XXXIX.—*Studies on the Walden Inversion. Part V.
The Kinetics and Dissociation Constant of
 β -Phenyl- α -bromopropionic Acid.*

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It was recently shown by Drew and one of us (T., 1915, **107**, 638; 1916, **109**, 1091) that when the halogen atom in ammonium phenylchloroacetate is displaced by the amino-group the sign of the resulting amino-acid depends on the nature of the solvent in which the reaction proceeds. Thus from solutions in liquid ammonia, in acetonitrile, and in ethyl alcohol an amino-acid of the same sign as the chloro-acid was obtained, whereas from water and *n*-heptyl and benzyl alcohols, the amino-acid had the opposite sign to the chloro-acid taken.

Other workers on the Walden inversion have found that the presence of the phenyl group appears to bring about abnormal results in displacement reactions. In phenylchloroacetic acid the phenyl group is directly attached to the asymmetric carbon atom, and in order to find how the results would be affected by a phenyl group further removed from the point at which substitution occurs, it was decided to investigate β -phenyl- α -bromopropionic acid, $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CHBr}\cdot\text{CO}_2\text{H}$, from this point of view.

The acid in question was resolved by Fischer and Carl (*Ber.*, 1906, **39**, 4000) by means of brucine, and they showed that when the *l*-acid is treated with aqueous ammonia, *d*-phenylalanine is obtained. The effect of liquid ammonia was not determined. McKenzie and Wren (T., 1910, **97**, 1355) found that the displacement of the bromine by hydroxyl took place very slowly, and that the resulting hydroxy-acid had the same sign as the original bromo-acid, independently of whether the displacement was effected by water, by aqueous sodium hydroxide, or by silver oxide and water.

In order to throw some light on the mechanism of these reactions, the dissociation constant of the acid at 25° and the kinetics of the displacement of bromine by hydroxyl have been examined, and the results are described in the present paper. The effect of the solvent on the sign of the product when the bromine atom is displaced by the amino-group is at present under investigation.

Preparation of the Acid.

β -Phenyl- α -bromopropionic acid was prepared by heating benzyl-bromomalonic acid under diminished pressure, and was purified by distillation in the vacuum obtained by means of a Gaede pump, as

described by Fischer and Carl (*loc. cit.*). These observers found that the acid passed over at 138–141°/0.2 mm. On keeping the colourless oil for some days at 0° it began to crystallise, and crystallisation was practically complete in a further four to five days. The crystals melted at 48–49°. Unsuccessful attempts were made to recrystallise the product from light petroleum.

Our results regarding the the boiling point of the acid confirm those of Fischer and Carl, but the distillate crystallised on remaining overnight at the ordinary temperature, and after a further twenty-four hours crystallisation was practically complete. The acid was recrystallised without much difficulty from light petroleum; it melted sharply at 52°. Our product was therefore purer than that obtained by Fischer and Carl.

Dissociation Constant of β -Phenyl- α -bromopropionic Acid.

The dissociation constant of the acid was determined at 25° by the electrical conductivity method, the measurements being made in the usual way with a Wheatstone bridge and telephone. The water used in making up the solutions had in no case a conductivity exceeding 1.5×10^{-6} mhos at 25°, and no correction was applied on this account to the experimental values for the conductivity of the solutions of the acid. In order to test the accuracy of the apparatus, the dissociation constant of succinic acid was determined. The value found was 0.000066 at 25° (concentration in mols. per litre), which is the mean of the most trustworthy values recorded in the literature.

As the acid is only very sparingly soluble in water, it was not practicable to work with solutions more concentrated than 0.01 molar. Two closely concordant series of measurements were made; the results are given in table I. As the displacement of bromine by hydroxyl proceeds very slowly at low temperatures, there is no appreciable error due to hydroxylation during the measurements. The temperature was $25 \pm 0.02^\circ$.

TABLE I.

