

333. *The Mechanism of Epoxide Reactions. Part III.<sup>1</sup> The Reactions of *p*-Bromo-(1,2-epoxyethyl)benzene and *p*-(1,2-Epoxyethyl)toluene with Benzylamine.*

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Rate constants at three temperatures have been determined for the first reactions of *p*-bromo-(1,2-epoxyethyl)benzene and *p*-(1,2-epoxyethyl)toluene with benzylamine. Product analyses have been carried out by infrared spectroscopy and the results have been used to separate the measured rate constants into rate constants for normal and for abnormal attack. It appears from these preliminary results that the effect of substituents is such that the normal reaction (attack at CH<sub>2</sub>) has a positive value for the Hammett reaction constant,  $\rho$ , while the abnormal reaction (attack at CH) has a negative  $\rho$ .

Of the epoxide-amine reactions reported in Parts I<sup>2</sup> and II,<sup>1</sup> the only one to give significant amounts of both normal and abnormal product was that between 1',2'-epoxyethylbenzene and benzylamine. This reaction was accordingly chosen as the starting point for an investigation into the effect of substituents on the rates of both normal and abnormal attack on an unsymmetrical epoxide, and the present paper records the results of a kinetic study of the reactions between benzylamine and the *p*-bromo- and *p*-methyl derivatives of 1',2'-epoxyethylbenzene. The bromo- and methyl groups may be taken as unambiguous examples of electron-withdrawing and electron-releasing groups, respectively, and, since they are in the *para*-position, the electronic effects should be uncomplicated by any steric effect.

Fuchs and VanderWerf<sup>3</sup> have shown that, in reaction with lithium borohydride, *p*-bromo-(1,2-epoxyethyl)benzene gives a higher proportion of normal product (84%), and *p*-(1,2-epoxyethyl)toluene a lower proportion (32%), than does 1',2'-epoxyethylbenzene (74%). No kinetic measurements were carried out, however, and the change in proportion of normal product could be due to a change in the rate of normal attack, or to a change in the rate of abnormal attack, or both. Fuchs<sup>4</sup> also studied the kinetics of the reactions of the same three epoxides with sodium thiosulphate in aqueous ethanol at 25° and found higher rates of reaction for *p*-bromo-(1,2-epoxyethyl)benzene ( $k = 3.07 \times 10^{-3}$  l. mole<sup>-1</sup> sec.<sup>-1</sup>) and *p*-(1,2-epoxyethyl)toluene ( $k = 2.40 \times 10^{-3}$  l. mole<sup>-1</sup> sec.<sup>-1</sup>) than for 1',2'-epoxyethylbenzene ( $k = 2.04 \times 10^{-3}$  l. mole<sup>-1</sup> sec.<sup>-1</sup>). However, no product analyses were carried out and it is not possible, therefore, to divide the overall rate constants into rate constants for normal attack and for abnormal attack.

The only other quantitative comparison of the three epoxides is the determination by Park and Fuchs<sup>5</sup> of the product ratios for the hydrogenations in the presence of platinum oxide in ethanol. Here the direction of change [100% abnormal product from 1',2'-epoxyethylbenzene and *p*-(1,2-epoxyethyl)toluene, 82% from *p*-bromo-(1,2-epoxyethyl)benzene] is the same as in the reactions with lithium borohydride. However, the hydrogenations are heterogeneous reactions and almost certainly do not involve the simple attack of a nucleophile at an epoxide carbon atom and they are, consequently, not comparable to the reactions with lithium borohydride, sodium thiosulphate, or benzylamine.

In Part II<sup>1</sup> the reaction between benzylamine and 1',2'-epoxyethylbenzene was followed by independent determinations of primary amine and of tertiary amine and the analytical figures were used to calculate rate constants both for the first reaction and for the second reaction (*i.e.*, reaction between the epoxide and the product of the first

<sup>1</sup> Part II, Isaacs and Parker, *J.*, 1960, 3497.

<sup>2</sup> Part I, Chapman, Isaacs, and Parker, *J.*, 1959, 1925.

<sup>3</sup> (a) Fuchs and VanderWerf, *J. Amer. Chem. Soc.*, 1954, **76**, 1631; (b) Fuchs, *ibid.*, 1956, **78**, 5612.

<sup>4</sup> Fuchs, *J. Org. Chem.*, 1958, **23**, 902.

