

888. *The Mechanism of Epoxide Reactions. Part X.¹ The Reactions of (Epoxyethyl)benzene with m-Chloro-, 3,4-Dimethyl-, and o-(Hydroxymethyl)-benzylamine*

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Rate constants have been determined at three temperatures for the reactions of (epoxyethyl)benzene with *m*-chloro- and 3,4-dimethyl-benzylamine in 99.8% ethanol. Product analyses have been carried out by infrared spectroscopy and the results used to calculate the rate constants for normal and for abnormal attack. Rate constants have also been obtained for the reaction of (epoxyethyl)benzene with *o*-(hydroxymethyl)benzylamine in ethanol and in methyl cyanide. The mechanism of the reactions is discussed and the effect of substituents analysed in terms of linear free-energy relations. The reaction with *o*-(hydroxymethyl)benzylamine shows some evidence of "built-in solvation."

ALTHOUGH a number of studies have been made of the effect of change of the attacking nucleophile on the ring-opening reactions of either a symmetrical epoxide^{2,3} or an unsymmetrical one undergoing essentially unidirectional attack,⁴⁻⁷ no systematic study has been made of the effect of change of nucleophile on the reactions of epoxides that undergo appreciable attack at both the normal and abnormal positions. (Epoxyethyl)benzene is such an epoxide and we have accordingly measured the rates of its reactions with two nuclear-substituted benzylamines. This is complementary to our previous investigation of the reactions of benzylamine with a series of nuclear-substituted (epoxyethyl)benzenes.⁸

The overall rate constants were obtained by following the decrease in concentration of the benzylamine, determined spectrophotometrically as its anil with salicylaldehyde, and the ratios of the isomeric products were determined by comparison of the infrared spectrum of the product with that of each pure isomer synthesised unambiguously. The reactions obeyed the second-order rate law and they were shown to be of the first order with respect to oxide and to amine. Hence the overall rate constants may be divided in the ratio of the isomeric products to give the second-order rate constants for normal (k_N) and for abnormal (k_A) attack. As before, complications due to further reaction of the products with (epoxyethyl)benzene were minimised by the use of a four-fold excess of amine.^{9,10}

In Parts VI¹¹ and VIII¹² it was shown that change of solvent has a marked effect on the reactivity at both positions of an unsymmetrical epoxide and, in particular, that hydroxylic solvents exert a specific rate-enhancing effect. In order to investigate this effect further and to determine whether a suitably placed hydroxylic group can provide "built-in solvation"¹³ in these reactions we have studied the reaction between (epoxyethyl)benzene and *o*-(hydroxymethyl)benzylamine in ethanol and in methyl cyanide. In this case it was not possible to obtain an accurate analysis of the isomeric reaction products, but the overall reaction was shown to follow the second-order rate law and to be of the first order with respect to oxide and to amine in both solvents.

¹ Part IX, R. E. Parker and A. W. Scaplehorn, preceding Paper.

² D. R. Boyd and E. R. Marle, *J.*, 1914, **105**, 2117.

³ J. P. Danehy and C. J. Noel, *J. Amer. Chem. Soc.*, 1960, **82**, 2511.

⁴ J. N. Brönsted, M. Kilpatrick, and M. Kilpatrick, *J. Amer. Chem. Soc.*, 1929, **51**, 428.

⁵ W. L. Petty and P. L. Nichols, *J. Amer. Chem. Soc.*, 1954, **76**, 4385.

⁶ J. Hansson, *Svensk kem. Tidskr.*, 1954, **66**, 351.

⁷ N. B. Chapman, N. S. Isaacs, and R. E. Parker, *J.*, 1959, 1925.

⁸ R. M. Laird and R. E. Parker, *J. Amer. Chem. Soc.*, 1961, **83**, 4277.

⁹ N. S. Isaacs and R. E. Parker, *J.*, 1960, 3497.

¹⁰ J. K. Addy, R. M. Laird, and R. E. Parker, *J.*, 1961, 1708.

¹¹ R. M. Laird and R. E. Parker, *J.*, 1963, 6065.

¹² R. E. Parker and B. W. Rockett, *J.*, 1965, 2569.

