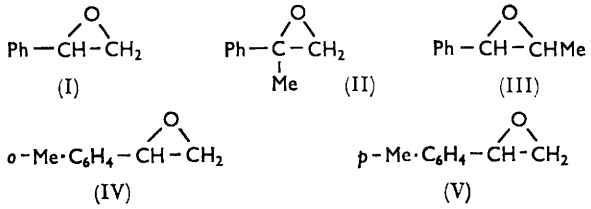
The Mechanism of Epoxide Reactions. Part XI.[1] The Reactions of Benzylamine with *o*-(1,2-Epoxyethyl)toluene, 1,2-Epoxy-2-phenylpropane, and *trans*-1,2-Epoxy-1-phenylpropane in Ethanol

By R. E. Parker and B. W. Rockett

Overall rate constants have been determined for the reactions of 1,2-epoxy-2-phenylpropane, *trans*-1,2-epoxy-1-phenylpropane, and *o*-(1,2-epoxyethyl)toluene with benzylamine in 99·8% ethanol at three temperatures. Product analyses have been carried out and rate constants and Arrhenius parameters calculated for the normal and abnormal reactions in each case.

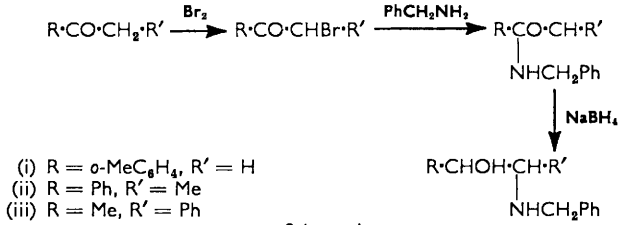
The results are discussed in terms of the electronic and steric effects of the substituent methyl group.

EARLIER Papers in this Series have reported the effects of *meta* and *para* substituent groups [2-4] and of protic and aprotic solvents [5] on the rates of the normal and abnormal ring-opening reactions of 1,2-epoxyethylbenzene (I) with benzylamine. The present Paper describes the effect of introducing a methyl group into the *alpha-*, *beta-*, or *ortho*-position of compound (I) on the rates of its normal and abnormal reactions with benzylamine in ethanol. No measurements of the rates of any reactions of these three epoxides appear to have been made, although some determinations of isomer yields have been carried out. Usually, however, the products were isolated under conditions which may have led to total or partial loss of one isomer and subsequent misleading results. Thus, reaction of 1,2-epoxy-2-phenylpropane (II) with an alkaline solution of hydrogen sulphide gave a 37% yield of 2-hydroxy-2-phenylpropane-1-thiol (the normal product).[6] *trans*-1,2-Epoxy-

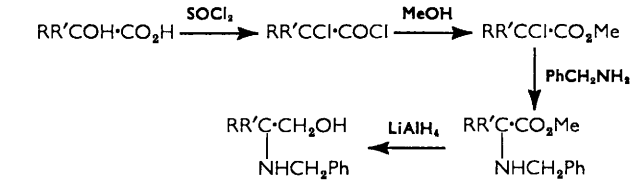


1-phenylpropane (III) with ethylenimine gave the "normal" isomer (*i.e.*, corresponding to attack on the carbon atom remote from the benzene ring) in 38% yield,[7] but with methylamine it gave 17% of the "normal" isomer and 65% of the "abnormal" isomer.[8]

In the present work a four-fold excess of benzylamine over epoxide was used in order to suppress the further reaction of the secondary-amine products with more epoxide.[2] Under these conditions the initial 55% of the first reaction is free from interference by the second reaction. The reactions were followed by measurements of the concentration of benzylamine, estimated spectrophotometrically as its anil with salicylaldehyde.[2] The overall rate constants (k_2) thus obtained were divided into their normal (k_N) and abnormal (k_A) components by means of an infrared (i.r.) method of product analysis.[9] For this purpose the products were unambiguously synthesised as outlined in Schemes A(i) and A(ii) (normal isomers), and A(iii), B(i), and B(ii) (abnormal isomers). The normal product from the reaction of compound (II) (a tertiary alcohol) was not synthesised unambiguously, but material isolated from the reaction of the epoxide with benzylamine was shown to be different from the unambiguously synthesised abnormal isomer. Although the normal product is a tertiary alcohol, it showed no tendency to decompose on distillation under reduced pressure.



