

A brief report of the preliminary pharmacological study of these compounds together with a discussion of some relationships between their structure and pharmacological action is given.

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[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY OF AMHERST COLLEGE]

PREPARATION OF DICHLOROACETIC ACID

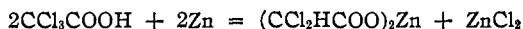
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In 1925 Doughty and Black² described the preparation of dichloroacetic acid by the reaction of copper powder with trichloroacetic acid or aniline trichloroacetate, in benzene. They obtained yields of aniline dichloroacetate, from which they prepared dichloroacetic acid, up to 75% of the theoretical. Other experimenters have used this method with varying success, and the irregularity of yield, as reported privately to the senior author, has led to a reëxamination of the procedure by the present authors. We first repeated the procedure of Doughty and Black and found that when insufficient hydrogen chloride is used for complete saturation in precipitating the copper chlorides and aniline hydrochloride, a complex substance containing copper and aniline is formed, which is unsatisfactory to work with. We did, however, obtain yields from 50 to 70% of the theoretical, without making especial effort for maximum yield.

The reaction of trichloroacetic acid in aqueous solution on various metals has been studied to some extent in this Laboratory, and in 1929 Doughty and Lacoss³ showed that the reaction between trichloroacetic acid and zinc in water proceeds quantitatively according to the equation



and it has also been found⁴ that cadmium, iron and copper act similarly with trichloroacetic acid in aqueous solution, while with magnesium and aluminum considerable quantities of hydrogen are formed and the reaction is evidently more complicated. In view of the difficulties which have been reported in obtaining consistent yields by the method of Doughty and Black, we decided to investigate the reaction in aqueous solution and, if practicable, develop a procedure for the preparation of dichloroacetic acid, though earlier attempts in this direction have given low yields. It seemed possible that the hydrolysis of trichloroacetic acid to chloroform and

¹ The work here reported is in partial fulfilment of the requirement for "Honors in Chemistry" by Gerhard J. Derge. The work has been checked by Howard W. Jones, to whom we wish to express our thanks.

² Doughty and Black, *THIS JOURNAL*, **47**, 1091 (1925).

³ Doughty and Lacoss, *ibid.*, **51**, 852 (1929).

⁴ Unpublished work by H. W. Doughty.

carbon dioxide might be the cause of the low yield, and that proper control of temperature might give better results. We therefore made a preliminary study of the hydrolysis of trichloroacetic acid as affected by temperature.

Hydrolysis of Trichloroacetic Acid.—At room temperature hydrolysis is very slow. A 1.007 molar solution of trichloroacetic acid in water was prepared on February 13. On May 10 it was found to be 0.9856 molar. Other determinations were made at approximately 60 and at 100°. The temperature control at 60° was within two or three degrees, and at the higher temperature the solution was simply boiled with return condenser, portions being removed from time to time for analysis. The velocity constants were calculated as for a first order reaction, as the water concentration remains constant, using the equation $k = (1/t) \log [a/(a-x)]$, where t is elapsed time in minutes, a is the original concentration of trichloroacetic acid, x is the moles of chloroform per liter produced, and therefore $a - x$ is the concentration of trichloroacetic acid at time t .

TABLE I
HYDROLYSIS OF TRICHLOROACETIC ACID AT 100°

t	Concentration of $\text{CCl}_3\text{COOH} + \text{HCl}$	Concentration of HCl	$(a - x) =$ Concentration of CCl_3COOH	k
0	0.9656 = a	0.0000	0.9656	
30	.7490	.0105	.7385	0.0039
90	.4669	.0190	.4479	.0037
330	.0774	.0341	.0433	.0040

Apparently there was some hydrolysis of the trichloromethyl group, either of the trichloroacetic acid or the resultant chloroform, as indicated by the hydrochloric acid found. Correction was made for this by subtracting the concentration of hydrochloric acid from the total acid found.

TABLE II
HYDROLYSIS OF TRICHLOROACETIC ACID AT 60°

t	Concentration of $\text{CCl}_2\text{COOH} + \text{HCl}$	Concentration of HCl	$(a - x) =$ Concentration of CCl_2COOH	k
0	0.9469	0.000	0.9469	
90	.9332	.0040	.9292	0.000091
240	.9101	.0087	.9014	.000088

From these results the temperature coefficient of the hydrolysis is found to be $k_{(t+10)}/k_t = 2.576$. Evidently the loss by hydrolysis would be relatively small if the temperature is kept at about 60° during the reaction of trichloroacetic acid with copper. The following procedure was accordingly adopted.

Preparation of Dichloroacetic Acid.—A solution of 55 g. (one-third mole) of trichloroacetic acid in 450 cc. of water is placed in a one-liter flask, which is provided with a mechanical stirrer and thermometer. The stirring is started at once, 35 g. of copper powder (approximately 0.5 gram atomic weight) is added, and the temperature raised

to 60°. (As stated in previous communications, we have found the so-called "dark copper bronze" powder used by decorators to be very satisfactory for use in this connection.) The reaction is quite strongly exothermic, and the heating may be discontinued after the desired temperature, 60°, is reached. After stirring for about one hour and a half, the solution is heated to boiling for about one hour, during which the solid portion of the mixture changes in color from a dirty green to white, due to the action of the excess of copper on the cupric chloride, precipitating cuprous chloride. This reaction always occurs to some extent, and unless an excess of copper is used over the amount calculated in terms of the corresponding reaction with zinc, trichloroacetic acid is found in the product. After the precipitate has become white and shows no excess copper, the mixture is cooled to allow maximum separation of cuprous chloride. It is then filtered and washed with small amounts of cold water. The filtrate is now saturated with hydrogen sulfide until the precipitation of copper sulfides is complete. The precipitate is removed by filtering with suction, washed, and the filtrate, which should be colorless or slightly yellow, is distilled under diminished pressure. The portion which boils above 50° at 20 mm. is fractionated at 20 mm. Dichloroacetic acid boils at 102° (20 mm.). The whole dilute solution of dichloroacetic acid is distilled under diminished pressure, as otherwise the yield is not satisfactory. This appears to be due to the presence of the hydrochloric acid formed during the precipitation of the copper sulfides, as experiment has shown that at 100° the hydrolysis of dichloroacetic acid is not more than 10% in twenty-four hours. The yield by this procedure is about 80%.

To check the purity of the product, the acid thus prepared was analyzed by titration with sodium hydroxide, and 2.1006 mg. moles of dichloroacetic acid required 2.0848 mg. moles of sodium hydroxide, indicating 99.25% purity. The density of the acid was found, by pycnometer, to be d_{22}^{22} 1.5594. Perkin⁵ gives d_4^4 1.5843 and d_{25}^{25} 1.5604, and Doughty and Black² found d_{20}^{20} 1.5666 and d_4^{20} 1.5634.

The melting point of our acid was between 5 and 6°. The melting point of dichloroacetic acid as given in successive issues of Beilstein is variously recorded as -4, -10.8, +10.8° and finally as reported by Kendall,⁶ -4.1° and +9.7° according to the rate of cooling and the degree of undercooling. Under ordinary conditions, therefore, the melting point of this acid cannot be regarded as a criterion of purity.

Summary

A simple and convenient method is described for the preparation of dichloroacetic acid by the reaction of copper with trichloroacetic acid in aqueous solution.

The hydrolysis of trichloroacetic acid has been studied at 60° and at 100° and the temperature coefficient found to be 2.576.

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⁵ Perkin, *J. Chem. Soc.*, 65, 422 (1894).

⁶ Kendall, *THIS JOURNAL*, 36, 1230 (1914).