 g.-atom), dissolved in phenol (30 ml.), was added to the preceding salt (3 g., 0·0125 mole) in phenol (20 ml.) and the whole kept at 60° for 12 hr. The solution was

[16] Fourneau, Tréfouel, and Tréfouel, *Bull. Soc. chim. France*, 1928, **43**, 454.
[17] Fischer, *Ber.*, 1904, **37**, 3062; Fischer and Carl, *Ber.*, 1906, **39**, 4002.
[18] Bradley, Forrest, and Stephenson, *J.*, 1951, 2877.
[19] Jones and Wilson, *J.*, 1949, 547.

made just acid with dilute hydrochloric acid, and phenol was removed by ether (3 × 100 ml.). The aqueous solution was then made just alkaline by 0·2N-sodium hydroxide, and the precipitated base extracted with ether. Removal of the ether and distillation gave 3-phenoxy-2-piperidinopropan-1-ol (V), b. p. 120°/0·038 mm. [2 : 4 : 6-*trinitrobenzenesulphonate*,



(III) (IV) (V)

prisms (from water), m. p. 157° (Found: C, 45·4; H, 4·3. $C_{20}H_{24}O_{11}N_4S$ requires C, 45·4; H, 4·5%)].

2-Ethoxy-1-phenylethanol. 1 : 2-Epoxyethylbenzene (25 g.) was added to a solution from sodium (2 g.) in ethanol (100 ml.) and kept at 60° for 24 hr. The ethanol was removed *in vacuo*, and the residue dissolved in ether and washed with dilute sulphuric acid, sodium carbonate solution, and water. The ethereal solution was dried (Na_2SO_4), the ether removed, and the residue distilled to give 2-ethoxy-1-phenylethanol, b. p. 97—98°/0·6 mm. Gas-chromatography of this product (on Silicone resin supported on Celite) showed two closely spaced peaks, the heights and distances from the origin of which indicated that the product consisted of two components present in a ratio of ~5 : 1. These two are probably 2-ethoxy-1- and -2-phenylethanol respectively, although we have not proved this since it is not important for our purpose.

Product Analysis.—Infrared analysis. For the reaction between 1 : 2-epoxy-3-phenylpropane and piperidine infrared spectra were determined for (*a*) the actual reaction product (obtained by allowing the reaction in ethanol to go to completion and removing the ethanol and excess of piperidine *in vacuo*), (*b*) the " normal " product, 1-phenyl-3-piperidinopropan-2-ol, and (*c*) the " abnormal " product, 3-phenyl-2-piperidinopropan-1-ol. Analogous determinations were carried out for the reaction between 1 : 2-epoxy-3-phenoxypropane and piperidine, and for that between 1 : 2-epoxyethylbenzene and piperidine. All the measurements were made on carbon tetrachloride solutions with a Unicam S.P. 100 double-beam, infrared spectrophotometer.

Ethanolysis investigation. The reaction between 1 : 2-epoxyethylbenzene and 2-methylpiperidine in ethanol was allowed to go to completion and the product, after removal of ethanol and excess of amine *in vacuo*, submitted to gas-chromatography on a column of Silicone resin supported on Celite. No peak was observed at the retention time corresponding to the product of reaction of 1 : 2-epoxyethylbenzene and ethanolic sodium ethoxide (see above). The 1 : 2-epoxyethylbenzene–2-methylpiperidine product containing 3% of added ethanolysis product was also submitted to gas-chromatography: the peak due to the ethanolysis product was clearly visible. We estimate that less than 1% of ethanolysis product in our product would have been detectable.

Results

The reaction between 1 : 2-epoxyethylbenzene and piperidine at 54·75° was carried out at three different initial concentrations, and, by application of the differential method of determining reaction orders,[20] was shown to be of the first order with respect both to the epoxide and to the amine (orders 1·00 and 0·99 respectively). This was assumed to hold for the other cases also, as they all obeyed the second-order rate law:

$$dx/dt = k_2(a - x)(b - x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

giving

$$t = \frac{2{\cdot}303}{k_2(a - b)} \log_{10} \frac{b}{a} + \frac{2{\cdot}303}{k_2(a - b)} \log_{10} \frac{a - x}{b - x}$$

where a is the initial concentration of epoxide and b is the initial concentration of amine. Values of the second-order rate constant, k_2, were determined graphically by plotting $\log_{10}[(a - x)/(b - x)]$ against t. The slope of the line is equal to $2{\cdot}303/[k_2(a - b)]$. The points all fell on good straight lines. A good proportion of the reaction was always followed, usually 10—70%, and all the runs were done in duplicate, the values of k_2 generally agreeing to better than 1%. Titrations at " infinite " time (at least thirty times the half-life) were

[20] Laidler, " Chemical Kinetics," McGraw-Hill, New York, 1950, p. 14.