Dilution, v , (Litres per mol.)	k .	Λ_m .	α .	$K = \frac{\alpha^2}{(1-\alpha)v}$.
100	0.001259	125.9	0.336	0.00170
200	0.000821	164.1	0.438	0.00170
500	0.000443	221.5	0.591	0.00171
1000	0.000267	267.0	0.711	0.00175
2000	0.000152	303.5	0.809	0.00172

In order to calculate the dissociation constant from the conductivity of the acid, the equivalent conductivity of the latter at infinite dilution, Λ_∞ , is required. This is obtained by adding

together the value for hydron, which may be taken as 347.0 at 25°, and that for the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ ion. The latter value was obtained in the usual way by means of measurements with the sodium salt in $N/1000$ - and $N/2000$ -solution, a correction being applied for the conductivity of the water. As a mean of two series of measurements, Λ_{1000} may be taken as 78.1 and Λ_{2000} as 78.8, and therefore Λ_∞ must be approximately 79.0. As the ionic velocity for sodion at 25° is 51, the value for the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ ion is 28 and Λ_∞ for the acid is therefore 375. With this number the values for α and for K in the table are calculated. The agreement in the values of K is satisfactory, and the dissociation constant of the acid may be taken as 0.00172 at 25°.

As the dissociation constant of α -bromopropionic acid at 25° is 0.00108, the phenyl group in the β -position increases the strength of the acid in the ratio 1.59:1. The effect of the phenyl group in the β -position appears to vary considerably with the nature of the compounds compared. Thus the factor obtained by comparison of β -phenylpropionic acid (benzylacetic acid) and propionic acid is 1.65, whereas the value obtained by comparison of β -phenyl- α -hydroxypropionic acid and α -hydroxypropionic acid is 1.36 (compare Findlay, Turner, and Owen, T., 1909, **95**, 942).

The Hydroxylation of β -Phenyl- α -bromopropionic Acid.

The kinetics of the displacement of bromine by hydroxyl in aqueous solution have been investigated by the methods described in previous papers (compare Senter, T., 1915, **107**, 908; Senter and Tucker, T., 1916, **109**, 690). The first step is to settle the exact nature of the reaction, as in addition to the formation of the hydroxy-acid, according to the equation

there is the possibility of the formation of cinnamic acid by elimination of hydrogen bromide:

This point can be examined by taking advantage of the fact that silver β -phenyl- α -hydroxypropionate is readily soluble and silver cinnamate almost insoluble in water. An $N/80$ -solution of the acid in water was heated in a sealed tube at 50° for forty-two days, then neutralised with ammonia, excess of silver nitrate added, and the liquid filtered. The acid obtained by acidifying the filtrate with hydrochloric acid and extracting with ether weighed 0.0272 gram, and gave the reactions for β -phenyl- α -hydroxypropionic acid. The cinnamic acid obtained by dissolving the slight residue on the filter in dilute ammonia and extracting as above weighed 0.0019 gram. As the proportion of cinnamic acid formed amounts at most to 7 per

cent. of that of the hydroxy-acid, the reaction which is measured is almost exclusively the displacement of bromine by hydroxyl. A separate experiment showed that in the presence of *N*/5-nitric acid the formation of cinnamic acid also proceeds very slowly in comparison with that of the hydroxy-acid.

As will be shown later, similar results were obtained with the neutral sodium salt of the bromo-acid, but in the presence of *N*/20-sodium hydroxide a considerable proportion of cinnamic acid is formed.

As β -phenyl- α -bromopropionic acid is only sparingly soluble in water, it was not practicable to use for the kinetic measurements solutions stronger than *N*/80. The solutions were heated in sealed tubes for definite periods at constant temperature, and the rate of reaction was followed by determining the increase of acidity by means of *N*/20-sodium hydroxide, using phenolphthalein as indicator, and the bromidion concentration by Volhard's method, using *N*/20-silver nitrate. The results of a typical series of measurements are given in table II. The velocity-coefficients, k_1 and k_2 , in the third and fifth columns are calculated by the formula for a uni-molecular reaction, $\log_{10} a/(a-x) = 0.4343kt$. The value of a , the concentration of the bromo-acid at the beginning of the reaction, was obtained as usual from the difference of the initial titration values, and those obtained after the reaction was complete. The results differ slightly for the alkali and silver nitrate (4.8 and 5.0 c.c. respectively for 20 c.c. of the reaction mixture) perhaps owing to a small amount of secondary reaction.

