The 4-aminoquinaldines appear to function as cationic bacteriostatic agents. This is in accord with the observation of Ormerod[5] on Antrycide in which it was shown that this compound acts as a cationic trypanocide. The unsubstituted 4-aminoquinaldines are strong bases and correlation of the bacteriostatic activity with the cationic concentration would be expected, providing the basic strength of the various derivatives showed significant differences. The compounds measured (Table III) exhibit the same order of basicity and, therefore, this property does not correlate with the differences observed for the bacteriostatic activity. When the 4-amino group was replaced or substituted, complete inactivity resulted. The 4-amino group of the quinaldine derivatives is responsible for the strong basic properties and appears to be essential for the bacteriostatic activity. This view is supported by our inhibition-reversal studies.[24] The inhibition of growth of test organisms by compound 40 could be quantitatively abolished with an anionic detergent, Aerosol OT (dioctyl sodiosulfosuccinate).

4,6-Diaminoquinaldine has a basic strength of the same order of magnitude as the 6-substituted derivatives, but shows no bacteriostatic activity. Only through an appropriate increase of the molecular weight above a necessary threshold value[25] is an active compound obtained. These compounds appear to act by virtue of being cations and as such they assume a coplanar configuration. Structural modifications which may lead to an increase in the coplanarity of the molecule as in the case of cinnamoyl derivatives enhances the observed bacteriostatic activity.

Acknowledgment.—The authors wish to thank Professors W. D. Kumler and L. A. Strait for some valuable discussions.

(24) C. T. Peng and T. C. Daniels, unpublished data.

(25) *Cf.* T. S. Work, *J. Chem. Soc.*, 1315 (1940); J. R. Keneford, *et al.*, *ibid.*, 2595 (1952).

SAN FRANCISCO 22, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BUCKNELL UNIVERSITY]

Intramolecular Substitution Reactions. VIII. The Formation of 2-Oxazolines from N-2-Bromoethylbenzamides[1]

BY HAROLD W. HEINE

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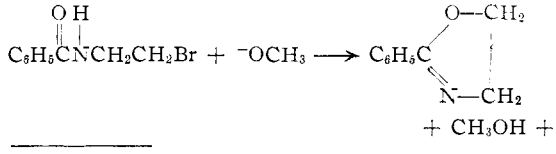
The reaction rates of some N-2-bromoethylbenzamides with methoxide ion have been studied. It was found that the kinetics was first order with respect to the N-2-bromoethylbenzamide and first order with respect to the methoxide ion and that the products were 2-oxazolines. Introduction of electron-withdrawing groups in the benzene ring enhanced the reactivity of the N-2-bromoethylbenzamides. Mechanisms are suggested to explain these results. The syntheses of a new N-2-bromoethylbenzamide and a new 2-oxazoline are reported.

A recent kinetic study of the alkaline methanolysis of some N-aryl-4-bromobutanamides[2] revealed that the reaction was first order with respect to the bromoamide and first-order with respect to methoxide ion and that N-arylpyrrolidones were formed in high yields. Furthermore, the rate of displacement of bromine was increased by the introduction of electron-withdrawing groups in the aryl system. To explain these kinetic results as well as the solvolytic products a two-step mechanism was proposed in which the first step was postulated to be a rapid-reversible transfer of a proton between the N–H group of the amide and the methoxide ion followed by a displacement of the bromine by the formed amido ion. An alternate possibility would be a concerted mechanism involving the removal of a proton from the nitrogen by the base simultaneously with displacement of the halogen by nitrogen.

We have now extended our studies to the kinetics of the alkaline methanolysis of some N-2-bromoethylbenzamides. In contrast to the N-aryl-4-bromobutanamides where internal N-alkylation takes place, the alkaline methanolysis of the 2-bromoethylbenzamides represents an example of internal O-alkylation, the products of which are the corresponding 2-oxazolines.



The kinetics of reaction as followed by release of bromide ion is first order with respect to methoxide ion and first order with respect to the N-2-bromoethylbenzamides. The benzamides selected for study indicate that the rate of formation of the 2-oxazolines depends in large part on the ease of removal of the proton from the nitrogen.

