was directly hydrogenated with Pd-C catalyst to ethyl 5-(*p*-hydroxyphenyl)-3-ketovalerate.

Ethyl 5-Phenyl-3-ketovalerate.[7]—Phenylpropionyl chloride was coupled to ethyl acetoacetate as previously described to give an 80% yield of ethyl 5-phenyl-3-keto-2-acetylvalerate, b.p. 88–94° (0.006 mm.).

Deacetylation with sodium methylate gave a 70% yield of the β-keto ester, b.p. 105–110° (1 mm.).

Enzyme Methods.—The enzyme utilized in this study was thrice-recrystallized Worthington α-chymotrypsin. The reaction was carried out in 10-ml. thermostated vessels, stirred magnetically, and the extent of hydrolysis determined by continuous potentiometric titration with 0.2 to 0.5 *N* NaOH essentially according to the procedure of Schwert, *et al.*[8] Insolubility of the substrates made it necessary to run the hydrolyses in 30% ethanol. Control determinations without enzyme at *p*H 7.8 showed less than 2% hydrolysis of the β-keto esters and β-keto acids in 20 hours. *p*-Hydroxyphenylpropionic acid was isolated from an 0.05 *M* terminal enzymic hydrolyzate of the β-keto ester by chilling in ice and acidification to *p*H 2.0. The crystalline precipitate, after filtration and recrystallization, was identified by melting point and mixed melting point with an authentic sample of *p*-hydroxyphenylpropionic acid.

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On Cyclic Intermediates in Substitution Reaction. VI. The Alkaline Solvolysis of N-β-Bromoethylaniline

BY HAROLD W. HEINE AND BRIJ LAL KAPUR

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The alkaline solvolysis of N-β-bromoethylaniline has been studied in 70% ethanol and it has been established that the reaction product is N-phenylethylenimine. The rate of solvolysis as measured by release of bromide ion satisfies the equation $d(Br^-)/dt = k'(\text{bromoamine}) + k''(OH^-)(\text{bromoamine})$, where k' represents a first-order constant for an internal nucleophilic displacement of the bromine by the anilino group, and k'' represents a second-order constant for the reaction of the base with N-β-bromoethylaniline to form N-phenylethylenimine.

In preceding papers of this series[1] examples of the participation of neighboring groups in displacement reactions as the distance between the seat of substitution and the nucleophilic groups was increased were discussed. It was observed that these nucleophilic groups through the formation of cyclic intermediates exert profound effects on the rate of the displacement reaction and other things being equal, the ease of participation of the neighboring nucleophilic group increases with the strainlessness of the ring formed. The work so far described has been concerned with the carboxylate ion, hydroxyl group and the alkoxide ion.

The present paper reports the results of a kinetic study of the alkaline solvolysis of N-β-bromoethylaniline. The product formed as described in the experimental section is N-phenylethylenimine. In contrast to earlier studies on the alkaline hydrolysis of β-halogenated primary amines[2] the rate is shown to be influenced by the concentration of sodium hydroxide.

Method of Rate of Measurement.—The measurements were carried out in a water-bath in which the temperature was thermostatically controlled to ±0.02°. Three to five mmoles of N-β-bromoethylaniline hydrobromide[3] was introduced into a 100-ml. volumetric flask previously immersed in a water-bath and which contained quantities of sodium hydroxide sufficient to make the concentration lie within the range 0.03–0.30 *M* and enough absolute ethanol to always give a 70% ethanol (by volume) solution. Ethanol (70%) preheated to the bath temperature was added to the mark and at convenient time intervals, 10-ml. aliquots were removed with a pipet and immediately delivered into a 125-ml. separatory funnel containing 50 ml. of chloroform and 15 ml. of distilled water. The mixture was shaken thoroughly and the chloroform removed. The water layer was then extracted with an additional 50 ml. of chloroform. Ten ml. of 6 *M* HNO_3 was then added to the water layer and the bromide ion was determined by the Volhard method. Extraction with chloroform was necessary because of the occurrence of undesirable color development during the Volhard titration which completely masked the end-point. Several experiments were carried out at higher ionic strength and added bromide ion to determine the possibility of a salt effect and a common ion effect, respectively.

In calculating the rate constants from the results of the titration, account must be taken of the fact that one-half of the total bromide ion determined in the infinity aliquot was due to the hydrobromide salt of the amine. The concentrations of sodium hydroxide recorded in the tables are after neutralization of the hydrobromide salt.