Scheme A



Scheme B

It should be noted that in the case of the reactions of compound (III) the terms normal and abnormal have no significance, since each carbon atom of the epoxide ring is equally substituted. For purposes of comparison, however, the term normal is here retained for reaction at the carbon atom remote from the benzene ring and the term abnormal for reaction at the carbon atom adjacent to the benzene ring.

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Ethanol (99·8% w/w) was used as solvent as in earlier investigations in this series.[2,3,9] No examinations for solvolysis were made, since it has been shown previously that solvolysis does not occur in systems very similar to the present ones.[9]

EXPERIMENTAL

Benzylamine and salicylaldehyde were purified as described in Part III;[2] ethanol was purified and the water content adjusted to 0·02% w/w as previously described.[2]

o-(1,2-*Epoxyethyl*)*toluene* (IV).—*o*-Tolualdehyde, prepared from α-bromo-*o*-xylene[10] by a modification of the Sommelet reaction,[11,12] was treated with methylmagnesium bromide at −5° to give 1-(*o*-tolyl)ethanol as a colourless oil, b. p. 106—110°/16 mm. (lit.,[13] 108°/20 mm.). The alcohol was dehydrated to the corresponding styrene by a modification of Eisenlohr's method.[14] 1-(*o*-Tolyl)ethanol (0·26 mole) was distilled at 100 mm. pressure with potassium pyrosulphate (0·05 mole) and a trace of hydroquinone. After collection of the aqueous fore-run the pressure was reduced to 15 mm. and the rate of heating increased so that the styrene distilled as quickly as possible. Fractionation of the product from a trace of hydroquinone gave *o*-methylstyrene, b. p. 103—105°/75 mm. (lit.,[14] 170—174°). Unlike Emde,[13] we observed no polymerisation during this fractionation. The styrene was converted into 2-bromo-1-(*o*-tolyl)ethanol essentially as described by Read and Reid[15] for the preparation of 2-bromo-1-phenyl ethanol, and the bromohydrin was heated under reflux with a well stirred aqueous solution of potassium hydroxide for 10 min.[16] Two fractionations of a dried ($MgSO_4$) ethereal extract through a 20 cm. Fenske column gave o-(1,2-*epoxyethyl*)*toluene* as a colourless oil with a faint epoxide odour, b. p. 89°/10 mm., n_D^{25} 1·5345 (Found: C, 81·0; H, 7·6; O, 11·7. $C_9H_{10}O$ requires C, 80·6; H, 7·5; O, 11·9%).

1,2-*Epoxy*-2-*phenylpropane* (II).—α-Methylstyrene was converted into 1-bromo-2-phenylpropan-2-ol, a pale yellow, lachrimatory liquid, by Read and Reid's method[15] and the bromohydrin (0·55 mole) was stirred with 15% aqueous potassium hydroxide (1·0 mole) for 40 min. at 30°. Distillation of the dried ($MgSO_4$) ethereal extracts and two fractionations of the product through a 20 cm. Fenske column gave compound (II), b. p. 71°/10 mm., n_D^{25} 1·5186 (lit.,[17] b. p. 81°/14 mm., n_D 1·52325).

trans-1,2-*Epoxy*-1-*phenylpropane* (III).—α-Bromopropiophenone, prepared by the low-temperature bromination of propiophenone in dry ether,[18] was obtained as a colourless, lachrimatory liquid which soon darkened on standing. Sodium borohydride (0·08 mole) was added to a freshly prepared solution of α-bromopropiophenone (0·13 mole) in aqueous dioxan (100 ml.) and the mixture was kept overnight at room temperature and then poured into water. Removal of the ether from a dried ($MgSO_4$) extract gave 2-bromo-1-phenylpropan-1-ol as a straw-coloured oil. The bromohydrin was heated under reflux with a 1·5-molar excess of 5% aqueous potassium hydroxide solution for 20 min. with vigorous stirring.[16] Two fractionations of the dried ($MgSO_4$) ethereal extract through a 20 cm. Fenske column gave compound (III), b. p. 83°/12 mm., n_D^{25} 1·5178 (lit.,[19] b. p. 82°/10 mm., n_D^{20} 1·5198).