TABLE 1. *Measured rate constants,* 10^4k_2 (*l. mole*$^{-1}$ *sec.*$^{-1}$).

(Figures in parentheses are temperatures in °C.)

	Piperidine	Morpholine	Diethanolamine
1 : 2-Epoxyethylbenzene	0·170 (0·00°)	0·446 (19·88°)	0·0787 (19·20°)
	1·50 (24·88)	1·47 (34·84)	0·414 (38·80)
	7·00 (44·00)	4·14 (49·28)	1·93 (60·03)
	14·8 (54·75)		
1 : 2-Epoxy-3-phenylpropane	1·54 (20·43)	1·06 (29·58)	0·129 (19·20)
	8·96 (44·22)	2·84 (44·35)	0·577 (38·84)
	16·90 (54·26)	7·18 (58·78)	2·27 (60·10)
1 : 2-Epoxy-3-phenoxypropane	3·05 (15·18)	1·31 (15·73)	0·488 (19·20)
	10·0 (29·67)	5·30 (34·41)	2·27 (38·75)
	27·7 (44·10)	20·14 (54·55)	9·43 (60·34)

	2-Methylpiperidine	3-Methylpiperidine	4-Methylpiperidine
1 : 2-Epoxyethylbenzene	0·236 (24·70)	1·67 (24·65)	1·60 (24·55)
	0·863 (39·75)	5·49 (39·80)	5·21 (39·75)
	3·95 (59·75)	21·4 (59·70)	20·4 (59·70)

TABLE 2. *Rate constants interpolated to* 35°, *and Arrhenius parameters.*

(k_2 and A in l. mole^{-1} sec.$^{-1}$; E in kcal. mole^{-1}.)

	Piperidine			Morpholine			Diethanolamine		
	10^4k_2 (35°)	E	$\log_{10}A$	10^4k_2 (35°)	E	$\log_{10}A$	10^4k_2 (35°)	E	$\log_{10}A$
1 : 2-Epoxyethylbenzene	3·43	14·42	6·76	1·47	14·40	6·38	0·271	15·59	6·53
1 : 2-Epoxy-3-phenylpropane	4·63	13·81	6·45	1·54	12·97	5·39	0·436	13·60	5·27
1 : 2-Epoxy-3-phenoxypropane	14·62	13·87	7·09	5·56	13·30	6·17	1·70	14·00	6·15

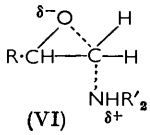
	2-Methylpiperidine			3-Methylpiperidine			4-Methylpiperidine		
1 : 2-Epoxyethylbenzene	0·579	15·64	6·86	3·80	14·45	6·83	3·67	14·25	6·67

carried out in several cases and gave values of 99·6—100·8% reaction. This shows that the reactions are irreversible and free from side-reactions.

The results are summarised in Table 1, and values of k_2 interpolated to 35°, together with the Arrhenius parameters are collected in Table 2.

DISCUSSION

Since the reactions all obey the second-order rate law and have been shown to be free from various possible complications, it is reasonable to assume that the mechanism is S_N2, involving attack of the nucleophile on the methylene group of the epoxide ring with simultaneous displacement of the ring-oxygen atom. Thus the transition state may be represented as (VI). The carbon–oxygen partial bond will be weaker than is usual in S_N2 transition states because of incomplete overlap of atomic orbitals. However, the same bond is also weaker than a normal carbon–oxygen bond in the initial state for the same reason and, to a first approximation therefore, this factor will not affect the rates. The charge separation involved in forming the transition state implies that the reactions should be strongly favoured by a change to a more powerfully solvating solvent and preliminary experiments showed that the reaction between 1 : 2-epoxyethylbenzene and piperidine was much slower in dioxan (a less strongly solvating solvent than ethanol) than in ethanol.

