

extract was dried with anhydrous potassium carbonate. After distillation of the solvent the residue was distilled under reduced pressure to give 2 g. (0.013 mole, 69% yield) of benzyl- $\alpha$ -*d* acetate, b.p. 93–95° (7 mm.) having  $\alpha^{25}_D -0.018 \pm 0.004^\circ$ ,  $\alpha^{20}_{465} -0.026 \pm 0.005^\circ$  (11). Redistillation gave material having  $\alpha^{25}_D -0.014 \pm 0.006^\circ$  and  $\alpha^{20}_{465} -0.016 \pm 0.009^\circ$  (11).

When benzyl bromide was carried through this procedure, it gave benzyl acetate having an infrared spectrum and index of refraction identical to that of freshly fractionated benzyl acetate.

(-)-Benzyl- $\alpha$ -*d* Acetate.—To a stirred mixture of 4 g. (0.037 mole) of benzyl- $\alpha$ -*d* alcohol having  $\alpha^{25}_D -0.860 \pm 0.004^\circ$ ,  $\alpha^{20}_{465} -1.044 \pm 0.007^\circ$  (14) (prepared by diluting the product of runs 1, 2 and 3 with ordinary benzyl alcohol), 15 ml. of pentane and 8 g. (0.1 mole) of pyridine maintained in an ice-bath was added 3.9 g. (0.05 mole) of acetyl chloride in 5 ml. of pentane. After stirring at room temperature for 4 hr., the mixture was diluted with pentane, washed with dilute acid and water and dried. Distillation through a small Vigreux column gave 5 g. (0.033 mole, 90% yield) of benzyl- $\alpha$ -*d* acetate, b.p. 99–100° (10–11 mm.), having  $\alpha^{25}_D -0.208 \pm 0.004^\circ$ ,  $\alpha^{20}_{465} -0.251 \pm 0.014^\circ$  (14).

Ethylene Glycol Diacetate.—Acetic anhydride was added to freshly fractionated commercial ethylene glycol diacetate, and the mixture was refluxed for 2 days. Fractional distillation through a 15-plate Oldershaw column gave ethylene glycol diacetate, b.p. 188.8–190.3°.

Lithium Bromide.—Mallinckrodt N.F. lithium bromide was dried in an oven at 180° for 2 days.

Anal.<sup>21</sup> Calcd. for LiBr: Br, 92.01. Found: Br, 92.00, 91.98.

(21) Analysis by the Microanalytical Laboratory, Department of Chemistry, University of California.

**Kinetics of Racemization of Benzyl- $\alpha$ -*d* Bromide with Lithium Bromide.**—A 0.06064 *M* solution of lithium bromide was prepared by making up 0.13170 g. of lithium bromide to a volume of 25 ml. with ethylene glycol diacetate. A 0.78 *M* solution of (+)-benzyl- $\alpha$ -*d* bromide was prepared by diluting 3.34 g. of benzyl- $\alpha$ -*d* bromide having  $\alpha^{25}_D +1.000$  (12) with ethylene glycol diacetate to a volume of 25 ml. at 20°. After equilibration of each solution in a 35° thermostat overnight the solutions were mixed and were used to fill a 4-dc. jacketed polarimeter tube maintained at 33.9  $\pm$  0.1° by circulating oil from a constant temperature bath. The optical rotation of the solution was measured as a function of time. Each rotation was the average of 2 readings, one taken immediately prior to and the other immediately after the time noted for the observed rotation. The rate was calculated from the data covering 75% completion of reaction by the method of least squares using the usual equation for a second-order rate constant.  $k_2$  was calculated to be  $9.46 \pm 0.21 \times 10^{-2}$  l. mole<sup>-1</sup> min.<sup>-1</sup>. The data are given in Fig. 1. The concentration of lithium bromide was corrected for solvent expansion using the coefficient of expansion of ethylene glycol diacetate determined by Sugden and Willis.<sup>15</sup> From the data of Sugden and Willis<sup>15</sup> the rate constant for exchange of benzyl bromide with lithium radiobromide at 33.9° was calculated to be  $9.36 \times 10^{-2}$  l. mole<sup>-1</sup> min.<sup>-1</sup>.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BUCKNELL UNIVERSITY]