TABLE II.

β -Phenyl- α -bromopropionic Acid, N/80. Temp. 50.8°.

t (min.).	$a-x_1$ (c.c. NaOH, <i>N</i> /20).	$k_1 \times 10^3$.	$a-x_2$ (c.c. AgNO ₃ , <i>N</i> /20).	$k_2 \times 10^3$.
0	4.8	—	5.0	—
1410	4.0	0.129	4.2	0.124
2850	3.6	0.102	3.6	0.115
7170	2.45	0.094	2.4	0.089
11490	1.95	0.078	1.7	0.086
18690	1.15	0.076	1.0	0.075

As the table shows, there is a gradual fall in the magnitude of the velocity-coefficients as the reaction proceeds. Similar results obtained in previous investigations were traced to the retarding effect of the halogen acid formed in the course of the reaction. The simplest way of testing this point is to determine the effect on the reaction velocity of halogen acid added at the beginning of the reaction. In the present case, accurate results could not be obtained in the presence of a fairly high concentration of hydro-

bromic acid as, owing to the necessarily small concentration of the bromo-acid, the change in titre during the reaction would be very small compared with the total titre of the solution, whether the titration be made with sodium hydroxide or silver nitrate. For this reason measurements were made in the presence of *N*/5-nitric acid and *N*/5-benzenesulphonic acid, and the bromidion concentration was determined at intervals by Volhard's method. The results are as follows:

<i>β</i> -Phenyl- <i>α</i> -bromopropionic acid, <i>N</i> /80	} at 50.8°	$k \times 10^3$
Benzenesulphonic acid, <i>N</i> /5		0.0109
<i>β</i> -Phenyl- <i>α</i> -bromopropionic Acid, <i>N</i> /80	} at 50.8°	0.0100
Nitric acid, <i>N</i> /5		

That in the presence of excess of a strong acid the reaction is strictly unimolecular is shown by some of the data quoted in another connexion in table III.

In previous papers (T., 1909, **95**, 1836; 1915, **107**, 908, etc.) it has been shown that the retarding influence of strong acids on hydroxylation is due to diminution in the concentration of the anion, which in most cases reacts more rapidly with water than does the non-ionised acid. This question can usually be tested most satisfactorily by comparison of the reaction velocity in the solution of the sodium salt (where the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ concentration is relatively great) with that in the solution of the bromo-acid in the presence of a strong acid (in which case the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ concentration is very low). As shown in the next section, the initial velocity-coefficient for the hydroxylation of *N*/80-sodium *β*-phenyl-*α*-bromopropionate is about 0.46×10^{-3} ; the anion concentration, assuming that the sodium salt is ionised to the extent of 90 per cent., is $0.0125 \times 0.9 = 0.001125$. The concentration of the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ ion in excess of a strong acid is readily obtained by substitution in the equation for the influence of a common ion on the dissociation of a weak acid, $[(a'/c)c_0]/(1-a')c = K$, where c is the concentration and K the dissociation constant of the weak acid and c_0 the concentration of the common ion, in this case the hydrogen ion. As *N*/5-nitric acid is ionised to the extent of about 90 per cent., and as c is 0.0125 and K is 0.0017, we find for a' , the new degree of dissociation of the bromo-acid, 0.0095 and the anion concentration $0.0095 \times 0.0125 = 0.000119$. It follows that the ratio of the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ concentration in the sodium salt solution and in the bromo-acid solution in the presence of excess of nitric acid is 0.90:0.0095 or 95:1, whereas the relative rates of reaction in the two solutions are 0.46:0.01 or 46:1. The rate of reaction in the acid solution is therefore double that which would be observed if the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ ion alone were reacting.