<sup>5</sup> Park and Fuchs, *J. Org. Chem.*, 1957, **22**, 93.

reaction). In the present work a four-fold excess of benzylamine was used and the second reaction was thereby suppressed to such an extent that it was insignificant for at least the first 50% of the first reaction. Under these conditions it is possible to follow the first reaction for the first 50% of its course by determinations of primary amine alone.

Product analyses were carried out as before,<sup>2</sup> by comparing the infrared spectrum of the reaction product with that of the normal isomer and of the abnormal isomer. It was also shown that, for *p*-bromo-(1,2-epoxyethyl)benzene at 49°, the same product ratio was obtained from a reaction with an eight-fold excess of benzylamine over epoxide as from one with a four-fold excess. It follows from this that the normal and the abnormal reaction must have the same kinetic order and that, since the overall reaction obeys the second-order rate law, they must both in fact be of second order.

Table 1 lists the measured fractions of normal and abnormal isomer and the rate constants for normal ( $k_N$ ) and abnormal ( $k_A$ ) attack. The Arrhenius parameters and the rate constants interpolated to 49° are collected in Table 2. It is clear from Table 2 that the rate of attack at the normal position is increased by the electron-withdrawing *p*-bromo-group and decreased by the electron-releasing *p*-methyl group. The normal reaction therefore has a positive value of the Hammett reaction constant,  $\rho$  (although the number

TABLE 1. *Isomer proportions and measured rate constants,  $10^5k$  (l. mole<sup>-1</sup> sec.<sup>-1</sup>).*

	Temp.	Normal	Abnormal	$k_N$	$k_A$
1',2'-Epoxyethylbenzene <sup>1</sup> .....	20·00°	0·83	0·17	1·15	0·24
	40·50	0·78	0·22	4·99	1·41
	59·68	0·73	0·27	18·5	6·8
<i>p</i> -Bromo-(1,2-epoxyethyl)benzene .....	20·10	0·85	0·15	2·20	0·39
	35·30	0·82	0·18	5·29	1·16
	49·20	0·79	0·21	11·6	3·1
<i>p</i> -(1,2-Epoxyethyl)toluene .....	25·85	0·45	0·55	0·99	1·21
	35·20	0·45	0·55	2·01	2·46
	49·00	0·45	0·55	5·2	6·3

TABLE 2. *Rate constants interpolated to 49°, and Arrhenius parameters. ( $k$  and  $A$  in l. mole<sup>-1</sup> sec.<sup>-1</sup>;  $E$  in kcal. mole<sup>-1</sup>).*

	Normal reaction			Abnormal reaction		
	$10^5k_N$	$E$	$\log A$	$10^5k_A$	$E$	$\log A$
1',2'-Epoxyethylbenzene <sup>1</sup> .....	9·3	13·5	5·1	3·0	16·2	6·5
<i>p</i> -Bromo-(1,2-epoxyethyl)benzene .....	11·3	10·7	3·3	3·0	13·4	4·6
<i>p</i> -(1,2-Epoxyethyl)toluene .....	5·2	13·7	5·0	6·3	13·7	5·1

These values of  $E$  and  $\log A$  for the abnormal reaction of 1',2'-epoxyethylbenzene are different from those given in Part II.<sup>1</sup> The latter are incorrect and arose because of an unfortunate transposition of 16·24 kcal. to 14·26 kcal., and the use of this incorrect value in the calculation of  $\log A$ .

of substituents studied is insufficient to justify an attempt to evaluate  $\rho$ ). The effect of substituents on the rate of attack at the abnormal position is less clear. While the electron-releasing *p*-methyl group undoubtedly increases the abnormal rate, the effect of the *p*-bromo-group is small and the direction of the effect depends on the choice of temperature for comparison of the abnormal rate constants of 1',2'-epoxyethylbenzene and *p*-bromo-(1,2-epoxyethyl)benzene. The last two rate constants, since they constitute only about 20% of the total measured rate constants in each case, are subject to greater uncertainty than the others. In spite of this, it seems very likely that the abnormal reaction has a negative value for  $\rho$ .