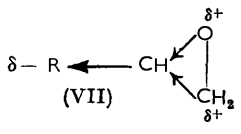


(VI)

The effect of the substituent group, R, on the rates might be expected to be different from the effect of substituent groups in S_N2 reactions of open-chain compounds. As Hinshelwood, Laidler, and Timm have shown,[21] the activation energy in such reactions can be considered approximately as being composed of two factors: (*a*) the repulsion

[21] Hinshelwood, Laidler, and Timm, *J.*, 1938, 848.

energy (energy necessary to bring up the reagent from infinity to its transition-state distance), and (*b*) the bond-stretching energy (energy necessary to stretch the C–O bond from its initial to its transition-state length). In S_N2 reactions of open-chain compounds (*e.g.*, alkyl halides) the polar effect of a substituent group on these two energy factors is in opposite directions. Thus an electron-withdrawing group will, by virtue of increasing the positive charge on the carbon atom attacked, lower the repulsion energy but increase the bond-stretching energy. The total effect is, therefore, ambiguous and the experimental results are difficult to interpret because of the simultaneous operation of a steric effect of the substituent group. In the reactions studied here, however, the polar effect of the substituent is unambiguous. An electron-withdrawing group will increase the positive charge on the carbon atom being attacked and therefore lower the repulsion energy. This increased positive charge will not greatly affect the bond-stretching energy *because the positive charge on the oxygen end of the* C–O *bond will be increased by a similar amount.* Thus if R is an electron-withdrawing group the charge situation will be as in (VII). Hence an electron-withdrawing group should, by its polar effect, facilitate the reaction. That this is so can be seen by comparing the reactions of 1 : 2-epoxy-3-phenoxypropane with those of 1 : 2-epoxy-3-phenylpropane, the phenoxymethyl group being more electron-withdrawing than benzyl and increasing the rate by a factor of 3—4.



(VII)

Since an electron-withdrawing group will increase the positive charge on the CH carbon more than that on the CH_2 carbon, it might have been expected that attack would have taken place at the former (although in this case the total effect of the substituent group on repulsion energy and bond-stretching energy would again be ambiguous). That this does not happen is no doubt due to the primary steric effects of the bulky substituent groups used here, together with the fact that the amines are all secondary and themselves, therefore, capable of producing appreciable primary steric effects.

An approximate analysis of the effect of substituent groups can be made in terms of Taft's polar and steric substituent constants σ^* and E_s.[22] Taft deduced the equation:

$$\log_{10} k - \log_{10} k_0 = \rho\sigma^* + E_s$$

where k_0 = rate of reaction of the parent compound, k = rate of reaction of a substituted derivative, σ^* = polar substituent constant, dependent only on the nature of the substituent, E_s = steric substituent constant, and ρ = reaction constant, measuring the susceptibility of the reaction to the polar effect of substituent groups. For alkaline ester hydrolysis Taft found $\rho = 2{\cdot}48$. If we assume that steric as well as polar effects of groups conform to a linear free-energy relation Taft's equation can be rewritten as:

$$\log_{10} k - \log_{10} k_0 = \rho\sigma^* + \rho' E_s$$

where ρ' is now a reaction constant measuring the susceptibility of the reaction to steric effects of substituent groups. Taking the reaction of 1 : 2-epoxypropane as standard and regarding the oxides used here as derived from 1 : 2-epoxypropane by replacement of the methyl group by phenyl, benzyl, and phenoxymethyl respectively, we may insert the values of σ^* and E_s given by Taft for these groups in the above equation, together with the values of k for the reactions with piperidine. This gives three simultaneous equations with three unknowns (k_0, ρ, and ρ') and there is, therefore, a unique solution. It must be emphasised that, because of this, our results do not in any way confirm Taft's equation. We assume the equation to hold and use the values of ρ and ρ' to give a measure of the susceptibility of the reaction to polar and steric effects of substituents, respectively. Similar calculations for the reactions with morpholine and with diethanolamine give values of k_0, ρ, and ρ' for these reactions also and the results are collected in Table 3.