Further, since in *N*/5-nitric acid bromidion is being set free at the same rate from the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ ion and the non-ionised acid, and since the degree of dissociation of the acid is 0.0095 under these conditions, and therefore the relative concentrations of non-ionised bromo-acid and anion are in the ratio 0.9905:0.0095 or approximately 100:1, it is clear that in equivalent concentration the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ ion would undergo hydroxylation about 100 times as fast as the non-ionised acid.

A little uncertainty is introduced into these calculations owing to the fact that the dissociation constant of the acid was determined at 25° and the velocity measurements were carried out at 50.8°. As, however, change of temperature has usually very little effect on the magnitude of the dissociation constant, the error introduced by using in the calculations the value of the dissociation constant at 25° is certainly small.

Although in the presence of *N*/5-nitric acid the reactivity of the non-ionised bromo-acid becomes of importance, it can easily be shown that in the hydroxylation of the free acid in *N*/80-solution (where the maximum concentration of the hydrobromic acid formed is only *N*/80) the reactivity of the non-ionised acid is negligible in comparison with that of the anion.

If the conclusion is justified that the reaction in the case of the free acid and of the sodium salt is identical, namely, the action of water on the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ ion, the temperature-coefficients of the two reactions should be the same. It will be shown in the section on the hydroxylation of the sodium salt that such is the case.

The above explanation of the mechanism of the reaction under discussion receives further confirmation when the data given in table I are substituted in the equation for reactions of this type given by Senter and Porter (T., 1911, **99**, 1049).

Comparison of the Reactivity of β -Phenyl- α -bromopropionic Acid and α -Bromopropionic Acid.—As it appeared from a comparison of the data for the rate of hydroxylation of β -phenyl- α -bromopropionic acid given in table II with previous observations on α -bromopropionic acid (Senter, T., 1909, **95**, 1827) that the bromine was displaced from the former acid less rapidly than from the latter at the same temperature, it was decided to make a careful comparison of the reactivities of the two acids under exactly equivalent conditions. The bromopropionic acid used was purified by fractional distillation, and its purity checked by determination of the melting point (25°). The results of one series of experiments are given in table III.

TABLE III.

<i>α-Bromopropionic Acid, N/80.</i>			<i>β-Phenyl-α-bromopropionic Acid, N/80.</i>		
No nitric acid; Temp. 57.0°.			No nitric acid; Temp. 57.0°.		
<i>t</i> (min.).	<i>a</i> - <i>x</i> .	<i>k</i> $\times 10^3$.	<i>t</i> (min.).	<i>a</i> - <i>x</i> .	<i>k</i> $\times 10^3$.
0	5.0	—	0	5.0	—
1456	2.6	0.452	1368	3.6	0.242
2885	1.5	0.422	2795	2.8	0.209
4315	0.9	0.390	4225	1.3	0.181
5755	0.7	0.350	5671	0.9	0.168

<i>N/5-HNO₃; Temp. 58.4°.</i>			<i>N/5-HNO₃; Temp. 58.4°.</i>		
<i>t</i> (min.).	<i>a</i> - <i>x</i> .	<i>k</i> $\times 10^3$.	<i>t</i> (min.).	<i>a</i> - <i>x</i> .	<i>k</i> $\times 10^3$.
0	5.0	—	0	5.0	—
1402	4.3	0.107	8535	4.05	0.025
4243	3.3	0.098	12950	3.65	0.024
8533	2.25	0.094	22960	2.90	0.024
12950	1.5	0.093	33040	2.20	0.025

The data in the upper part of the table show that bromine is eliminated rather more rapidly from α -bromopropionic acid than from β -phenyl- α -bromopropionic acid, a result which is not in accord with previous observations as to the influence of the phenyl group on such reactions. As shown in previous papers, the relative rates of displacement of chlorine from phenylchloroacetic acid and chloroacetic acid is of the order 3600:1.