The rate of release of bromide ion followed a first-order rate law but, as shown in the example of Table I, and as summarized in Table II and Fig. 1, the rate of release of bromide ion is accelerated by increasing the concentration of the base.

TABLE I

RATE OF SOLVOLYSIS OF N-β-BROMOETHYLANILINE IN 70% ETHANOL AT 30.00°

Time (min.)	Vol. of 0.0505 *N* $AgNO_3$ (ml.)		10^2k (min.$^{-1}$)
0.03 *M* N-β-Bromoethylaniline and 0.06 *M* NaOH			
10.20	0.57		0.99
20.36	1.16		1.07
30.23	1.61		1.05
40.23	2.07		1.07
50.28	2.47		1.07
60.53	2.81		1.06
70.28	3.10		1.05
∞	5.93	(Mean)	1.06

N-Phenylethylenimine.—In the present study it is necessary to show that N-phenylethylenimine is the only product formed in the alkaline solvolysis of N-β-bromoethylaniline. Two and one-half liters of a solution 0.05 *M* with N-β-bromoethylaniline and 0.25 *M* with NaOH in 70% ethanol was allowed to react at 30° until all the bromide was displaced. With this concentration of hydroxide ion and at this temperature the half-life of the second-order process would be approximately 140 minutes. The half-life of the first-order process at the same temperature is 74 minutes. Thus, if the second-order process was leading to another

(1) H. W. Heine and W. Siegfried, THIS JOURNAL, **76**, 489 (1954); H. W. Heine, A. D. Miller, W. H. Barton and R. W. Greiner, *ibid.*, **75**, 4778 (1953); H. W. Heine, E. Becker and J. F. Lane, *ibid.*, **75**, 4514 (1953); J. F. Lane and H. W. Heine, *ibid.*, **73**, 1348 (1951).

(2) G. Salomon, *Helv. Chim. Acta*, **19**, 743 (1936).

(3) W. J. Pearlman, THIS JOURNAL, **70**, 871 (1948).

TABLE II

RATE CONSTANTS FOR THE FIRST-ORDER ALKALINE SOLVOLYSIS OF N-β-BROMOETHYLANILINE IN 70% ETHANOL AT 30.00°

Bromoamine, *M*	NaOH, *M*	$NaNO_3$, *M*	Added NaBr, *M*	10^2k (min.$^{-1}$)
0.03	0.03	0	0	1.00
.03	.06	0	0	1.06
.05	.10	0	0	1.13
.03	.12	0	0	1.19
.05	.15	0	0	1.23
.03	.18	0	0	1.30
.05	.20	0	0	1.34
.03	.307	0	0	1.56
.05	.05	0.05	0	1.03
.03	.03	0.15	0	1.03
.05	.05	0.20	0	1.06
.03	.307	0	0.03	1.53
.03	.18	0	0.02	1.28
.03	.06	0	0.05	Drifts upward 0.88–1.00

product, it would account for an appreciable quantity of the N-β-bromoethylaniline. When the reaction mixture was carefully worked up for product according to the procedure recently described[4] the yield of N-phenylethylenimine was 85%. A 5% yield of poly-N-phenylethylenimine which resulted from the polymerization of N-phenylethylenimine during the distillation was also obtained. The total yield of N-phenylethylenimine was thus 90%.

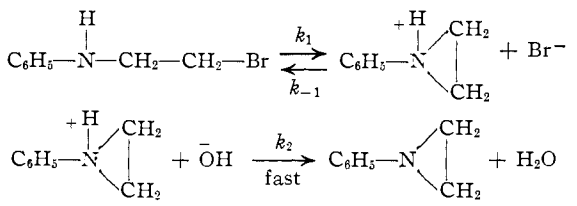
Another approach to this problem was through mass spectrometry. A 0.049 *M* standard solution of N-phenylethylenimine in 0.23 *M* sodium hydroxide solution was prepared and analyzed by the use of the mass spectrometer. A solution that was 0.05 *M* with respect to N-β-bromoethylaniline and 0.28 *M* with respect to sodium hydroxide was allowed to hydrolyze until all the bromide was displaced. This solution gave the identical mass spectrum as the standard and analyzed for 0.048 and 0.045 *M* N-phenylethylenimine on two separate runs. From these data it is concluded that the formation of N-phenylethylenimine is quantitative.[5]

Discussion

As Tables I and II and Fig. 1 show, the observed pseudo first-order rate constant for the release of bromide ion is increased by the addition of sodium hydroxide. Several runs with sodium nitrate revealed that the increase in rate is not due to a salt effect. These results require an expression of the kinetic form

$$dBr^-/dt = k'[\text{Bromoamine}] + k''[\bar{O}H][\text{Bromoamine}] \quad (I)$$

where k' represents the first-order constant for an internal nucleophilic displacement of the bromide by the anilino group, *i.e.*