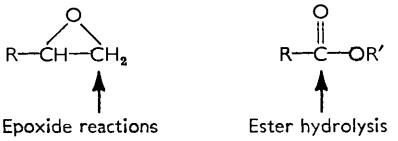
[22] Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 2729, 3120; 1953, **75**, 4231, 4534, 4538.

TABLE 3. *Reactions of epoxides in 99·8% ethanol at 35°*

(k_0 is the rate constant for the reaction of the parent 1 : 2-epoxypropane.)

Reagent	ρ	ρ'	$10^4 k_0$ (l. mole^{-1} sec.$^{-1}$)
Piperidine	0·8	0·2	3
Morpholine	0·9	0·2	1
Diethanolamine	0·9	0·2	0·3

Because of the frequent occurrence of deviations from linear free-energy relations, and because our measurements cover only three substituent groups, the results in Table 3 are subject to considerable uncertainty. Nevertheless it seems worthwhile to compare them with those found by Taft for the alkaline hydrolysis of esters ($\rho = 2{\cdot}48$, $\rho' = 1$). It is significant that the values of ρ for our reactions are about three times smaller than those for ester hydrolysis, where the substituent group is one carbon atom nearer the position of attack:



The values of ρ' for the reactions studied here are about five times smaller than those for alkaline ester hydrolysis, even though the amine reagents are all considerably more bulky than the hydroxide-ion reagent in ester hydrolysis. If the reagents were comparable in size to the hydroxide ion the difference in ρ would no doubt be even greater. These results emphasise the fact that steric effects of groups often fall off more rapidly than polar effects as the substituent group is moved further from the point of attack.

The effect of varying the amine on the rates of reaction with a given epoxide has been most fully investigated for 1 : 2-epoxyethylbenzene, which has been allowed to react with six secondary amines. The rates of reaction at 25° in ethanol are compared with the basic strengths of the amines at 25° in water in Table 4. A plot of pK_a against log k is approximately linear for piperidine, morpholine, and 3- and 4-methylpiperidine. The points for

TABLE 4. *Reactions with 1 : 2-epoxyethylbenzene in ethanol at 25°.*

Amine	log k	pK_a (in water at 25°)
Piperidine	−3·824	11·13 [23]
Morpholine	−4·177	8·38 [24]
Diethanolamine	−4·886	8·88 [23]
2-Methylpiperidine	−4·625	10·87 [25] (11·15 [26], 10·98 [23])
3-Methylpiperidine	−3·775	10·92 [25] (11·14 [26])
4-Methylpiperidine	−3·796	10·89 [25]

diethanolamine and 2-methylpiperidine lie off the line, so that both these amines react more slowly than their basic strengths would suggest: this in undoubtedly due to primary steric effects, which must be of approximately the same magnitude for the reactions of these two amines since the relevant points lie an almost equal distance from the line. The introduction of a methyl group into the 3- or the 4-position of piperidine should not alter the steric requirements of the reagent and the order of rates found, 3-methylpiperidine > 4-methylpiperidine > piperidine, is what would be expected on the basis of the inductive effect of the methyl group.

The Arrhenius parameters for all the reactions studied are collected in Table 2. The energies of activation all lie within the range 13·0—14·5 kcal./mole except for the reactions of 1 : 2-epoxyethylbenzene with diethanolamine and with 2-methylpiperidine, which both have energies of 15·6 kcal./mole. The last two are the reactions of the most bulky epoxide

[23] Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3479.
[24] Ingram and Luder, *ibid.*, 1942, **64**, 3043.
[25] N. S. Isaacs, unpublished work.
[26] Horowitz and Rila, *J. Amer. Chem. Soc.*, 1958, **80**, 433.

with the two most bulky amines and the high energies are clearly due to primary steric effects. The values of $\log_{10} A$, *i.e.*, the entropy of activation factor, vary within the range 5·27—7·09 and, because of this, it is evident that the differences in energy of activation involve changes of kinetic energy as well as potential energy and cannot, therefore, be correlated directly with structural changes. It is more rewarding in these reactions to consider structural variations in terms of changes in free energy of activation at 25° (as measured by log k for 25°) than in terms of changes in energy of activation. This has already been done in the above application of the Taft equation.

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