¹³ J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5051, 5165; J. D. Chanley and E. Feageson, *ibid.*, 4002; T. C. Bruice and T. H. Fife, *ibid.*, 1962, **84**, 1973; J. A. Zaslowsky and E. Fisher, *J. Phys. Chem.*, 1963, **67**, 959.

EXPERIMENTAL

Materials.—Ethanol was dried and adjusted to 99.8% w/w as in Part I.⁷ Methyl cyanide was purified as in Part VIII.¹²

(Epoxyethyl)benzene was purified as in Part I.⁷

m-Chlorobenzylamine. *m*-Chlorobenzyl bromide (90 g.) was added during 15 min. to a boiling solution of potassium phthalimide (90 g.) in dimethylformamide (400 ml.) and the mixture was heated for a further 15 min. before isolation of the product, *N*-(*m*-chlorobenzyl)phthalimide (89.5 g., 70%), by the method of Shehan and Bolhofer.¹⁴ The phthalimido-compound (89 g.) was added to a solution of hydrazine hydrate (20 g.) in ethanol (700 ml.) and the resulting suspension heated under reflux for 8 hr. The product was worked up by the method of Ing and Manske¹⁵ except that acidification was omitted until the whole procedure had been repeated once. *m*-Chlorobenzylamine, obtained in 55% overall yield, had b. p. 50°/0.02 mm., n_D^{18} 1.5620.

3,4-Dimethylbenzylamine. 3,4-Dimethylbenzyl chloride was conveniently converted in 31% yield by the method of Delépine¹⁶ into 3,4-dimethylbenzylamine, b. p. 50°/0.02 mm., n_D^{18} 1.5329; *hydrochloride*, m. p. 216° (Found: C, 62.5; H, 7.9; Cl, 20.2; N, 8.2. $C_9H_{14}ClN$ requires C, 63.0; H, 8.2; Cl, 20.7; N, 8.2%).

o-(*Hydroxymethyl*)benzylamine. Lithium aluminium hydride reduction of methyl *o*-cyano-benzoate¹⁷ in ether or of *o*-(hydroxymethyl)benzamide¹⁸ in tetrahydrofuran gave *o*-(hydroxymethyl)benzylamine, which was isolated as its *hydrochloride*, m. p. 225° (from dioxan) (Found: C, 55.3; H, 7.1; Cl, 19.9; N, 7.9. $C_8H_{12}ClNO$ requires C, 55.4; H, 7.0; Cl, 20.4; N, 8.1%). The free base was very soluble in water, moderately soluble in tetrahydrofuran and dioxan, and sparingly soluble in ether, and had m. p. 39—40° and b. p. 112°/0.03 mm.

Rate Measurements.—The reactions were carried out in the same way as in Part III.¹⁰ The anils of 3,4-dimethyl-, *m*-chloro-, and *o*-(hydroxymethyl)-benzylamine had their absorption maxima at 404, 406, and 404 μ (ϵ 475, 265, and 559), respectively, in ethanol at 16°. The absorption due to ionisation of salicylaldehyde in the presence of the secondary-amine reaction products was shown to be negligible at these wavelengths.

Synthesis of Products.—The product isomers were synthesised by the routes used previously,⁸ the normal isomers from phenacyl bromide and the appropriate benzylamine. In the preparation of the abnormal isomers methyl α -bromophenylacetate (recently available by an improved method) was used instead of the less reactive α -chloro-compound with which there is some loss due to ammonolysis of the ester group.⁸

2-(3,4-Dimethylbenzylamino)-1-phenylethanol was obtained in 70—80% yield and had m. p. 99.5—100° (from ethanol—light petroleum) (Found: C, 79.9; H, 8.2; N, 5.6. $C_{17}H_{21}NO$ requires C, 80.0; H, 8.3; N, 5.5%).

2-(3,4-Dimethylbenzylamino)-2-phenylethanol. A few drops of thionyl chloride were added to mandelic acid (28 g.) and phosphorus pentabromide (80 g.) and, after the initial reaction had subsided, the mixture was added to methanol (500 ml.) and set aside overnight. The resulting solution was diluted to 2 l. with water and extracted with ether. Working up gave a 74% yield of methyl α -bromophenylacetate, b. p. 94—96°/0.03 mm., n_D^{18} 1.5456.