2-*Benzylamino*-1-(o-*tolyl*)*ethanol*.—*o*-Methylacetophenone, obtained from the reaction of *o*-methylbenzoyl chloride with an excess of dimethylcadmium in dry ether, had b. p. 84°/12 mm. (lit.,[20] 108°/30 mm.) and gave a 2,4-dinitrophenylhydrazone, m. p. 161° (lit.,[21] 160°). The ketone was brominated at 0° in glacial acetic acid[22] and the freshly prepared *o*-methylphenacyl bromide (0·025 mole) added to a solution of benzylamine (0·05 mole) in di-isopropyl ether (10 ml.). The solution was filtered from the immediate precipitate of benzylamine hydrobromide and added to a solution of sodium borohydride (0·03 mole) in aqueous dioxan (5 ml.). After 12 hr. the mixture was acidified and extracted with ether. The aqueous layer was made alkaline and again extracted with ether. Removal of solvent from the latter dried ($MgSO_4$) ethereal extract and crystallisation of the residue from ethanol gave 2-*benzylamino*-1-(o-*tolyl*)*ethanol*, m. p. 86·5—87·5° (Found: C, 79·4; H, 7·8; N, 6·2. $C_{16}H_{19}NO$ requires C, 79·7; H, 7·9; N, 5·8%).

2-*Benzylamino*-2-(o-*tolyl*)*ethanol*.— *o*-Tolualdehyde was converted into its cyanohydrin and thence by hydrolysis with concentrated hydrochloric acid into *o*-methylmandelic acid,[23] m. p. 105—106° (from di-isopropyl ether) (lit.,[24] 95—97°). Thionyl chloride (0·19 mole) containing a few drops of pyridine was added to *o*-methylmandelic acid (0·069 mole) and, after the initial reaction had subsided, the solution was heated on the steam-bath for 1 hr. Hydrogen chloride and excess of thionyl chloride were removed by pumping. The residual α-chloro-*o*-tolylacetyl chloride was poured into stirred methanol (400 ml.) and the mixture maintained at 60° for 12 hr. Removal of methanol and fractionation gave *methyl* α-*chloro*-o-*tolylacetate*, b. p. 82—83°/0·35 mm. (Found: C, 60·5; H, 5·5; Cl, 17·5. $C_{10}H_{11}ClO_2$ requires C, 60·4; H, 5·6; Cl, 17·8%). Benzylamine (0·02 mole) was added to methyl α-chloro-*o*-tolylacetate (0·01 mole) in di-isopropyl ether (20 ml.) and the solution maintained at 60° for 60 hr. After filtration from the theoretical amount of benzylamine hydrochloride the solution was added to a suspension of lithium aluminium hydride in ether. The mixture was heated under reflux for 4 hr. and set aside overnight. Working up in the usual way gave 2-*benzylamino*-2-(o-*tolyl*)*ethanol*, b. p. 160—170°/0·1 mm., m. p. 88·5—89·5° (from cyclohexane) (Found: C, 79·4; H, 7·8; N, 6·0. $C_{16}H_{19}NO$ requires C, 79·7; H, 7·9; N, 5·8%).

1-*Benzylamino*-2-*phenylpropan*-2-*ol*.—A solution of 1,2-epoxy-2-phenylpropane (0·04 mole) and benzylamine (0·16 mole) in ethanol (50 ml.) was maintained at 60° for 12 hr. Removal of ethanol and excess of benzylamine under reduced pressure left a yellow liquid, which was dissolved in dry ether (250 ml.) and treated with dry

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hydrogen chloride. The flocculent white precipitate was collected and crystallised three times from benzene–chloroform to give 1-benzylamino-2-phenylpropan-2-ol hydrochloride as fine needles, m. p. 178—180°. An aqueous solution of the salt was decomposed by excess of sodium hydroxide solution and the free base extracted with ether. Removal of ether from the dried ($MgSO_4$) extract left *1-benzylamino-2-phenylpropan-2-ol* as a colourless oil (Found: C, 79·9; H, 7·7; N, 5·9. $C_{16}H_{19}NO$ requires C, 79·7; H, 7·9; N, 5·8%).