## Intramolecular Substitution Reactions. IX. The Methanolysis of Some N-2-Bromoethylbenzamides<sup>1</sup>

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The kinetics of methanolysis of some N-2-bromoethylbenzamides were studied. It was shown that the kinetics were of first order and that electron-withdrawing groups substituted on the benzene ring decrease the rate of release of bromide ion. The products of solvolysis were N-2-methoxyethylbenzamides and either an oxazolinium bromide or a 2-aminoethylbenzoate hydrobromide. Addition of acetate ion did not affect the rate of methanolysis of N-2-bromoethyl-*p*-chlorobenzamide, although the reaction product was the corresponding oxazoline. The syntheses of a new oxazolinium bromide, a 2-aminoethylbenzoate hydrobromide and two N-2-methoxyethylbenzamides are reported.

In an earlier paper of this series<sup>3</sup> a kinetic study of the reaction of some N-2-bromoethylbenzamides with methoxide ion was described. The kinetics of the reaction was first order with respect to the benzamide and first order with respect to the base and the products were 2-oxazolines. Introduction of electron-withdrawing groups in the aryl system facilitated the formation of 2-oxazolines which indicated that the rate of reaction depends in part on the ease of removal of the hydrogen from the nitrogen. It was also observed that an appreciable displacement of bromine occurred when the N-2-bromoethylbenzamides were dissolved in methanol in the absence of methoxide ion. A kinetic study and product analysis of this solvolysis are presented here.

The rate of solvolysis as measured by the release of bromide ion followed first-order kinetics.

(1) Presented in part at the American Chemical Society Meeting-in-Miniature at Philadelphia, Penna., February 16, 1956.

(2) On leave of absence; at Dow Chemical Co., Bldg. 258, Midland, Michigan.

(3) H. W. Heine, *THIS JOURNAL*, **78**, 3708 (1956).

In contrast to the reactivity observed in the alkaline methanolysis, substitution of electron-withdrawing groups in the aryl system decreased the reaction rate. In a particularly critical study of the products of methanolysis of N-2-bromoethyl-*p*-chlorobenzamide, it was possible to isolate N-2-methoxyethyl-*p*-chlorobenzamide and in addition either *p*-chlorophenyloxazolinium bromide or 2-aminoethyl-*p*-chlorobenzoate hydrobromide, depending upon the method of working up the reaction mixture.

The methanolysis of N-2-bromoethyl-*p*-chlorobenzamide in the presence of acetate was investigated as well. First-order kinetics were again exhibited, the rate constant being identical with that obtained from the reaction of the benzamide in methanol. The product isolated under these experimental conditions was 2-*p*-chlorophenyl-2-oxazoline.

### Experimental

**Method of Rate Measurement.**—The measurements were carried out analogously to the alkaline methanolysis.<sup>3</sup> The

rate constants were steady over the reaction range indicated in Table II after which time downward drifts in the constants were detected. The drifting of the rate constants probably was due to the occurrence of the reverse reaction of bromide ion with the formed oxazolinium ion. To check this possibility a few runs were made on the methanolysis of N-2-bromoethyl-*p*-chlorobenzamide in the presence of added sodium bromide. Retardation in the rate of reaction was observed.

In calculating the rate constants the first sample was taken as the starting point of the reaction. A sample run for the methanolysis of N-2-bromoethylbenzamide is given in Table I, while Table II summarizes the data on the various N-2-bromoethylbenzamides investigated.

**Preparation of N-2-Bromoethylbenzamides.**—The benzamides used in this study were prepared by the method of Leffler and Adams<sup>4</sup> and were characterized in the previous paper of this series.<sup>3</sup>

**Reaction Products of the Methanolysis of N-2-Bromoethyl-*p*-chlorobenzamide.**—One hundred ml. of a methanol solution 0.05 *M* with respect to the substituted benzamide was placed in a water-bath at 22.90° for 4 weeks. The methanol was evaporated off by means of a water aspirator and the residue stirred with 10 ml. of water and filtered. The water-insoluble residue weighed 200 mg. and melted at 87–89°. Recrystallization from aqueous ethanol gave a product melting at 95–97°. Admixture of the product with an authentic sample of N-2-methoxyethyl-*p*-chlorobenzamide, prepared by reaction of 2-methoxyethylamine and *p*-chlorobenzoyl chloride, failed to depress the melting point.

