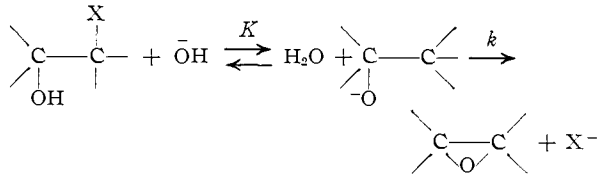
The rate equation would be

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

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]

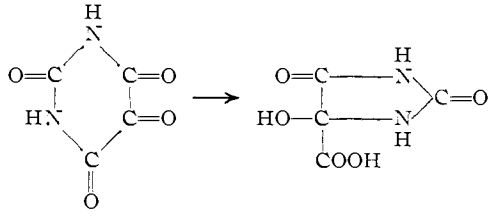
Some Anionic Cleavage Reactions of Alloxan

BY FRANK R. FISHER AND ALLAN R. DAY

RECEIVED MARCH 24, 1955

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

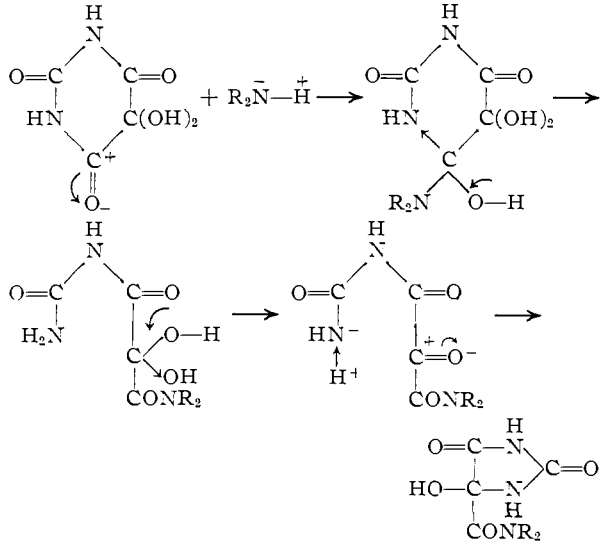
(1) F. Wohler and J. Liebig, *Ann.*, **26**, 241 (1838); Schlieper, *ibid.*, **55**, 265 (1845); H. Biltz, M. Heyn and M. Bergius, *ibid.*, **413**, 68 (1916).
(2) J. S. Dunn, *et al.*, *Lancet*, **1**, 484 (1943).
(3) D. Seligson and H. Seligson, *J. Biol. Chem.*, **190**, 647 (1951); *Proc. Soc. Exptl. 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.

alloxanate and alloxan. Treatment of alloxan with sodium *n*-butoxide in *n*-butyl alcohol gave similar results.

Alloxan reacted in aqueous solution with morpholine, piperidine, pyrrolidine and dimethylamine to form the corresponding amides of alloxanic acid. The amides were obtained as their monohydrates. The same compounds were obtained from methyl alloxanate and the secondary amines in aqueous solution.

Efforts to remove water from the monohydrates failed. For example, heating 4-alloxanoylmorpholine monohydrate at 100° *in vacuo* over phosphorus pentoxide did not remove the water. However, when it was heated *in vacuo*, just above its melting point (111°), it lost the calculated amount of morpholine and carbon dioxide and was converted to 5-hydroxyhydantoin. From these observations it was assumed that hydrolysis of the amide occurred and the resulting alloxanic acid was decarboxylated to the 5-hydroxyhydantoin.

The conversion of alloxan to derivatives of alloxanic acid probably involves the attack of a suitable anion on a solvated alloxan molecule according to the mechanism



Experimental

All melting points are corrected unless otherwise noted. Anhydrous alloxan was prepared by heating commercial alloxan monohydrate *in vacuo* at 200° for two hours.