2-Benzylamino-2-phenylpropan-1-ol.— Atrolactic acid (0·03 mole), prepared from acetophenone by Eliel and Freeman's method,[25] was warmed to 30° for 2 hr. with thionyl chloride (0·08 mole) containing a few drops of pyridine. Hydrogen chloride and excess of thionyl chloride were removed by pumping at 30°, and the residual brown liquid was poured into dry, stirred methanol and the solution was set aside for 24 hr. at room temperature. Removal of methanol left crude methyl α-chloro-α-phenylpropionate, which was taken up in di-isopropyl ether (30 ml.). The filtered solution was added to benzylamine (0·06 mole) and maintained at 60° for 4 hr. After removal of benzylamine hydrochloride the solution was reduced with lithium aluminium hydride and worked up in the usual way to give *2-benzylamino-2-phenylpropan-1-ol*, b. p. 130—140°/0·1 mm. (Found: C, 81·1; H, 7·9; N, 6·8. $C_{16}H_{19}NO$ requires C, 79·7; H, 7·9; N, 5·8%). This compound could not be purified further as it decomposed slowly on distillation. A second distillation gave material with an even worse analysis.

2-Benzylamino-1-phenylpropan-1-ol.— α-Bromopropiophenone (see above) was converted into α-benzylaminopropiophenone and thence into 2-benzylamino-1-phenylpropan-1-ol by the methods used for the preparation of 2-benzylamino-1-(*o*-tolyl)ethanol. The product had b. p. 156—160°/0·2 mm. and crystallised from cyclohexane as white needles, m. p. 99·5—100·5° (lit.,[26] 99°).

1-Benzylamino-1-phenylpropan-2-ol.— Bromination of phenylacetone in glacial acetic acid at 0° gave 1-bromo-1-phenylacetone,[22] which was converted into 1-benzylamino-1-phenylacetone and thence into 1-benzylamino-1-phenylpropan-2-ol by the methods used for the preparation of 2-benzylamino-1-(*o*-tolyl)ethanol. The *product* had b. p. 138—144°/0·1 mm. (Found: C, 79·4; H, 7·7; N, 5·9. $C_{16}H_{19}NO$ requires C, 79·7; H, 7·9; N, 5·8%). On long standing (three months) it crystallised and had m. p. 69—70·5° (from cyclohexane).

Rate Measurements.—The reactions were carried out and their rates measured as described in Part III.[2]

Product Analyses.—The analyses of the products were also carried out as described previously,[2] the i.r. spectra of the products, isolated by distillation at 0·1 mm., being compared with those of several synthetic mixtures of the pure isomers.

RESULTS

The measured overall rate constants (k_2) were divided into their normal (k_N) and abnormal (k_A) components by the method previously described [3] and these values are listed in Table 1, together with the isomer proportions. Table 2 records the values of the normal and abnormal rate constants interpolated to 40°, the Arrhenius parameters, and the entropies of activation. Duplicate determinations showed that the error in the measured rate constants is less than ±3%. The errors in the normal and abnormal rate constants, introduced by the product-ratio determinations, vary inversely with the proportion of the relevant isomer and we estimate that the rate constants for all the normal reactions are accurate to ±6% or better, while the abnormal rate constants vary in accuracy from ±6% for the reaction of compound (IV) to ±50% for the reactions of compounds (II) and (III). A maximum error of ±6% in the rate constant corresponds to maximum errors of ±0·6 or 1·2 kcal. mole^{-1} in E, ±0·4 or 0·8 unit in log A, and ±1·8 or 3·6 cal. mole^{-1} deg.$^{-1}$ in $\Delta S^{\ddagger}$ [the lower figure in each case referring to the reactions of compounds (II) and (IV), which were carried out over a 40° range, and the higher figures to the reactions of compound (III), which were carried out over a 20° range]. The maximum errors in the Arrhenius parameters and entropies of activation for the abnormal reactions of compounds (II) and (III) are, of course, very much greater than this and approximate values only for these quantities are given in parentheses in Table 2.

TABLE 1

Measured rate constants, proportions of normal isomers, and rate constants for normal and abnormal attack for the reactions of substituted 1,2-epoxyethylbenzenes with benzylamine in ethanol (k_2, k_N, and k_A in l. mole^{-1} sec.$^{-1}$)

Substituent	Temp.	10^7k_2	% Normal isomer	10^7k_N	10^7k_A
α-Me (II)	20·0°	34·7	97	33·7	1·0
	39·8	172	94	162	10
	59·5	632	91	575	57
trans-β-Me (III)	39·8	7·50	96	7·20	0·30
	50·3	22·6	93	21·0	1·6
	59·7	56·1	90	50·5	5·6
o-Me (IV)	19·9	62·6	46	28·8	33·8
	39·7	293	46	135	158
	59·6	1120	46	515	605