*Anal.* Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>NCl: N, 6.55. Found: N, 6.30.

The aqueous filtrate was slowly evaporated to dryness (several days) and the residue of 920 mg. was found to be very soluble in water and insoluble in benzene. An aqueous solution of this material gave an immediate precipitate with silver nitrate solution. The substance was purified by dissolving in a minimum of methanol, adding benzene and cooling. The melting point was 162–165°. The product proved to be 2-aminoethyl *p*-chlorobenzoate hydrobromide. It failed to depress the melting point when admixed with an authentic sample of 2-aminoethyl *p*-chlorobenzoate hydrobromide prepared by the method of Goldberg and Kelly.<sup>5</sup> A bromine analysis corresponded to the theoretical.

*Anal.* Calcd. for C<sub>9</sub>H<sub>11</sub>O<sub>2</sub>NBrCl: Br, 28.50. Found: Br, 28.41.

If the residue remaining after the evaporation of methanol is treated with ether instead of water, in order to dissolve the N-2-methoxyethyl-*p*-chlorobenzamide, 520 mg. of an ether-insoluble substance remains which melts at 110–112°. This substance is water soluble and contains ionic bromide. The compound showed no depression in melting point when mixed with 2-*p*-chlorophenyloxazolinium bromide prepared from *p*-chlorophenyl-2-oxazoline by treatment with hydrogen bromide in ether.

*Anal.* Calcd. for C<sub>9</sub>H<sub>9</sub>ONBrCl: Br, 30.46. Found: Br, 30.40.

**Methanolysis of N-2-Bromoethyl-*p*-nitrobenzamide.**—In an analogous manner as described above methanolysis of 100 ml. of a 0.05 *M* solution of N-2-bromoethyl-*p*-nitrobenzamide over a 4-week period formed N-2-methoxyethyl-*p*-nitrobenzamide. The yield was 95 mg. and the crude product melted at 102–104°. Recrystallization from aqueous ethanol gave a product melting at 112–113°. The melting point when mixed with an authentic sample of N-2-methoxyethyl-*p*-nitrobenzamide was not depressed. No attempt was made to isolate the *p*-nitrophenyl-2-oxazolinium bromide.

**N-2-Methoxyethyl-*p*-chlorobenzamide.**—To an aqueous solution of 0.10 mole of 2-methoxyethylamine in 150 ml. of water was added portionwise a solution of 19.25 g. of *p*-chlorobenzoyl chloride dissolved in 50 ml. of benzene. The emulsion was shaken, and a solution containing 4.4 g. of sodium hydroxide in 95 ml. of water was added gradually. After 2 hr. of shaking, the solid residue was filtered and washed with dilute sodium carbonate solution and then dried. The yield of the crude product was 20.1 g. and the melting point was 94–96°. Recrystallization from dilute

ethanol gave a product melting at 97–98° and having the same properties as the product isolated from the methanolysis of N-2-bromoethyl-*p*-chlorobenzamide.

**N-2-Methoxyethyl-*p*-nitrobenzamide.**—Analogously as described above, 21.4 g. of *p*-nitrobenzoyl chloride when treated with 2-methoxyethylamine gave 18.2 g. of crude N-2-methoxyethyl-*p*-nitrobenzamide. The recrystallized product melted at 112–113°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>4</sub>N<sub>2</sub>: N, 12.50. Found: N, 12.80.

***p*-Chlorophenyloxazolinium Bromide.**—Following the procedure of Goldberg and Kelly<sup>6</sup> the *p*-chlorophenyl-2-oxazolinium bromide was prepared and found to melt at 113–115°.

**2-Aminoethyl-*p*-chlorobenzoate Hydrobromide.**—One gram of *p*-chlorophenyl-2-oxazolinium bromide was dissolved in 7 ml. of water and the reaction mixture heated at 90° for 1 hr. The water was evaporated off and 0.90 g. of product melting at 164–166° was obtained. As shown by Gabriel and Heymann<sup>7</sup> as well as Goldberg and Kelly,<sup>6</sup> heating aqueous solutions of 2-oxazolinium halides causes hydrolysis to the 2-aminoethyl benzoate hydrohalides.