Reaction of Alloxan with Sodium Methoxide.—Three grams of anhydrous alloxan was dissolved in 50 ml. of dry methanol and filtered. To the filtrate was added an equivalent of sodium dissolved in dry methanol. There was an immediate color change to orange followed by precipitation. After cooling for two hours, the product was removed by filtration and dried, yield 97%. All attempts to recrystallize this compound failed. An analytical sample was prepared as above, using threefold excess of solvent. The product decomposes at 237–240°.

Anal. Calcd. for $C_5H_5O_5N_2Na$: C, 30.62; H, 2.57; N, 14.29; Na, 11.73. Found: C, 30.53; H, 2.53; N, 14.25; Na, 11.56.

In cases where excess sodium methoxide was used, a red, gummy substance was formed in addition to the sodium salt of methyl alloxanate.

Six grams of the sodium salt, suspended in 100 ml. of dry methanol, was treated with dry hydrogen chloride. The orange salt dissolved and the color changed to yellow. The solution was filtered and the filtrate evaporated to dryness. The residue was extracted with acetone and chloroform added to the warm extract until it became cloudy. After cooling, 4.2 g. (79%) of crude product was obtained. Colorless crystals of methyl alloxanate were obtained by another recrystallization from acetone–chloroform; m.p. 170.1–171.3°.

Anal. Calcd. for $C_5H_6O_5N_2$: C, 34.49; H, 3.47; N, 16.09. Found: C, 34.43; H, 3.58; N, 16.12.

A mixed melting point with methyl alloxanate prepared according to Biltz[5] showed no depression.

Reaction of Alloxan with Sodium Ethoxide.—Three grams of anhydrous alloxan was dissolved in 55 ml. of dry ethanol and the solution filtered. To the filtrate was added 15 ml. of dry ethanol containing slightly less than one equivalent of sodium ethoxide. A pink precipitate formed and after cooling it was removed by filtration, dec. 255–260°. The analytical data for this compound did not agree with the theoretical values for the sodium salt of ethyl alloxanate.

A sample (0.3 g.) of this product was suspended in 10 ml. of dry ethanol and saturated with dry hydrogen chloride. After standing for 3 hours, the insoluble inorganic salt was removed by filtration and the filtrate evaporated to dryness. The residue was extracted with acetone and the ethyl alloxanate precipitated by the addition of chloroform. A small amount of gummy material separated at first. This was removed and the filtrate was cooled overnight to obtain the ester. The latter was recrystallized from acetone–chloroform and colorless crystals were obtained, yield 33%, m.p. 115–116°. A mixed melting point with ethyl alloxanate prepared by Biltz's method[4] gave no depression on melting.

The ethyl ester was obtained in better yield by treating a suspension of the sodium salt of methyl alloxanate in dry ethanol with dry hydrogen chloride.

Reaction of Alloxan with Sodium *n*-Butoxide.—To a filtered solution of 3 g. of anhydrous alloxan in 250 ml. of *n*-butyl alcohol was added a solution prepared by dissolving 0.45 g. of sodium in 15 ml. of *n*-butyl alcohol. After cooling, the pink precipitate was removed and dried at 100°, yield 3.5 g., dec. 224–228°. The analytical data for this compound did not agree with the theoretical values for the sodium salt of *n*-butyl alloxanate.

Two grams of this product was suspended in 60 ml. of *n*-butyl alcohol and saturated with dry hydrogen chloride. After standing for two hours, the solution was evaporated to dryness and the residue extracted with dry acetone. The acetone extract was evaporated to dryness and the residue dissolved in a minimum amount of dry ether. Petroleum ether then was added until the solution became cloudy. (In some cases a small amount of a viscous oil separated which was separated by decantation and discarded.) After cooling for 2 hours, the colorless crystals were removed and again crystallized from dry ether–petroleum ether, yield 40%, m.p. 134.8–135.6°.

Anal. Calcd. for $C_8H_{12}O_5N_2$: C, 44.44; H, 5.60; N, 12.96. Found: C, 44.38; H, 5.62; N, 13.03.