This effect of a given substituent of increasing the reactivity at one position and decreasing it at another within the same molecule is believed to be unique. It is easy to understand why the abnormal reaction should have a negative  $\rho$ , for the opening of the highly strained three-membered ring should not require very much help from the reagent and would be expected to take place by a mechanism in which bond-breaking is more important

than bond-making.<sup>6</sup> Such mechanisms, of course, result in a negative  $\rho$ . It is not immediately obvious why the normal reaction does not also have a negative  $\rho$ , since the same considerations of ring-strain apply. However, as has been pointed out in Part I,<sup>2</sup> the reaction at the normal position of an unsymmetrical epoxide is an unusual type of bimolecular substitution in which the substituent group is almost exactly equidistant from both ends of the breaking bond. Thus, even though bond-breaking may still be the dominant factor, the effect of a substituent on the bond-breaking energy will be small or non-existent. The remaining effect of the substituent, that on the bond-making energy (*i.e.*, the repulsion energy), will then be dominant and this will give rise to a positive  $\rho$ .

This work is being extended to include *meta*- and other *para*-substituted 1',2'-epoxyethylbenzenes, and the results so far obtained support the above interpretation.

#### EXPERIMENTAL

*Materials.*—*p*-Bromo-(1,2-epoxyethyl)benzene, prepared by Fuchs and VanderWerf's method,<sup>3a</sup> had m. p. 26—27°, b. p. 91—93°/2 mm. *n*-(1,2-Epoxyethyl)toluene, prepared by Fuchs's method,<sup>3b</sup> had b. p. 51—52°/0.1 mm.,  $n_D^{26}$  1.5277. Benzylamine was purified as in Part II.<sup>1</sup> Ethanol was dried and adjusted to 99.80% w/w as in Part I.<sup>2</sup>

*Rate Measurements.*—The reactions were carried out in the same way as those in Part I,<sup>2</sup> but with an initial concentration of epoxide of *ca.* 0.1M and of amine of *ca.* 0.5M. They were followed by determinations of benzylamine alone and these were carried out as in Part II,<sup>1</sup> except that the aliquot parts (1 ml.) were added to 20 ml. of 1% ethanolic salicylaldehyde and the resulting solutions were set aside for at least 12 hr. before being made up to 100 ml.

*Synthesis of Products.*—2-Benzylamino-1-*p*-bromophenylethanol *p*-Bromo-(1,2-epoxyethyl)benzene (3 g., 0.015 mole) was added to benzylamine (7.7 g., 0.075 mole) in absolute ethanol (15 ml.) and the solution was kept at 50° for 3 days. Removal of ethanol and excess of benzylamine at 100°/15 mm., followed by crystallisation of the residue from ethanol, gave 2-benzylamino-1-*p*-bromophenylethanol, m. p. 109.5° (Found: C, 59.6; H, 5.4; N, 4.7. C<sub>15</sub>H<sub>16</sub>BrNO requires C, 58.9; H, 5.3; N, 4.6%).

2-Benzylamino-2-*p*-bromophenylethanol.—4-Bromobenzyl bromide was prepared from *p*-bromotoluene by Weizmann and Patai's method<sup>7</sup> and the crude product (m. p. 61—62°) was converted into 4-bromobenzyl cyanide according to Adams and Thal's method<sup>8</sup> for benzyl cyanide. Hydrolysis of the cyanide by Misra and Shukla's method,<sup>9</sup> followed by crystallisation of the product from water, gave *p*-bromophenylacetic acid, m. p. 114° (lit.<sup>9</sup> 114°). Treatment of this acid according to Hahn and Walter's method<sup>10</sup> for phenylacetic acid gave ethyl  $\alpha$ -bromo-*p*-bromophenylacetate, b. p. 132—133°/1 mm. (Found: C, 37.4; H, 3.2; Br, 49.9. C<sub>16</sub>H<sub>16</sub>Br<sub>2</sub>O<sub>2</sub> requires C, 37.3; H, 3.1; Br, 49.6%).

The bromo-ester (20 g., 0.06 mole) in dry ether was added to an excess of benzylamine (20 g., 0.19 mole), and the mixture was kept at 25° for 18 hr. and filtered from precipitated benzylamine hydrobromide. Removal of the ether and distillation *in vacuo* of the residue gave ethyl  $\alpha$ -benzylamino-*p*-bromophenylacetate, b. p. 180°/0.01 mm. (Found: C, 58.7; H, 5.3; N, 4.0; Br, 22.6. C<sub>17</sub>H<sub>18</sub>BrNO<sub>2</sub> requires C, 58.6; H, 5.2; N, 4.0; Br, 23.0%). The amino-ester (8 g., 0.023 mole) in dry ether was added dropwise to a slurry of lithium aluminium hydride (1 g., 0.026 mole) in boiling ether (100 ml.). The mixture was heated under reflux for a further 2 hr., after which water was added. After filtration, the ethereal layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. Crystallisation of the residue from light petroleum (b. p. 60—80°) gave 2-benzylamino-2-*p*-bromophenylethanol, m. p. 63° (Found: C, 59.5; H, 5.2; N, 4.5. C<sub>15</sub>H<sub>16</sub>BrNO requires C, 58.9; H, 5.3; N, 4.6%).