TABLE 2

Rate constants interpolated to 40°, Arrhenius parameters, and entropies of activation for the normal and abnormal reactions of substituted 1,2-epoxyethylbenzenes with benzylamine in ethanol (k_N, k_A, and A in l. mole^{-1} sec.$^{-1}$; E in kcal. mole^{-1}; $\Delta S^{\ddagger}$ in cal. mole^{-1} deg.$^{-1}$)

	Normal reactions				Abnormal reactions			
Substituent	10^7k_N	E	log A	$\Delta S^{\ddagger}$	10^7k_A	E	log A	$\Delta S^{\ddagger}$
H [9]	490	13·5	5·1	−37	138	16·2	6·5	−31
α-Me (II)	162	13·9	4·9	−38	10·0	(20)	(8)	(−25)
trans-β-Me (III)	7·50	20·3	8·0	−24	0·34	(30)	(14)	(+2)
o-Me (IV)	135	14·0	4·9	−38	158	14·0	5·0	−38
p-Me [2]	274	13·7	5·0	−38	337	13·7	5·1	−37

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DISCUSSION

Perhaps the most striking feature of the results is the similarity in isomer proportions and the parallelism in rate constants between the reactions of the *o*-methyl compound (IV) and those of its *p*-methyl isomer (Table 2). The isomer ratio is identical within experimental error in the two cases, and for both normal and abnormal reactions the rate constant for the *o*-methyl compound at 40° is about half that for the *p*-isomer.

It has previously been shown that, in the absence of steric effects, the polar effects of substituent groups on epoxide reactions exhibit a definite pattern, electron-releasing groups decreasing the rate of the normal reactions and increasing that of the abnormal reactions,[3] and this is illustrated in Table 2 by a comparison of the figures for the *p*-methyl compound and the parent compound. Since the replacement of a *p*-methyl by an *o*-methyl group here reduces the rates of both reactions, steric effects cannot be absent. If we assume that the polar effect of an *o*-methyl group is the same as that of a *p*-methyl group, the results in Table 2 show that, for the abnormal reactions, this polar effect is almost exactly counterbalanced by the steric effect of the *o*-methyl group, giving an order: *p*-Me > *o*-Me ~ H.

In the normal reactions the polar and steric effects are additive and the order is H > *p*-Me > *o*-Me. This order is the same as that for the reactions involving the bimolecular displacement of bromide ion from substituted phenacyl bromides by pyridine [where the relative rate constants at 20° are 1·00 (H), 0·94 (*p*-Me), and 0·70 (*o*-Me) [27]] and there is no doubt that the two series of reactions are mechanistically similar.

Another striking point of similarity to emerge from the figures in Table 2 is that between the normal reactions of the α-methyl compound and its *o*-methyl isomer. Not only are the rate constants at 40° similar for the two reactions, but also the Arrhenius parameters are almost identical, and this presumably indicates a close similarity between both the polar and the steric effects of the α-methyl and *o*-methyl groups for reaction at the (remote) normal position. As far as steric effects are concerned, such a conclusion is shown to be a reasonable one by inspection of models.

The similarity between the normal reactions of the α-methyl and *o*-methyl compounds has no counterpart in the abnormal reactions of these compounds. The abnormal rate constant at 40° for the reaction of the α-methyl compound is about 16 times less than that for the reaction of the *o*-methyl compound, largely because of a substantially increased energy of activation, and it seems clear that the cumulative steric effect of a phenyl and a methyl group attached to the same carbon atom becomes very real when it is this carbon atom that is undergoing attack.

Surprisingly, the cumulative effect of two substituent groups in the epoxide ring becomes even greater when they are attached to different carbon atoms, as shown by the results in Table 2 for the reactions of the *trans*-β-methyl compound. This is especially so for reaction at the carbon atom adjacent to the benzene ring (the so-called abnormal reaction), where the presence of the β-methyl group reduces the rate constant at 40° by over 400 times. The probable explanation of this very much lowered reactivity is that with only one substituent group in the epoxide ring, or even with two if they are attached to the same carbon atom, steric compressions can be relieved by deformation of the transition state, but with two groups attached to different carbon atoms such deformation becomes much more difficult.

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