**Product of Methanolysis of N-2-Bromoethyl-*p*-chlorobenzamide in the Presence of Potassium Acetate.**—Five mmoles of N-2-bromoethyl-*p*-chlorobenzamide were placed in a flask containing 100 ml. of methanol and 15 mmoles of potassium acetate, and the reaction mixture was allowed to stand 8 days at room temperature. The methanol was evaporated off and residue washed with water to remove the excess potassium acetate. There was obtained 835 mg. of crude product melting at 72–76°, which upon recrystallization and admixture with an authentic sample of *p*-chlorophenyl-2-oxazoline<sup>3</sup> failed to depress the melting point.

TABLE I  
RATE OF METHANOLYSIS OF N-2-BROMOETHYLBENZAMIDE AT 22.90°

Time, sec.	Vol. AgNO <sub>3</sub> (0.0497 N), ml./10-ml. aliquot	<i>k</i> × 10 <sup>3</sup> , sec. <sup>-1</sup>
6426	1.21	2.21
11706	2.16	2.33
15670	2.88	2.44
23040	3.43	2.28
27440	4.23	2.30
—	9.02	Mean 2.31

TABLE II  
RATE CONSTANTS FOR THE METHANOLYSIS OF SOME N-2-BROMOETHYLBENZAMIDES AT 22.90°

N-2-Bromoethylbenzamide	Benzamide, <i>N</i>	KOAc, <i>N</i>	<i>k</i> × 10 <sup>3</sup> , sec. <sup>-1</sup>	<i>A</i> , %
C <sub>6</sub> H <sub>5</sub> C(=O)NCH <sub>2</sub> CH <sub>2</sub> Br	0.0488	0	2.31	45
	.0397	0	2.40	57
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> C(=O)NCH <sub>2</sub> CH <sub>2</sub> Br	.0486	0	1.70	16
	.0460	0	1.63	18
	.0485	0.05	1.71	42
	.0480	.10	1.68	74
	.0490	.15	1.71	74
<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> C(=O)NCH <sub>2</sub> CH <sub>2</sub> Br	.0483	0	0.503	11
	.0462	0	.478	8
	.0474	0	.480	10

\* Reaction range over which the rate constants held steady.

## Discussion

The kinetic results as well as the various products isolated are in conformity with a mechanism proceeding by a rate-determining nucleophilic displacement of halogen by the benzamido group to form an oxazolinium ion (I). This step is followed by a subsequent reaction of the oxazolinium ion with either methanol, water or acetate ion to give N-2-methoxy-*p*-chlorobenzamide (II), 2-amino-

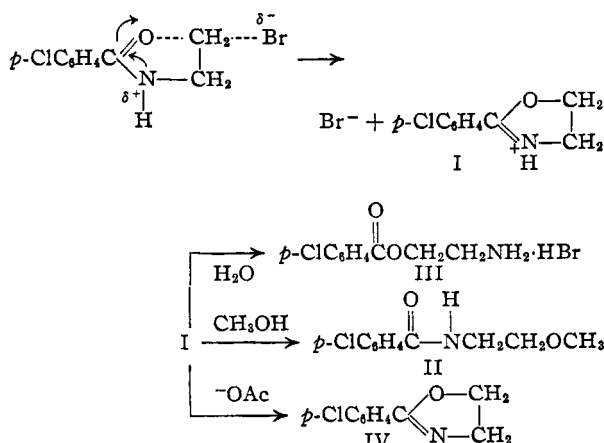
(4) M. T. Leffler and R. Adams, *THIS JOURNAL*, **59**, 2252 (1937).

(5) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1919 (1948).

(6) Methanolysis terminated after one week.

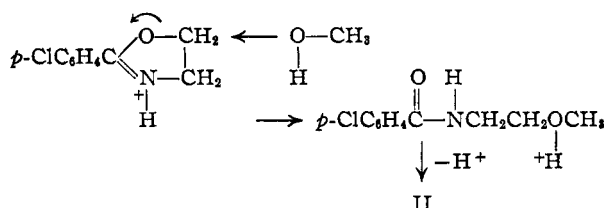
(7) S. Gabriel and T. Heymann, *Ber.*, **23**, 2495 (1890).

ethyl *p*-chlorobenzoate hydrobromide (III) or *p*-chlorophenyl-2-oxazoline (IV), respectively.