2-Benzylamino-1-*p*-tolylethanol.—4-Methylphenacyl bromide, prepared by Bose's method,<sup>11</sup> was allowed to react with benzylamine (2 mol.) in dioxan at 60° for 5 min. The theoretical amount of benzylamine hydrobromide was filtered off and the solution of the unstable aminoketone was reduced with aqueous sodium borohydride. Working up in the usual way and

<sup>6</sup> Parker and Isaacs, *Chem. Rev.*, 1959, **59**, 737.

<sup>7</sup> Weizmann and Patai, *J. Amer. Chem. Soc.*, 1946, **68**, 150.

<sup>8</sup> Adams and Thal, *Org. Synth.*, 1922, **2**, 9.

<sup>9</sup> Misra and Shukla, *J. Indian Chem. Soc.*, 1951, **28**, 480.

<sup>10</sup> Hahn and Walter, *Annalen*, 1907, **354**, 127.

<sup>11</sup> Bose, *J. Indian Chem. Soc.*, 1926, **3**, 205.

crystallisation from ethanol gave *2-benzylamino-1-p-tolyloethanol*, m. p. 119—120° (Found: C, 79.9; H, 8.0; N, 5.6.  $C_{16}H_{19}NO$  requires C, 79.9; H, 7.9; N, 5.8%). Identical material was obtained from the reaction of *p*-(1,2-epoxyethyl)toluene with benzylamine in ethanol, by crystallisation of the crude product from ethanol.

*2-Benzylamino-2-p-tolyloethanol*.—Methyl  $\alpha$ -chloro-*p*-tolylacetate was prepared by Baker, Ollis, and Poole's method<sup>12</sup> and, after careful purification, had b. p. 100—118°/0.6—1 mm.,  $n_D^{19}$  1.524. In view of the boiling range the material was submitted to gas chromatography on a column of Silicone resin supported on Celite and was thereby shown to be homogeneous (Found: C, 60.3; H, 5.6; Cl, 18.0. Calc. for  $C_{10}H_{11}ClO_2$ : C, 60.4; H, 5.6; Cl, 17.9%). Reaction with benzylamine (2 mol.) in di-isopropyl ether at 60° for 20 hr. gave a theoretical amount of benzylamine hydrochloride which was removed by filtration. After several unsuccessful attempts to isolate methyl  $\alpha$ -benzylamino-*p*-tolylacetate by distillation, the solution of amino-ester was reduced directly with an excess of lithium aluminium hydride. Working up in the usual way gave *2-benzylamino-2-p-tolyloethanol*, b. p. 120°/3  $\times 10^{-4}$  mm.,  $n_D^{24}$  1.5675 (Found: C, 81.4; H, 8.0; N, 6.2.  $C_{16}H_{19}NO$  requires C, 79.9; H, 7.9; N, 5.8%). A further quantity of this material was isolated from the reaction of *p*-(1,2-epoxyethyl)toluene with benzylamine in ethanol, by working-up of the mother-liquor remaining after crystallisation of *2-benzylamino-1-p-tolyloethanol*. The liquid product solidified on long storage and, after crystallisation from light petroleum (b. p. 40—60°), had m. p. 72—73° (Found: C, 80.0; H, 7.9; N, 5.7%). The two preparations had identical infrared spectra.

*Product Analysis*.—*Infrared analysis*. Infrared spectra were determined for (a) the actual reaction product (obtained by allowing the reaction in ethanol to go to completion and distilling the product *in vacuo* in such a way as to obtain the total secondary amine fraction free from other compounds), (b) the normal product, (c) the abnormal product, and (d) various synthetic mixtures of the normal and abnormal product. All the measurements were made on chloroform solutions with a Unicam S.P. 100 double-beam, infrared spectrophotometer.

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<sup>12</sup> Baker, Ollis, and Poole, *J.*, 1950, 1548.