The ester was converted into 2-(3,4-dimethylbenzylamino)-2-phenylethanol, b. p. 140—160°/4 \times 10⁻⁴ mm., n_D^{16} 1.5702 (Found: C, 80.0; H, 8.5; N, 5.6. $C_{17}H_{21}NO$ requires C, 80.0; H, 8.3; N, 5.5%).

2-(*m*-Chlorobenzylamino)-1-phenylethanol was obtained in 58% yield and had m. p. 70—70.5° (from ethanol—light petroleum) (Found: C, 68.8; H, 6.2; Cl, 13.5; N, 5.3. $C_{15}H_{16}ClNO$ requires C, 68.7; H, 6.2; Cl, 13.6; N, 5.4%).

2-(*m*-Chlorobenzylamino)-2-phenylethanol. Because of the low solubility of *m*-chlorobenzylamine in di-isopropyl ether the following modified procedure was used.

m-Chlorobenzylamine (4.9 g.) was allowed to react with methyl α -bromophenylacetate (4.3 g.) in ethanolic di-isopropyl ether at 60° for 2 hr. The precipitate of *m*-chlorobenzylamine hydrobromide (3.4 g., 87%) was removed and the filtrate diluted with diethyl ether and extracted twice with dilute hydrochloric acid. The extract was cautiously made alkaline with dilute aqueous sodium hydroxide and extracted four times with ether. The combined ethereal extracts

¹⁴ J. C. Shehan and W. A. Bolhofer, *J. Amer. Chem. Soc.*, 1950, **72**, 2786.

¹⁵ H. R. Ing and R. H. F. Manske, *J.*, 1926, 2348; H. J. Barber and W. R. Wragg, *J.*, 1947, 1331.

¹⁶ M. Delépine, *Bull. Soc. chim. France*, 1895, **13**, 358.

¹⁷ D. R. Boyd and D. E. Ladhams, *J.*, 1928, 2089.

¹⁸ J. Blair, J. J. Brown, and G. T. Newbold, *J.*, 1955, 712.

were washed, dried (Na_2SO_4), and then reduced with lithium aluminium hydride to give 2-(*m*-chlorobenzylamino)-2-phenylethanol (1.5 g.), m. p. 56.5° (from light petroleum) (Found: C, 69.1; H, 6.0; Cl, 14.1; N, 5.5. $\text{C}_{15}\text{H}_{16}\text{ClNO}$ requires C, 68.8; H, 6.2; Cl, 13.6; N, 5.4%).

2-(*o*-(Hydroxymethyl)benzylamino)-1-phenylethanol was obtained only as a viscous, hygroscopic oil, b. p. $310^\circ/10^{-4}$ mm. (decomp.) (Found: C, 73.5; H, 7.6; N, 5.9. $\text{C}_{16}\text{H}_{19}\text{NO}_2$ requires C, 74.7; H, 7.4; N, 5.4%).

Analysis of Products.—The ratios of isomeric products were determined as before.⁸ Although distillation of the products from the reaction of *o*-(hydroxymethyl)benzylamine resulted in some decomposition, the product mixtures isolated from this reaction at different temperatures and in the two solvents had spectra that were similar to each other and to that of the synthesised normal isomer.

RESULTS

Table 1 lists the measured rate constants (k_2), the measured proportions of normal isomers, and the rate constants for normal (k_N) and abnormal (k_A) attack. The Arrhenius parameters and entropies of activation, together with the rate constants interpolated to 40° , are collected in Table 2. We estimate that the measured rate constants for the overall reactions

TABLE 1

Measured rate constants, proportions of normal isomers, and rate constants for normal and abnormal attack for the reactions of (epoxyethyl)benzene with substituted benzylamines in 99.8% ethanol (k_2 , k_N , and k_A in l. mole⁻¹sec.⁻¹)

Substituent	Temp.	$10^5 k_2$	Normal product (%)	$10^5 k_N$	$10^5 k_A$
3,4-Me ₂	30.4°	3.84	72	2.76	1.08
	40.0	7.12	72	5.13	1.99
	59.4	21.7	72	15.6	6.1
<i>m</i> -Cl	25.3	1.51	76	1.15	0.36
	39.7	4.50	76	3.42	1.08
	59.7	15.0	77	11.6	3.4
<i>o</i> -CH ₂ OH	40.0	7.0			
	40.0	0.11 *			
	60.4	0.32 *			

* Reactions in methyl cyanide.