Experimental

Method of Rate Measurement.—The procedure for following the rate of release of bromide ion from the N-2-bromoethylbenzamides was the same as the method employed in measuring the rates of pyrrolidone formation.[1] In the case of N-2-bromoethylbenzamide and to a lesser extent of N-2-bromoethyl-*p*-chlorobenzamide the measurement of the second-order process was complicated because of a concurrent first-order solvolytic process also taking place. In order to evaluate the true second order rate constants for these two compounds the equation for a simultaneous first- and second-order reaction was integrated,

$$d[Br^-]/dt = k_1(b - x) + k_2(a - x)(b - x) \quad (1)$$

$$\frac{t[k_1 + k_2(a - b)]}{2.303} = \log \frac{b[k_1 + k_2(a - x)]}{(b - x)(k_1 + k_2a)} \quad (2)$$

and the first-order solvolytic constants determined experimentally. The first-order constants for N-2-bromoethylbenzamide and N-2-bromoethyl-*p*-chlorobenzamide were 2.36 and 1.52×10^{-5} sec.$^{-1}$, respectively. Various values of k_2 were then assumed until one was found which equated the two sides of equation 2. This is essentially the same method employed by Chadwick and Pacsu[3] for determining the second-order constants for the alkaline hydrolysis of 2-bromopropanoic acid.

Typical rate data for the alkaline methanolysis of N-2-bromoethyl-*p*-nitrobenzamide, which is uncontaminated by the first-order process and also N-2-bromoethylbenzamide are presented in Table I. The constants listed in Table I for N-2-bromoethylbenzamide were calculated by the use of equation 2. Table II is a summary of the kinetic studies for all the N-2-bromoethylbenzamides investigated. In cal-

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

(2) H. W. Heine, P. Love and J. L. Bove, THIS JOURNAL, **77**, 5120 (1955).

(3) A. P. Chadwick and E. Pacsu, *ibid.*, **65**, 392 (1943).

culating the rate constants the first sample was taken as the starting point of the reaction.

TABLE I

RATES OF ALKALINE SOLVOLYSIS OF N-2-BROMOETHYLBENZAMIDES AT 22.90°

0.0419 *N* $NaOCH_3$ Time, sec.	Mmoles Br^-/10 ml.	0.0419 *N* Bromobenzamide $k \times 10^2$, l. moles^{-1} sec.$^{-1}$
N-2-Bromoethyl-*p*-nitrobenzamide		
247.2	0.066	1.81
480.0	.109	1.75
788.4	.153	1.75
1084	.184	1.73
1393	.210	1.73
1749	.234	1.73
	Mean	1.75
0.0925 *N* $NaOCH_3$ Time, sec.	Mmoles Br^-/10 ml.	0.0423 *N* Benzamide $k \times 10^2$, l. moles^{-1} sec.$^{-1}$
N-2-Bromoethylbenzamide[a]		
594.0	0.053	0.223
1736	.129	.216
2458	.167	.218
3387	.206	.216
4261	.237	.216
	Mean	.218

[a] k calculated by means of equation 2.

TABLE II

SECOND ORDER RATE CONSTANTS FOR THE ALKALINE METHANOLYSES OF SOME N-2-BROMOETHYLBENZAMIDES AT 22.90°

N-2-Bromoethylbenzamide	$NaOCH_3$, *N*	Benzamide, *N*	$k_2 \times 10^2$, l. moles^{-1} sec.$^{-1}$
N-2-Bromoethyl-*p*-nitrobenzamide	0.0419	0.0419	1.75
	.0402	.0402	1.65
	.0450	.0241	1.73
		Mean	1.71
N-2-Bromoethyl-*p*-chlorobenzamide	0.0885	0.0385	0.456
	.0358	.0358	.450
		Mean	.453
N-2-Bromoethylbenzamide	0.0925	0.0423	0.218
	.0945	.0438	.220
	.0284	.0284	.221
		Mean	.220

Preparation of N-2-Bromoethylbenzamides.—These compounds were prepared by the method of Leffler and Adams.[4] The N-2-bromoethyl-*p*-nitrobenzamide melted at 121–123°; reported value[4] 121–122°. The N-2-bromoethylbenzamide melted at 104–105°; Gabriel[5] gave a value of 105–106°. The N-2-bromoethyl-*p*-chlorobenzamide had not been prepared previously. Using the procedure of Adams and thrice recrystallizing from benzene a 85% yield of the N-2-bromoethyl-*p*-chlorobenzamide was obtained which melted at 117–118°.