The reverse reaction of the immonium ion with bromide ion becomes significant only when the total bromide ion present (that added plus the bromide ion acquired from the neutralization of the hydrobromide salt) exceeds the quantity of hydroxide present. For example as shown in Table II retardation in rate was only observed in the last experiment listed where the total bromide was 0.08 *M* and the hydroxide was 0.06 *M*. In addition the effect of added neutral salts on the measured first-order rate constant is small and contrary to expectations if the above equilibrium were important.

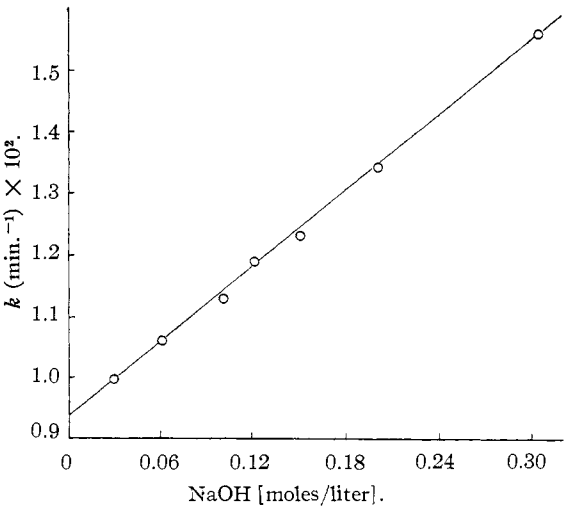
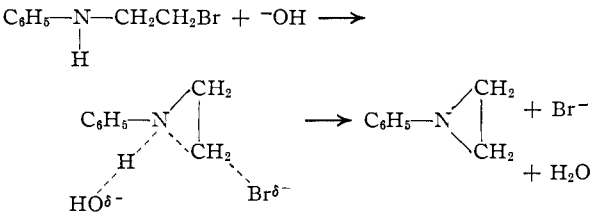
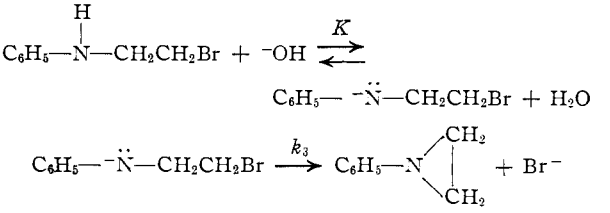


Fig. 1.—The dependence of the experimentally determined first-order constant for the release of bromide ion from N-β-bromoethylaniline on the sodium hydroxide concentration.

The k'' of equation I represents a second-order constant for the reaction of the base (either hydroxide or formed ethoxide ion) with N-β-bromoethylaniline to form N-phenylethylenimine. The second-order reaction with base can be pictured as proceeding either by a concerted mechanism with attack of hydroxide ion on the proton simultaneously with loss of the bromide ion, *i.e.*



or by a two-step process involving an equilibrium between the base and the anilino group of the bromoamine to form an anilino ion followed by a first-order displacement of the bromine by the anilino ion, *i.e.*



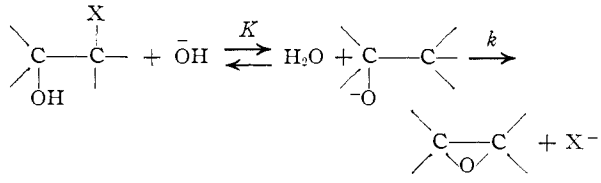
(4) H. W. Heine, B. L. Kapur and C. L. Mitch, THIS JOURNAL, 76, 1173 (1954).

(5) The authors are indebted to Dr. Fred W. McLafferty of the Dow Chemical Company for the mass spectra analyses. This method has a sensitivity of ±5%.

The rate equation would be

$$d(Br^-)/dt = k_3(C_6H_5\text{—}\ddot{N}\text{—}CH_2CH_2Br) = k_3K(C_6H_5\text{—}N\text{—}CH_2CH_2Br)(OH^-)$$

The k'' of equation I would then be equal to k_3K and thus depends upon the acidity of the bromoamine (which is enhanced by the presence of the halogen in the β-position) and upon the rate of displacement of the bromine by the anilino ion. This mechanism is similar to the one proposed by Winstein and Lucas[6] for the reaction of hydroxide on halohydrins to form ethylene oxides. Here too the first step is a rapid reversible proton transfer and the second, the unimolecular, rate-determining decomposition of the ion of the halohydrin.