The investigation of the kinetics of the two acids first mentioned has led to the conclusion that the reactivity of undissociated α -bromopropionic acid and the anion is of the same order (T., 1909, 95, 1836), whereas it has now been shown that non-ionised β -phenyl- α -bromopropionic acid has a much smaller reactivity than the corresponding anion. The conclusion was therefore drawn that nitric acid in equivalent concentration should lessen the reactivity of the latter acid to a much greater extent than that of the former acid, since the diminution of the $\text{CH}_3\cdot\text{CHBr}\cdot\text{CO}_2^-$ ion concentration will be partly compensated by the greater concentration of the fairly reactive non-ionised acid. This is entirely borne out * by the data in the lower portion of table III.

* This striking verification of the prediction regarding the effect of nitric acid on the two reactions affords further evidence in support of the theory, on which much work has recently been done by Arrhenius, Bredig and Snethlage, Goldschmidt, Dawson, Lapworth, Taylor, Acree, the author, and others, that both ionised and non-ionised molecules are active in chemical changes. The credit for this fruitful advance is often ascribed, especially abroad, to Goldschmidt (*Zeitsch. Elektrochem.*, 1909, 15, 6) and Bredig and Snethlage (*Zeitsch. Elektrochem.*, 1912, 18, 539). As Lapworth has recently pointed out, however, (T., 1915, 107, 860) the pioneering work on this subject was carried

It is difficult to find a satisfactory explanation of the depressing effect of the phenyl group in the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ ion on the reactivity of the bromine. It is possible that the phenyl group exerts a "steric hindrance" on the reaction which more than counterbalances any accelerating effect. The latter effect would in any case be relatively small when the phenyl group is in the β -position.

Hydroxylation of Sodium β -Phenyl- α -bromopropionate.

The main reaction between sodium β -phenyl- α -bromopropionate is represented by the equation :

but there is also the possibility of the formation of a small amount of cinnamic acid owing to the separation of hydrogen bromide. It was found, however, by the method described in connexion with the free acid, that the proportion of cinnamic acid does not exceed 4 per cent. of the total acid produced.

The results of a series of measurements in $N/80$ -solution at $50\cdot8^\circ$ are given in the accompanying table.

TABLE IV.

Sodium β -Phenyl- α -bromopropionate, $N/80$.

<i>t.</i> (min.).	$\alpha-x_1$.	$k_2 \times 10^3$.	$\alpha-x_2$.	$k_3 \times 10^3$.
0	5.0	—	5.0	—
1367	2.9	0.40	2.8	0.43
2810	1.75	0.38	1.8	0.36
4127	1.3	0.33	1.3	0.33
7127	0.7	0.28	0.7	0.28

As in the case of the free acid, the titrations with silver nitrate and sodium hydroxide agree within the limits of experimental

out independently and almost simultaneously by the author (T., 1907, **91**, 467) and by Acree and his co-workers (*Amer. Chem. J.*, 1907, **37**, 410; **38**, 258); the application of these principles to the special case of the catalytic activity of acids was first made by Lapworth himself (T., 1908, **93**, 2198) and later independently by Goldschmidt (*loc. cit.*). Lapworth's statement does not make clear that "the possibility of distinguishing between the simultaneous changes in the ionised and non-ionised constituents" was definitely proved in the author's earlier papers (compare T., 1907, **91**, 46, and 1909, **95**, 1836) as well as in those of Acree. The fact that the author and his co-workers have been largely concerned with acids of medium strength, in which the ratio of ions to non-ionised molecules can be varied within wide limits, has afforded very convincing proofs of the validity of the theory in question —G.S.

error. The falling off in the magnitude of the unimolecular velocity-coefficients as the reaction proceeds is doubtless due to the formation of hydrobromic acid and hydroxy-acid, which convert part of the remaining sodium salt of the bromo-acid to the free acid; the latter is less rapidly hydroxylated than the sodium salt.