Anal. Calcd. for $C_9H_9ONBrCl$; Br, 30.46. Found: Br, 30.40.

Preparation of 2-Oxazolines.—Leffler and Adams[4] previously described the alkaline ethanolysis of N-2-bromoethyl-*p*-nitrobenzamide and reported the isolation of the corresponding 2-oxazoline in 91% yield. Likewise Gabriel and Stelzner[5] reports the product of alkaline solvolysis of N-2-bromoethylbenzamide as the 2-oxazoline. Since the N-2-*p*-chlorophenyl-2-oxazoline has not been previously characterized, the isolation of this compound will be described in detail.

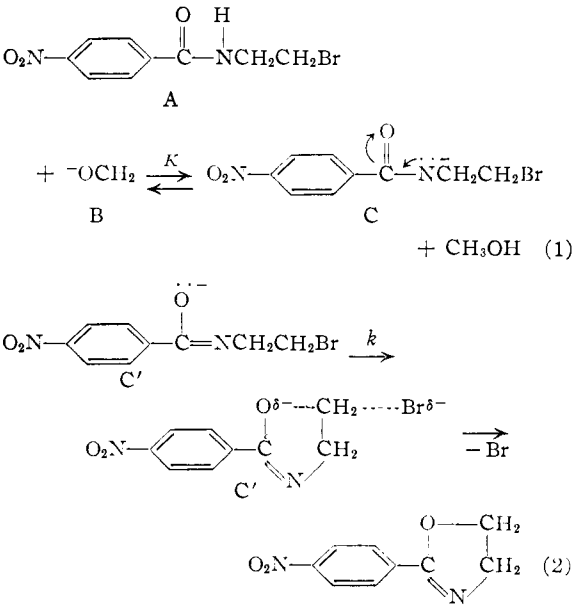
A flask containing 100 ml. of a methanol solution 0.05 *M* with respect to sodium methoxide and 0.05 *M* with respect to N-2-bromoethyl-*p*-chlorobenzamide was placed in a water-bath at 22.9° until all the bromide ion was released. The methanol was evaporated off by means of a water aspirator and the residue washed with water to remove the sodium bromide. A 94% yield of crude *p*-chlorophenyl-2-oxazoline was obtained which melted at 77–81°. Two recrystallizations from 50% ethanol gave a product melting at 85–87°.

Anal. Calcd. for C_9H_8ONCl: N, 7.70. Found: N, 7.51.

Discussion

As shown by Table II the formation of oxazolines from the reaction of N-2-bromoethylbenzamides with methoxide ion is a rapid process, even at room temperature and substitution of the electron-withdrawing chloro and nitro groups in the *para* position of the aromatic ring accelerates displacement of the bromine. Obviously, removal of the hydrogen from the nitrogen is involved in the rate-determining step, the more acidic N-2-bromoethyl-*p*-nitrobenzamide being 8 times as active as N-2-bromoethylbenzamide.

One interpretation consistent with these results is a stepwise mechanism whereby a rapid reversible proton exchange takes place between the methoxide ion and the benzamide to form a benzamido ion, which has a structure intermediate between forms C and C′, followed by a displacement of bromine by the negatively charged oxygen of the benzamido ion, *i.e.*



Here the release of bromide ion is given by

$$d[Br^-]/dt = k[C]$$

and since the concentration of the benzamido ion can be expressed in terms of the equilibrium step 1

$$[C] = K[A][B]$$

the rate of appearance of bromide would be

$$d[Br^-]/dt = kK[A][B]$$

It would be expected that the N-2-bromoethylbenzamido ion would be more active than the N-2-bromoethyl-*p*-nitrobenzamido ion in displacing the

(4) M. T. Leffler and R. Adams, THIS JOURNAL, **59**, 2252 (1937).
(5) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

bromine. However, this effect is overshadowed by the fact that the more acidic N-2-bromoethyl-*p*-nitrobenzamide produces a greater number of ions than the unsubstituted benzamide homolog.