This ester also was prepared from acid potassium alloxanate[6] by treating a suspension of the salt in *n*-butyl alcohol with dry hydrogen chloride, yield 65%, m.p. 134.8–135.6°, mixed m.p. showed no depression.

Reactions of Alloxan Hydrate with Secondary Amines.—It was found that the melting points of the amides, obtained from the reactions of alloxan and secondary amines, taken in a capillary tube which was evacuated and sealed were sharp, whereas the melting points obtained by the usual procedure had a range of 3–5°. All melting points reported in this section were taken in evacuated capillary tubes.

Reaction of Alloxan Hydrate with Morpholine.—To a solution of 2 g. of alloxan monohydrate (0.0125 mole) in 15 ml. of water was added 1.1 ml. (0.0125 mole) of morpholine. The solution was boiled for a few minutes until it became yellow. Dry ethanol (220 ml.) was added and the solution cooled at 0° overnight. The product so obtained was recrystallized several times from dry methanol–ether as colorless crystals, yield 65%, m.p. 119.8–120.8°.

Anal. Calcd. for $C_8H_{11}O_5N_3 \cdot H_2O$: C, 38.87; H, 5.30; N, 17.00. Found: C, 38.87; H, 5.31; N, 17.00.

Attempts to remove the water of hydration by heating at

(5) H. Biltz and F. Lachman, *J. prakt. Chem.*, **113**, 309 (1926).

(6) H. Biltz and F. Lachman, *ibid.*, **113**, 333 (1926).

100° *in vacuo* were unsuccessful. When the compound was heated at 111° *in vacuo*, a 77.7-mg. sample lost 39.9 mg. The theoretical loss in weight is 41.7 mg. (carbon dioxide and morpholine). The residue was soluble in water and insoluble in ethanol. It turned dark brown at about 185° and decomposed at 195–200°. This compares favorably with the physical properties reported for 5-hydroxyhydantoin.[7]

Reaction of Alloxan Hydrate with Piperidine.—The above procedure was used with piperidine in place of morpholine; yield of 1-alloxanoylpiperidine monohydrate 50%, m.p. 133–133.5°.

Anal. Calcd. for $C_9H_{13}O_4N_3 \cdot H_2O$: C, 44.08; H, 6.17; N, 17.13. Found: C, 44.06; H, 6.13; N, 17.14.

Better yields were obtained by evaporating the reaction mixture to dryness *in vacuo* and recrystallizing the residue from dry methanol–ether. This amide was prepared also from methyl alloxanate and piperidine. Mixed melting points showed no depression.

(7) H. Biltz and M. Kobel, *Ber.*, **54**, 1802 (1921).

Reaction of Alloxan Hydrate with Pyrrolidine.—The above procedure was used with pyrrolidine except that the solution was allowed to stand for two days instead of refluxing for a few minutes. Dry ethanol–ether was added to precipitate the 1-alloxanoylpyrrolidine monohydrate. The latter was recrystallized from methanol; yield 40%, m.p. 121.6–122.7°.

Anal. Calcd. for $C_8H_{11}O_4N_3 \cdot H_2O$: C, 41.56; H, 5.67; N, 18.17. Found: C, 41.49; H, 5.78; N, 18.33.

Reaction of Alloxan Hydrate with Dimethylamine.—A solution of 2 g. of alloxan monohydrate in 15 ml. of water was saturated with dimethylamine and the reaction mixture worked up by the general procedure; yield of N,N-dimethylalloxanamide monohydrate 50%, m.p. 126.4–127.3°.

Anal. Calcd. for $C_6H_9O_4N_3 \cdot H_2O$: C, 35.12; H, 5.41; N, 20.48. Found: C, 35.19; H, 5.55; N, 20.38.

This amide was prepared also from methyl alloxanate and dimethylamine. Mixed melting points showed no depression.

PHILADELPHIA 4, PENNA.