TABLE 2

Rate constants interpolated to 40° , Arrhenius parameters, and entropies of activation for the reactions of (epoxyethyl)benzene with substituted benzylamines in 99.8% ethanol (k_N , k_A , and A in l. mole⁻¹sec.⁻¹; E in kcal. mole⁻¹; ΔS^\ddagger in cal. mole⁻¹ deg.⁻¹)

Substituent	Normal reactions				Abnormal reactions			
	$10^5 k_N$	E	$\log A$	ΔS^\ddagger	$10^5 k_A$	E	$\log A$	ΔS^\ddagger
3,4-Me ₂	5.13	11.7	3.9	-42.7	1.99	11.7	3.5	-44.5
H ⁹	4.90	13.5	5.1	-37.3	1.38	16.2	6.5	-30.9
<i>m</i> -Cl	3.37	13.3	4.8	-38.7	1.04	13.1	4.1	-41.9

are accurate to $\pm 3\%$ or better, those for the normal reactions to $\pm 10\%$, and those for the abnormal reactions to $\pm 20\%$. These uncertainties of ± 10 and $\pm 20\%$ in the rate constants correspond to uncertainties in E of ± 0.9 and ± 1.8 , in $\log A$ of ± 0.6 and ± 1.2 , and in ΔS^\ddagger of ± 2.7 and ± 5.5 , respectively.

DISCUSSION

Hammett ρ Values.—The effect of substituents in the benzylamine molecule on the rate of its reaction with (epoxyethyl)benzene should be unambiguous in direction, since it will be felt only on the bond-forming step. The rate constants should be increased by electron-releasing substituents and decreased by electron-withdrawing substituents. This is certainly the case for the overall reactions where the differences are much greater than the maximum possible error of 3% in the rate constants. It is also the case for the normal

and abnormal reactions at 40° (Table 2), although here the possible errors are greater and, at their maximum, are just sufficient to cause some blurring of the substituent effects. Because of this and because there are results for only three different benzylamines it may be thought hardly justifiable to derive Hammett ρ values.¹⁹ However, the two substituted benzylamines were carefully chosen, both to give a reasonable range of Hammett σ values and to have a minimum of interfering absorption in the infrared region used for the isomer analysis. The values of ρ obtained at 40° in ethanol, -0.27 ± 0.13 for the normal reactions and -0.42 ± 0.26 for the abnormal reactions, are therefore believed to be meaningful, the limits of error indicated being the maximum possible. In all that follows these limits of error have been taken into account.

It is interesting to compare these values of ρ for the susceptibility of the (epoxyethyl)-benzene-benzylamine reaction to substitution in the amine with those obtained for substitution in the oxide, $+0.87$ for the normal reactions and -1.15 for the abnormal reactions (also at 40° in ethanol).⁸ For substitution in the amine, both values of ρ are negative, as expected, and similarly small in magnitude. The smallness of the values supports the previous conclusion²⁰ that bond-breaking is more important than bond-forming in these reactions (*i.e.*, that their transition states lie towards the S_N1 extreme in the range of S_N2 transition states).

In the transition states for the normal reactions the two benzene rings are approximately equidistant from the forming bond (Figure 1). Since it has previously been argued²⁰

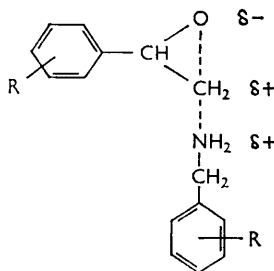


FIGURE 1. Transition state for normal reactions

that the effect of substituents in the benzene ring of the oxide is likely to be largely, if not entirely, on the bond-forming process in the normal reaction (because of the geometry of the three-membered ring) and, since the effect of substituents in the benzene ring of the amine will certainly also be on the bond-forming process, it might have been expected that the ρ values for substitution in the two benzene rings would be similar in magnitude (although opposite in sign). The fact that this is not so and that the ρ value for substitution in the oxide (± 0.87) is much greater numerically than that for substitution in the amine (-0.27) may be due to the possibilities for conjugation in the oxide molecule. The benzene ring can conjugate with the three-membered oxide ring and, in the transition state, therefore, the effect of a substituent in the benzene ring can be transmitted directly to the forming bond through a conjugated system. No such easy transmission is possible from a substituent in the benzene ring of the amine because of the effective insulation by the CH_2 group of the benzylamine.