TABLE III

RATES OF ALKALINE METHANOLYSIS OF N-2-BROMOETHYLBENZAMIDES AND N-ARYL-4-BROMOBUTANAMIDES AT 22.90°

Compound	$k \times 10^3$, l. moles^{-1} sec.$^{-1}$
N-2-Bromoethyl-*p*-chlorobenzamide	4.53
N-*p*-Chlorophenyl-4-bromobutanamide	9.41
N-2-Bromoethylbenzamide	2.20
N-Phenyl-4-bromobutanamide	3.00

An alternate interpretation which will equally well accommodate the data is a concerted mechanism whereby the methoxide ion removes the proton while at the same time the oxygen is executing a nucleophilic displacement of the bromine. Finally, it is of interest to compare under the same experimental conditions the relative rates of alkaline solvolyses of the N-2-bromoethylbenzamides to form the oxazolines with the alkaline solvolyses of the N-aryl-4-bromobutanamides which give the N-arylpyrrolidones. These results are shown in Table III.

Evidently there is no great difference in the rate of O-alkylation to form oxazolines and N-alkylation to form pyrrolidones.

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LEWISBURG, PENNSYLVANIA

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Reactions of Elemental Sulfur. I. The Uncatalyzed Reaction of Sulfur with Triarylphosphines[1]

BY PAUL D. BARTLETT AND GARBIS MEGUERIAN[2]

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The uncatalyzed reaction between ordinary sulfur, S_8, and triphenylphosphine under nitrogen to yield triphenylphosphine sulfide is of the second order. Its rate is strongly increased by ionizing solvents and by electron-releasing substituents in the phenyl groups, the reaction having a value of $\rho = -2.5$ in the Hammett equation. It is concluded that this reaction begins as a nucleophilic displacement of sulfur on sulfur by the basic phosphine, with opening of the sulfur ring to a dipolar ion which then reacts rapidly in a series of follow-up reactions with more triphenylphosphine. Two other forms of elemental sulfur, the rhombohedral hexatomic form of Aten and the amorphous form produced by irradiation in solution, react immeasurably fast with triphenylphosphine, affording a tritation method both for total sulfur and for S_8 in the presence of other forms.

Introduction.—The eight-membered ring structure of the common rhombic or monoclinic sulfur has been fully established by X-ray methods,[3] and an interesting explanation has been offered for the stability of this eight-membered ring in comparison to all other structural forms of sulfur.[4] At temperatures above the melting point the thermal interconversion of different molecular forms of sulfur proceeds readily, and in the neighborhood of 140° the equilibrium favors very high polymers of biradical[5] or cyclic[6] character. In sulfur vapor at much higher temperatures the equilibrium shifts back ultimately in favor of the species S_2 and S_1.[7]

Among the many reactions of elemental sulfur with organic compounds, the well-known processes of dehydrogenation and of the vulcanization of rubber take place at such high temperatures that rapid interconversion of a number of molecular forms of sulfur may be assumed. There are, however, certain reactions into which sulfur enters with organic compounds under such mild conditions that the mechanism by which the eight-membered ring is opened and the sulfur distributed to a number of different molecules presents a challenging problem. When sulfur acts as an inhibitor of the polymerization of olefinic substances[8,9] or reacts with triphenylmethyl radicals[10] or with liquid ammonia,[11] the conditions are so mild that the products must be formed by a series of steps commencing with the direct opening of the eight-membered ring of sulfur. While it is likely that the reactions of sulfur with free radicals are of the homolytic type, the importance of ammonia, hydroxy compounds, amines and sulfides as redistributors of sulfur[12,13] suggests that the sulfur ring may be opened also by heterolytic or polar mechanisms. The present work is concerned with a reaction clearly of this type.

The Reaction of Sulfur with Tertiary Phosphines.—Trialkylphosphines react vigorously with sulfur to yield trialkylphosphine sulfides.[14,15] Replacement of one alkyl by a phenyl group leaves the

(1) This work was supported in part by a grant from the Research Corporation. Reported at the Fifth Conference on Reactions Mechanisms, Durham, N. H., September 10, 1954.

(2) Corina Borden Keen Fellow from Brown University, 1950–1951.

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(15) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Chapter 6.