It is of interest to note that other evidence for an anilino type ion has appeared recently. Pachter and Kloetzel[7] observed that treatment of *p*-amino-*p'*-nitrodiphenylamine with potassium hydroxide and methyl iodide gave an 83% yield of *p*-amino-*p'*-nitrodiphenylmethylamine. In this case a proton from the more acidic secondary amino group was removed by the base followed by displacement of the iodine by the *p*-amino-*p'*-nitrodiphenylamino ion.

The constant k' for the first-order process can be estimated from Fig. 1 by extrapolating to zero base concentration and is 9.4×10^{-3} min.$^{-1}$ In a separate rate run at zero hydroxide concentration, it was found that the experimental first-order velocity coefficients drifted downward rapidly. This was due to the rapid formation of hydrobromic acid which reacted with the N-β-bromoethylaniline to form the N-β-bromoethylanilinium ion which would not undergo the cyclization process. The *p*H of such a solution after 3 minutes reaction time was 4.6.

The second-order rate constant k'' can be estimated from the slope of the line in Fig. 1. The value thus obtained for the second-order process is 2.0×10^{-2} liter mole^{-1} min.$^{-1}$.

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LEWISBURG, PENNSYLVANIA

(6) S. Winstein and H. J. Lucas, THIS JOURNAL, **61**, 1576 (1939).
(7) I. J. Pachter and M. C. Kloetzel, *ibid.*, **74**, 1321 (1952).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Some Anionic Cleavage Reactions of Alloxan

BY FRANK R. FISHER AND ALLAN R. DAY

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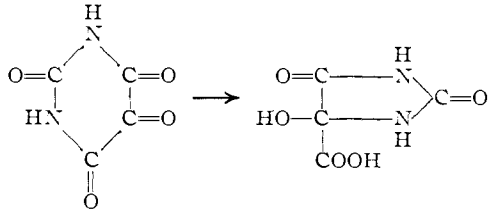
Treatment of anhydrous alloxan with sodium alkoxides gave sodium salts which are converted to the corresponding esters of alloxanic acid by reaction with hydrogen chloride. Reaction of alloxan hydrate with secondary amines formed the corresponding amides of alloxanic acid. A mechanism has been proposed for the conversion of the six-membered alloxan ring to the five-membered alloxanic acid ring.

It has long been known that alloxan when treated with alkalies is converted to salts of alloxanic acid.[1] This reaction involves the conversion of a six-membered ring to a five-membered ring.



Alloxan is of interest because of its ability to cause experimental diabetes in animals if it reaches the pancreas unchanged.[2] It is known that alloxan is rapidly converted to alloxanic acid in the blood stream and it is this rapid destruction of alloxan which normally prevents it from reaching the pancreas.[3]

The conversion of alloxan to alloxanic acid has been observed only in basic media. In view of the probable mechanism involved in these reactions, it was believed that similar ring shrinkages would be brought about by alkoxides and secondary amines. The present paper describes the reactions of alloxan with the latter reagents.[4]

Anhydrous alloxan reacted with sodium methoxide in methanol to give excellent yields of the sodium salt of methyl alloxanate from which the free ester was obtained by treatment with anhydrous hydrogen chloride. The reaction with sodium ethoxide in ethanol also gave a voluminous precipitate which appeared to be a sodium salt. Analytical data for this product did not agree with the formula for the sodium salt of ethyl alloxanate. Treatment of this compound with dry hydrogen chloride gave ethyl alloxanate. Alloxan was recovered also from these reactions, suggesting that the original precipitate was a complex containing both ethyl

(1) F. Wohler and J. Liebig, *Ann.*, **26**, 241 (1838); Schlieper, *ibid.*, **55**, 265 (1845); H. Biltz, M. Heyn and M. Bergius, *ibid.*, **413**, 68 (1916).
(2) J. S. Dunn, *et al.*, *Lancet*, **1**, 484 (1943).
(3) D. Seligson and H. Seligson, *J. Biol. Chem.*, **190**, 647 (1951); *Proc. Soc. Exptl. Biol. Med.*, **77**, 547 (1951).
(4) It has long been known that ammonia, primary aliphatic amines and amino acids react with alloxan to form murexide. Primary aromatic amines form simple addition compounds or the corresponding anils. Alloxanic acid derivatives have not been reported as being formed in these reactions.