Comparison of the ρ values for the abnormal reactions (-1.15 and -0.42) is less revealing because here the effect of a substituent in the benzene ring of the oxide is largely on the bond-breaking process (as is evident from the negative sign of ρ).

Nucleophilicity and Basic Strength of the Benzylamines.—The nucleophilicity in the series of substituted benzylamines would be expected to parallel their basicity, as measured by the $\log K_b$ values in water for which ρ is -0.72 .^{19,21} Although the solvents are different

¹⁹ H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.

²⁰ R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 737.

²¹ W. H. Carothers, C. F. Bickford, and G. J. Hurwitz, *J. Amer. Chem. Soc.*, 1927, **49**, 2908.

and exact comparison is therefore not possible, it is noticeable that the ρ values for the reactions of the benzylamines with (epoxyethyl)benzene (-0.27 and -0.42) are lower numerically than the value for their reaction with hydrogen ion (-0.72). Furthermore, the values for the reactions with oxide would almost certainly be smaller numerically in water than in ethanol (cf. the smaller values in methanol than ethanol¹¹) and the difference would therefore be accentuated. Such a difference again supports the postulate that in the oxide reactions the bond-forming process has not proceeded very far in the transition state.

*Reaction with *o*-(Hydroxymethyl)benzylamine.*—*o*-(Hydroxymethyl)benzylamine was chosen as a reagent in the belief that its reaction in an aprotic solvent might exhibit "built-in solvation."¹³ Models show that in its reaction with (epoxyethyl)benzene this amine can give rise to a cyclic transition state, with the amine hydroxyl group forming a hydrogen bond to the epoxide oxygen atom (the leaving group) and thereby stabilising the developing negative charge on this atom. In such a transition state the whole process of proton transfer can take place without the intervention of an external solvent molecule. Figure 2 shows the arrangement of the transition state for the normal reaction.

Since product analyses could not be carried out on this reaction it is possible to compare only the overall rate constants. At 40° the reaction with benzylamine (where "built-in solvation" is not possible) is 193 times faster in ethanol than in methyl cyanide ($10^5 k_{EtOH} = 6.28^8$ and $10^7 k_{MeCN} = 3.26^{12}$), whereas the reaction with *o*-(hydroxymethyl)benzylamine is only 64 times faster (Table 1). In other words the reaction with *o*-(hydroxymethyl)benzylamine in methyl cyanide is about three times faster than would otherwise

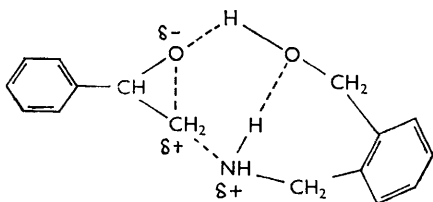


FIGURE 2. Cyclic transition state for normal reaction with *o*-(hydroxymethyl)benzylamine

be expected and this is evidence for "built-in solvation." The effect is not a large one and this is probably because of the difficulty of forming the fused six- and seven-membered rings (Figure 2)¹³ and because the direction of the hydrogen bond in the seven-membered ring is the reverse of that in *o*-(hydroxymethyl)benzylamine itself.

The close similarity between the rates of the reactions in ethanol with benzylamine and with *o*-(hydroxymethyl)benzylamine suggests that the combined electronic and primary steric effect of the *o*-hydroxymethyl group is very small and this is in agreement with the findings of Sprengling and Lewis from their study of the ionisation of phenols.²²

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²² G. R. Sprengling and C. W. Lewis, *J. Amer. Chem. Soc.*, 1953, **75**, 5709.