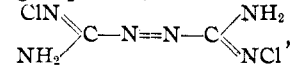
[CONTRIBUTION FROM THE RESEARCH LABORATORY, WALLACE AND TIERNAN PRODUCTS COMPANY, BELLEVILLE, N. J.]

N,N'-Dichloroazodicarbonamidine (Azochloramid), an N-Chloro Derivative of the Oxidant in an Oxidation–Reduction System

BY F. C. SCHMELKES AND H. C. MARKS

A review of the literature of the organic N-chloro compounds[1] reveals many variations in stability. A new, very stable member of this group, N,N' - dichloroazo - dicarbonamidine,  , referred to in this paper as azochloramid, has been synthesized in this Laboratory.

The compound has been prepared by the careful chlorination of azo-dicarbonamidine, $HN{=}C(NH_2)N{=}N(NH_2)C{=}NH$ or hydrazodicarbonamidine, $HN{=}C(NH_2)NH{-}HN(NH_2)C{=}NH$, salts with hypochlorites or chlorine gas.

The preparation of azo-dicarbonamidine and hydrazo-dicarbonamidine has been reported by Thiele.[2]

The fact that the chlorination produces no other change in the molecule than that shown above is further proved by the reduction of azochloramid to azo-dicarbonamidine or hydrazodicarbonamidine (according to the experimental conditions) and the re-chlorination of these products to azochloramid.

Experimental Details

Seven grams of azo-dicarbonamidine sulfate was suspended in 100 cc. of water, immersed in an ice-bath and 50 cc. of 2.5 *N* NaOCl was added from a dropping funnel with efficient stirring, the temperature being 10–15°. The yellow product was filtered off, washed with a little cold water and either recrystallized from boiling water, or preferably dried and recrystallized from ethyl acetate; yield, 4.5 to 5 g. (90%).

If desired 6 g. of hydrazo-dicarbonamidine sulfate can be used, this requiring 75 cc. of 2.5 *N* NaOCl.

Anal. Calcd. for $C_2H_4N_6Cl_2$: C, 13.12; H, 2.20; N, 45.93; Cl, 38.75. Found: C, 13.19; H, 2.42; N, 45.94; Cl, 38.58. *Iodimetric Titration.* Calcd.: 183.01 g. (1 mole) contains 4 equivalents due to 2 N-chloro groups and 2 equivalents due to the azo group: total, 6 equivalents. Found: 5.987 equivalents.

The compound displays dimorphism crystallizing either in bright yellow needles or plates. This suggests the possibility of a *syn-anti* isomerism.[3] It decomposes without melting at 155.5° and when pure is odorless and practically tasteless. The solubilities in non-aqueous solvents are as follows: benzene 0.05%; ether, amyl acetate and glycerin, about 0.5%; ethyl alcohol, ethyl acetate, butyl acetate, methyl propyl ketone, methyl isobutyl ketone and ethylene glycol, about 1%; di-ethylene glycol and methyl ethyl ketone, about 2%; methyl alcohol and acetone, about 3%; ethylene glycol mono-methyl ether, ethylene glycol mono-ethyl ether, di-ethylene glycol mono-ethyl ether, di-ethylene glycol di-ethyl ether, and di-ethylene glycol mono-butyl ether, about 4–6%; penta-ethylene glycol mono-ethyl ether, 9%. The solubility in water was at 1°, 150; 20°, 280; 27.5°, 370; 40°, 610; 61°, 1490 mg. per liter. Many of the solutions are unstable but a number of others, particularly certain esters such as ethyl acetate, butyl acetate, diethyl phthalate and triacetin, apparently can be kept indefinitely.

It is indicative of the stable nature of the compound that unlike the great majority of N-chloro compounds, it does not immediately liberate any iodine from potassium iodide unless the solution has been made quite acid.

A qualitative test is the formation of a brick-red, amorphous precipitate with ammoniacal silver, which is soluble in excess ammonia, therein differing from the similar precipitate obtained with azodicarbonamidine.