The temperature-coefficient of the reaction was determined by comparative measurements in *N*/80-solution at 46.7° and 55.7°. The relative times taken for the concentration to fall from 5.0 to 0.8 were in the ratio 11,428 minutes to 2850 minutes, so that the coefficient for 9° is 4.0 and for 10° 4.6. The temperature-coefficient for the acid was determined between the same limits of temperature, the intervals being chosen four times as long at the lower as at the higher temperature. In twenty hours at the higher temperature and eighty hours at the lower temperature the concentrations altered from 4.95 to 4.1; in forty-three hours at the high temperature and one hundred and seventy hours at the low temperature the concentration had fallen in both cases to 3.3. As these figures show, the temperature-coefficient in this case also is exactly 4.0 for 9° or 4.6 for 10°, thus confirming the deduction from the kinetic measurements that the reaction which is measured is the same for the free acid as for the sodium salt (p. 452).

This temperature-coefficient, allowance being made for the relatively high temperature, is probably the highest ever observed for a pseudo-unimolecular reaction (a reaction in which the solvent takes part), but higher temperature-coefficients have been observed for unimolecular reactions, although probably not for multimolecular reactions (compare von Halban, *Zeitsch. physikal. Chem.*, 1909, **67**, 168).

Hydroxylation of Sodium β -Phenyl- α -bromopropionate in the Presence of Excess of Sodium Hydroxide.—In order to determine the products formed in the presence of sodium hydroxide, an *N*/80-solution of the sodium salt in *N*/25-sodium hydroxide was heated for several days at 50.5°. An examination of the product by the method described in connexion with the free acid showed the presence of 0.0163 gram of hydroxy-acid and 0.0133 gram of cinnamic acid. As the proportion of cinnamic acid formed is so great, it would be difficult to determine the exact mechanism of the reaction by kinetic measurements, and only two concordant series of measurements were made at 50.8°. The results of one series are given in table V.

TABLE V.

*Sodium β -Phenyl- α -bromopropionate, N/80.**Sodium Hydroxide, N/25.*

<i>t.</i>	<i>a-x.</i>	<i>b-x.</i>	<i>k</i> $\times 10^3$.
0	14.15	4.9	—
120	13.3	4.05	0.111
240	12.8	3.55	0.109
420	11.95	2.70	0.109
1290	10.25	1.00	0.107

By comparison of the figures in the third column (concentration of sodium salt) with those in the second column of table IV it is clear that the reaction proceeds more rapidly in alkaline solution, presumably owing to the direct action of hydroxyl ions on the sodium salt. This point has not been further investigated, owing to complications introduced by the formation of cinnamic acid. The figures in the fourth column show that the reaction is strictly bimolecular.

Discussion of Results.

Most of the results have already been discussed in connexion with the experimental data. From the point of view of the Walden inversion, it has already been mentioned that a hydroxy-acid of the same sign is obtained from the active bromo-acid, whether the displacement is effected in the free acid or in the sodium salt by water or by alkali. This is in accordance with the conclusions given in the present paper as far as the free acid and the neutral sodium salt is concerned, the reactions being identical, but in alkaline solution the reaction appears to be a different one, and the formation of a product of the same sign would not necessarily be anticipated.

Summary.

1. The dissociation constant of β -phenyl- α -bromopropionic acid at 25° is 0.00172 (concentration in mols. per litre).

2. The reaction which is measured when the bromine is displaced by hydroxyl in β -phenyl- α -bromopropionic acid and its sodium salt in neutral solution is in both cases the action of water on the $\text{CH}_2\text{Ph}\cdot\text{CHBr}\cdot\text{CO}_2'$ ion.

3. The temperature-coefficient for 10° of this reaction in the neighbourhood of 50° is 4.6.

4. The introduction of a phenyl group in the β -position into α -bromopropionic acid diminishes to a considerable extent the reactivity of the bromine atom.

5. When β -phenyl- α -bromopropionic acid and its neutral sodium

salt are heated with water, the product consists almost exclusively of the hydroxy-acid, but even in *N*/25-sodium hydroxide a considerable proportion of cinnamic acid is formed.

In conclusion, we desire to thank Dr. W. H. Hurtley for the loan of a Gaede pump, which has enabled us to prepare the bromo-acid in a pure condition. We also desire to express our obligations to Mr. H. D. K. Drew for assistance in the preparation and purification of the acid, and to thank the Government Grant Committee of the Royal Society for a grant which has defrayed the cost of this investigation.

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