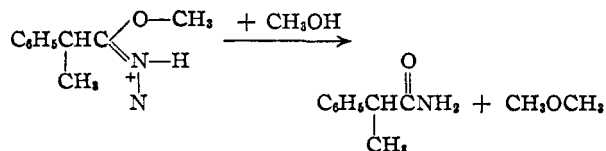


As anticipated and as shown in Table II, introduction of groups in the aryl system causing electron recession from the benzamido group decreases the rate of release of bromide ion. Such groups markedly enhance the rate in the alkaline methanolysis where a proton transfer from nitrogen to base is involved in the rate-determining step.<sup>8</sup>

The formation of N-2-methoxyethyl-*p*-chlorobenzamide in 18.7% yield after four weeks standing at room temperature of the N-2-bromoethyl-*p*-chlorobenzamide in methanol probably occurs by a slow attack of the oxazolinium ion by a solvent molecule as



Presumably longer reaction time would increase the yield of II. This reaction can be correlated with the methanolysis of methyl  $\alpha$ -phenylimino-propionate.<sup>8</sup> Here too an amide and an ether were among the products of solvolysis

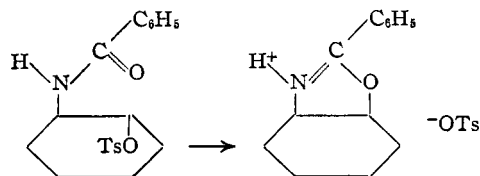


It is of interest that in the related solvolysis of *trans*-2-benzamidocyclohexyltosylate in boiling ethanol for 66 hr.<sup>9</sup> no ether formation was reported,

(8) S. M. McElvain and C. L. Stevens, *THIS JOURNAL*, **69**, 2663 (1947).

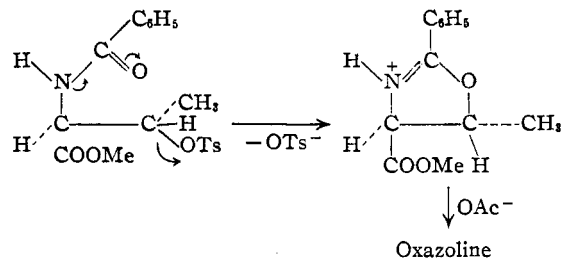
(9) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950).

although 2-phenyl-4,5-tetramethyleneoxazoline tosylate was formed in 73% yield.



As described in the Experimental section the 2-aminoethyl *p*-chlorobenzoate hydrobromide (III) was produced by the hydrolysis of the oxazolinium salt. This well-known reaction was first described for the conversion of 2-phenyloxazoline hydrochloride to 2-aminoethylbenzoate hydrochloride.<sup>7</sup> More recently and in harmony with our results it was shown that the hydrolysis of oxazoline salts is a slow process at low temperatures.<sup>5</sup>

Attention is drawn to the solvolysis experiments of N-2-bromoethyl-*p*-chlorobenzamide with acetate ion. Here the oxazoline is the product and the rate of reaction is unaffected by the presence of acetate ion. This indicates that the proton transfer takes place in a subsequent step to the displacement of halogen not just prior or simultaneous with halogen release as in the case with methoxide ion.<sup>8</sup> The reaction is similar to that reported for the conversion of the *p*-toluenesulfonate of N-benzoyl-allothreonine methyl ester to the corresponding oxazoline in ethanol containing potassium acetate.<sup>10</sup> Here too an oxazolinium ion is proposed as the intermediate, *i.e.*



An oxazolinium ion was also postulated for the reaction of *trans*-2-benzamidocyclohexyl *p*-toluenesulfonate with sodium acetate in ethanol.<sup>11</sup>

Finally it is of interest to report that a cursory investigation of the methanolysis of N-2-bromoethyl-*p*-nitrobenzamide established that the addition of acetate ion increased the rate of displacement of bromide ion. A second-order reaction of acetate ion with the more acidic N-2-bromoethyl-*p*-nitrobenzamide analogous to the reaction with methoxide ion may be responsible for this observation.

#### LEWISBURG, PENNSYLVANIA

(10) J. Attenburrow, D. F. Elliot and G. F. Penny, *J. Chem. Soc.*, 310 (1948).

(11) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *THIS JOURNAL*, **71**, 637 (1949).