When a water suspension of N,N'-dichloroazo-dicarbonamidine is treated with an excess of chlorine in the cold, a brown, amorphous product is obtained which decomposes between 80–85°, is generally unstable, is insoluble in water, and soluble in acetone. Iodimetric titration gives a figure corresponding to that for trichlorazodicarbonamidine.

Like all N-chloro compounds, azochloramid has bactericidal properties, but unlike the majority of such compounds its reactivity with extraneous organic matter is very low. Consequently, this compound is effective against microorganisms in the presence of material which, acting as an acceptor, destroys the efficiency of many other compounds.

Reduction to Azo-dicarbonamidine Salts.—A saturated solution of azochloramid in acetone or ethylene glycol mono-ethyl ether is treated below 25–30° with an excess of sulfur dioxide gas. The yellow sulfate is filtered off, washed with acetone until the latter is no longer colored, and then recrystallized from water at 60°.

If hydrogen sulfide or preferably hydrogen chloride gas is used, the hydrochloride is obtained and is recrystallized from a mixture of equal parts of methyl alcohol and ether to which has been added sufficient azochloramid to impart a distinct yellow color.

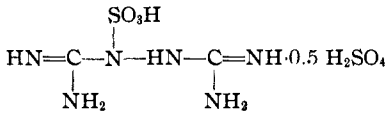
Reduction to Hydrazo-dicarbonamidine Salts.—An aqueous suspension of azochloramid is treated in the cold with hydrogen sulfide or sulfur dioxide gas until only a faint yellow coloration remains. After filtering off the sulfur it is evaporated to dryness and the white residue recrystallized from 50% ethyl alcohol. With hydrogen sulfide the hydrochloride is obtained and with sulfur di-

(1) Houben, "Die Methoden der organischen Chemie," Georg Thieme, Leipzig, 1925, Vol. IV, p. 398–416.

(2) Thiele, *Ann.*, **270**, 39, 42 (1892); **273**, 140 (1893).

(3) "Hand- und Jahrbuch der chemischen Physik," Akademische Verlagsgesellschaft, m. b. H., Leipzig, 1933, Vol. IV, Goldschmidt, "Stereochemie."

oxide the sulfate. However, if the product is precipitated at room temperature by the addition of alcohol to the solution obtained from the sulfur dioxide reduction, there is obtained a derivative containing a sulfonic group in anhydrized linkage. This compound is less soluble in water than the hydrazo derivative and is not as readily converted to azochloramid with sodium hypochlorite. It forms a crystalline, heliotrope-colored salt with ammoniacal copper and does not reduce ammoniacal silver as does the hydrazo derivative. This fact indicates that the sulfonium group is attached to the molecule at the azo linkage and suggests the following structure.



The difference between the two sulfuric acid residues can readily be shown by first precipitating with excess barium chloride in the cold, filtering off the barium sulfate, and then heating the filtrate for a few minutes, preferably to the boiling point, whereupon a second precipitate of barium sulfate is obtained. From the weights of the two precipitates, the disposition of the sulfuric acid in the molecule is determined. The final filtrate is found to contain hydrazo-dicarbonamidine hydrochloride.

Anal. Calcd. for $C_2H_7N_6SO_3H \cdot 0.5\ H_2SO_4$: C, 9.79; H, 3.70; N, 34.28; SO_3, 32.65; SO_4, 19.58. Found: C, 9.81; H, 3.73; N, 34.11; SO_3, 31.73; SO_4, 19.55.

Attempts to Prepare Related Compounds.—Neither bromine nor iodine derivatives could be obtained; bromine merely oxidizes hydrazo-dicarbonamidine to the azo compound. Neither was it possible to prepare any methyl, ethyl, formal or benzal derivatives. When such derivatives of hydrazo-dicarbonamidine were chlorinated, either no product or the unsubstituted N-chloro derivative was obtained.