[CONTRIBUTION FROM THE U. S. NAVAL ORDNANCE LABORATORY]

The Michael Reaction in Non-alkaline Media. I. The Synthesis of 5-(2-Nitro-1-arylethyl)-barbituric Acids

BY MORTIMER J. KAMLET

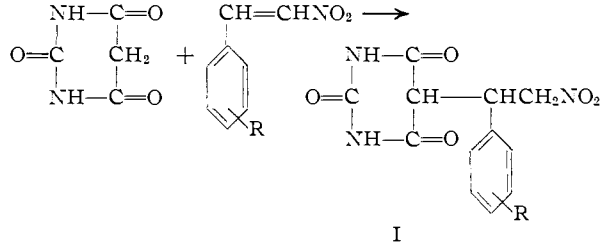
RECEIVED APRIL 2, 1955

Barbituric acid reacts with a series of substituted β-nitrostyrenes in the absence of catalysts to form the 5-(2-nitro-1-arylethyl)-barbituric acids. The structure of these compounds has been established by oxidative degradation to dialuric acid and by conversion to the corresponding arylsuccinic acids on refluxing with concentrated hydrochloric acid.

Ingold[1] has suggested that the rate-determining step in the Michael addition involves a nucleophilic attack by the anion of the adding active methylene compound at the β-carbon atom of the α,β-unsaturated molecule. Since the ionization constants of most pseudo-acidic addenda are so low that only infinitesimal amounts of the anionic species are furnished by dissociation in neutral media, the typical Michael addition requires alkaline catalysis. It would seem, however, that the addition should require no extraneous base in media of higher dielectric constant than those commonly used for this reaction and with an active methylene compound of sufficiently low pK.

Since barbituric acid (pK 4.05 in water at 25°) fulfills the requirement set forth above, it was chosen as a model compound in a study of the kinetics of the Michael addition in neutral and acidic media.[2] The use of this compound in the Michael reaction has been recorded by Bahner,[3] who obtained a series of 5-(2-nitroalkyl)-barbiturates by treating the potassium or benzyltrimethylammonium salt with nitroölefins in boiling aqueous ethanol. Neutralization with mineral acid yielded the free 5-substituted barbituric acids. In the course of the present study it has been confirmed that where this compound adds to conjugated olefinic systems the addition occurs quite readily in the absence of catalysts while competing side reactions are minimized.

When dissolved in minimal amounts of aqueous dioxane, aqueous methanol or aqueous acetic acid, barbituric acid reacted smoothly at room temperature with β-nitrostyrene to give the 1:1 adduct, 5-(2-nitro-1-phenylethyl)-barbituric acid (I, R = H) in good yields. Analogous 1:1 adducts were

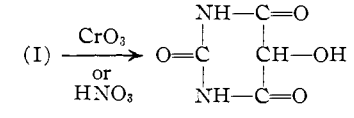


I

R = H, *p*-$(CH_3)_2N$, *p*-CH_3O, *p*-Cl, 3,4-CH_2O_2, *m*-NO_2

formed with *m*,β-dinitro-, *p*-chloro-β-nitro-, 3,4-methylenedioxy-β-nitro-, *p*-methoxy-β-nitro- and *p*-dimethylamino-β-nitrostyrene (Table I), but attempts to effect similar reactions with cinnamic acid, acrylic acid, methyl acrylate and diethyl benzalmalonate under a variety of conditions were unsuccessful as were attempts to join 5-nitrobarbituric acid or indandione-1,3- with the nitrostyrenes.

Chromic or nitric acid oxidation of I to dialuric acid indicated that addition to the nitrostyrene had occurred at the methylene carbon rather than at one of the imino nitrogens or at the hydroxyl position of an enolic tautomer, while the conversion of I to the corresponding arylsuccinic acid on prolonged refluxing with concentrated hydrochloric acid served further to confirm the assigned structure.



(1) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 694.

(2) M. J. Kamlet and D. J. Glover, to be published.

(3) C. T. Bahner, U. S. Patent 2,527,293 (Oct. 24, 1950).