Such closely related compounds as azo-dicarbonamid,[4,5] $(CONH_2)N{=}NCONH_2$, and hydrazo-dicarbonamid,[5] $(CONH_2)NHHN(CONH_2)$, yielded no N-chloro derivatives, confirming Darapsky.[6] The same was true of the corresponding thiamid,[7] amidoguanazole,[8] $HN{=}\overline{CNHHNC(NH)}NNH_2$, and amido-urazole,[9] $O{=}\overline{CNHNHC(O)}NNH_2$. Recently a yellow, amorphous N-chloro derivative of guanazole[10] was obtained by Stollé and Dietrich.[11]

Discussion

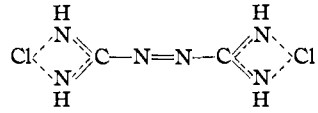
A comparison of azochloramid with other N-chloro compounds with respect to stability and reactivity toward organic acceptors reveals certain relations between structure and stability. Most compounds of this class in solution, even when protected from light, are relatively unstable. In some cases, such as dichloro-urea,[12,13] this relative instability is presumably due to the great extent to which the N-chloro linkage is hydrolyzed, while in others such as N-chloroacetanilide,[14,15] it is necessary to take into account not only the greater hydrolysis of its N-chloro group,[16] but also the possibility of substituting chlorine in the benzene nucleus.[17,18] In the N-chlorophenylguanidines this reaction may proceed with explosive violence.

Preliminary measurements, using an adaptation of the method described by Soper,[16] indicate that the N-chloro linkage in azochloramid is only very slightly hydrolyzed—as suspected from the length of time required to liberate iodine from a potassium iodide solution. However, while there is the possibility of substituting chlorine in the nucleus, the quinone-chlorimides[19] resemble azochloramid more closely than any other N-chloro compounds studied. And here, again, the explanation may be the slight extent of hydrolysis, *e. g.*, N-chloroquinone-imide-4 liberates iodine very slowly from potassium iodide solutions and exhibits no chlorinous odor.

But also it should be noted that both of these compounds are N-chloro derivatives of oxidants in reversible oxidation–reduction systems.[20] Such derivatives in general possess an unexpected degree of stability and low reactivity, particularly if compared with similar compounds, not derived from such systems, and with the unchlorinated oxidants themselves. Thus the contrast between N,N'-dichloroquinone diimide-1,4 (a stable crystalline solid) and N,N'-dichlorophenylene diamine-1,3 (an unstable, yellow oil) would seem to be more than an insignificant coincidence. And, again, azochloramid is much more stable than azo-dicarbonamidine and the same holds true for the quinone-chlorimides; in each case chlorination renders the molecule less reactive and more rigid. These considerations indicate that the ordinary method of picturing the struc-

(4) Thiele, *Ann.*, **271**, 129 (1892).
(5) Curtius and Heidenreich, *J. prakt. Chem.*, [2] **52**, 468–80 (1895).
(6) Darapsky, *ibid.*, [2] **76**, 448 (1907).
(7) Freund and Wischewiansky, *Ber.*, **26**, 2877 (1893).
(8) Pellizzari, *Gazz. chim. ital.*, **35**, 300 (1905); **37**, 321 (1907).
(9) Linch, *J. Chem. Soc.*, **101**, 1756 (1912).
(10) Pellizzari, *Gazz. chim. ital.*, **24**, I, 491–495 (1894).
(11) Stollé and Dietrich, *J. prakt. Chem.*, **127**, 98 (1934).
(12) Chattaway, *Proc. Roy. Soc.* (London), **A81**, 381 (1908).
(13) Chattaway, *J. Chem. Soc.*, **95**, 464 (1909).
(14) Bender, *Ber.*, **19**, 2272 (1886).
(15) Chattaway and Orton, *J. Chem. Soc.*, **75**, 1050 (1899).
(16) Soper, *ibid.*, **127**, 98 (1925).
(17) Armstrong, *ibid.*, **77**, 1047 (1900).
(18) Chattaway and Orton, *ibid.*, **79**, 274 (1901).
(19) Willstätter and Mayer, *Ber.*, **37**, 1498 (1904).
(20) Our measurements indicate that in the system hydrazo-dicarbonamidine : azo-dicarbonamidine E^0 is unusually high for an organic system.

ture of such compounds is inadequate. Thus in the structural formula of azochloramid given above, the chlorine was arbitrarily bound to the imino group with the realization that such a picture as the following would probably convey a much closer idea of the properties of the compound.



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Summary

1. A method of preparing N,N′-dichloroazodicarbonamidine from azo-dicarbonamidine or hydrazo-dicarbonamidine salts has been described. Solubility data together with other physical properties of the compound and reactions which can be used for its detection and estimation have been given.

2. Methods of reducing azochloramid to azo-dicarbonamidine or hydrazo-dicarbonamidine and the formation of a derivative of azo-dicarbonamidine containing a sulfonic group in anhydrized linkage have been described and evidence offered for the structure of the latter compound.

3. Some of the factors underlying the stability of N-chloro compounds have been discussed.

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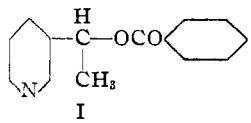
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

A Pyridyl Dimethylaminopropyl Benzoate[1]

BY JOHN M. SNELL AND S. M. MCELVAIN

In a previous paper[2] the benzoate and *p*-aminobenzoate of β-pyridylmethylcarbinol were described. Both of these compounds, in the form of their hydrochlorides, show extremely low intravenous toxicities to white rats and, while the *p*-aminobenzoate is inactive for surface anesthesia, the benzoate (I) produces a longer duration of anesthesia of the rabbit's cornea than does cocaine. This benzoate, however, causes considerable irritation of the rabbit's eye, an effect which, it seemed, might possibly be ascribed to the acidity of the salt of such a weak base. For this reason it was thought that the introduction of another basic group into the molecule would sufficiently neutralize the acidity of the salt to make it considerably less irritating. Work in this direction has resulted in the synthesis of β-pyridyl-β-dimethylaminoethylcarbinyl benzoate. It was isolated in the form of its monohydrochloride (II).



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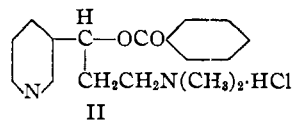
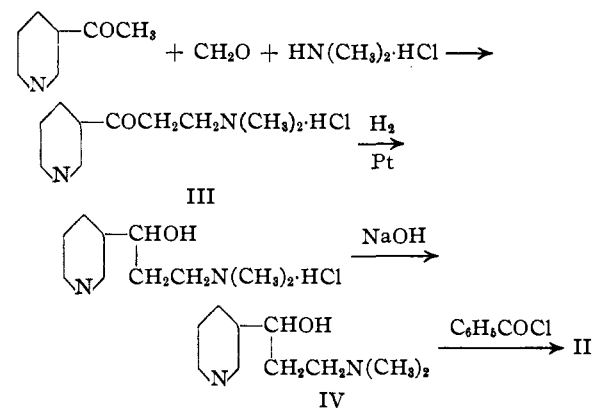


II

The compound II was prepared by the application of the Mannich reaction[3] to β-acetylpyridine, the reduction of the resulting amino ketone (III) to the corresponding carbinol (IV), and finally the benzoylation of this carbinol to produce the desired compound (II). These reactions are illustrated thus



Pharmacological Report.—The compound II is being studied pharmacologically by Mr. Charles L. Rose of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. A preliminary report of its pharmaco-

(1) This work was supported in part by a grant from the Wisconsin Alumni Research Foundation.

(2) Strong and McElvain, THIS JOURNAL, **55**, 816 (1933).

(3) Mannich, *et al.*, *Arch. Pharm.*, **255**, 261 (1917); **265**, 589 (1927).