

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY.]

THE PREPARATION OF DICHLORO-ACETIC ACID FROM CHLORAL.

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The work described in this paper was undertaken at the suggestion of Professor Treat B. Johnson, and represents a part of a prolonged research dealing with the development of new methods of synthesizing organic combinations which possess both biochemical and therapeutical interest.

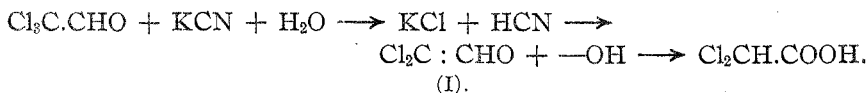
The fact that chloral can be converted into dichloro-acetic acid has been known since 1873, when Wallach¹ discovered that this change could be brought about by the action of potassium cyanide, or potassium ferrocyanide, on the aldehyde in aqueous solution. The transformation



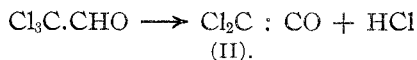
is one of both theoretical and practical interest, and the fact that it can be accomplished by the action of cyanides of alkali metals in aqueous solution is unique, in view of the fact that the action of even weak alkaline reagents, such as magnesium hydroxide,² cause chloral to decompose readily into chloroform and formic acid.



Different theories have been advanced to explain the mechanism of this interesting reaction. Wallach² first interpreted the change as one involving the formation of potassium chloride and prussic acid by the combined action of potassium cyanide and water on chloral. He assumed an intermediate unsaturated halogen derivative (I), which reacted with a hydroxyl group to form dichloro-acetic acid. According to this explanation, the hydroxyl group of the water by dissociation functions in a double capacity, namely, as an oxidizing and a reducing agent according to the following equation:



The next interpretation proposed by Wallach³ was one involving a direct dissociation of chloral into hydrochloric acid and dichloroketene (II), under the influence of potassium cyanide as a catalytic agent. Then hydrochloric acid

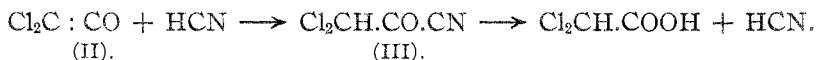


¹ Wallach, *Ann.*, **173**, 288 (1874).

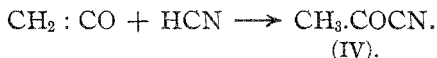
² Wallach, *Ber.*, **10**, 1526 (1877).

³ *Loc. cit.*

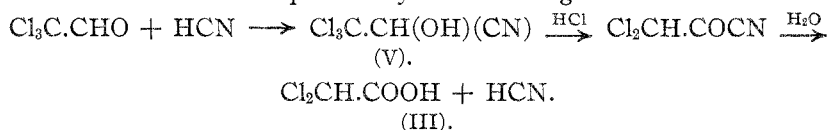
interacts with the alkali cyanide to produce prussic acid which adds to the ketene (II) to form dichloro-acetyl cyanide (III). This substance, in turn is transformed by hydrolysis into dichloro-acetic and prussic acids.



That such an interpretation is not applicable to this reaction can be concluded from the work on ketene $\text{CH}_2 : \text{CO}$, and its derivatives carried on by Staudinger and his co-workers. These investigators were unable to prepare dichloro-ketene (II)¹ on account of its great tendency to polymerize. Furthermore, if it were formed from chloral in aqueous solution it would undoubtedly add water in preference to prussic acid in accordance with the well known behavior of ketene towards this acid. Deakin and Wilsmore,² as well as Chick and Mortimer³ have shown that prussic acid does not add to ketene to form acetyl cyanide (IV).



The correct interpretation of the mechanism of this change, and the one which finds further confirmation experimentally in our work, is that recently proposed by Kötzt.⁴ He has proven conclusively that a cyanogen radical and water are essential factors in this reaction, and also that chloral-cyanohydrin (V) is formed as an intermediate product. The latter (V), when heated with water or amines in aqueous solution is converted into dichloro-acetyl cyanide which immediately undergoes hydrolysis with water to give dichloro-acetic and prussic acids. The complete transformation is expressed by the following formulas:



Therefore, chloral-cyanohydrin (V), by the action of water, undergoes a decomposition similar to that which is produced when tetrachloro-ethyl ether (VI) is treated with alkali.⁵ The primary product of dissociation in both cases is the corresponding unsaturated ethylene derivative represented by Formulas VII and VIII, respectively. While the unsaturated ether (VII) is a stable derivative, Compound VIII, on the other hand, contains a mobile hydrogen atom which causes it to rearrange at once to give the corresponding acyl cyanide (III), a substance unstable in the presence of water.

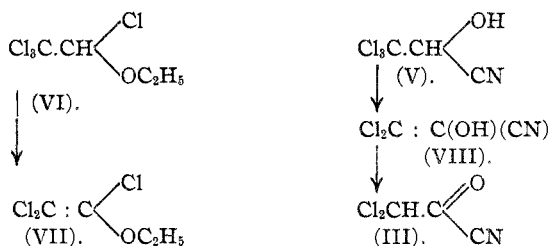
¹ Staudinger, *Ann.*, **256**, 53 (1907).

² Deakin and Wilsmore, *Proc. Chem. Soc. (London)*, **97**, 1968 (1911).

³ Chick and Mortimer, *ibid.* **24**, 77 (1908).

⁴ Kötzt, *J. prakt. Chem.*, **88**, 531 (1914).

⁵ Henry, *Ber.*, **12**, 1839 (1879).



New facts supporting this mechanism of the reaction are presented in the experimental part of this paper.

The applications of dichloro-acetic acid for synthetical purposes have been very limited. It has been necessary for us to prepare the reagent in large quantities for our researches. This we have accomplished without the use of potassium salts. We find that a good yield of chloro-acetic acid can be produced by the interaction of chloral with an aqueous solution of commercial sodium cyanide. This simple method of making the reagent in any quantity desired is described in the experimental part of this article.

Experimental Part.

Procedure Employed for the Preparation of Dichloro-acetic Acid in Small Units.

The apparatus used for our preliminary experiments, that is, during the study of the chloral method of synthesis, consisted of a 500-cc. flask connected by a rubber stopper with a return condenser and a dropping funnel, and a stirring device which operated through a mercury seal. Chloral hydrate was first introduced into the flask in aqueous solution; then the solution of sodium cyanide was added at such a rate that the temperature of the mixture did not rise above 50°. The solution was stirred constantly during this operation and the reaction was complete after about 2 hours. This solution was evaporated to dryness on a water bath, and the dry residue of crude sodium dichloro-acetate and sodium chloride was suspended in anhydrous benzene. By saturation of this mixture with hydrochloric acid, the free acid was obtained. It was separated from the benzene by fractional distillation. Finally, it was purified by distillation under diminished pressure.

Action of Sodium Cyanide on Chloral Hydrate.

In order to determine what effect the substitution of commercial sodium cyanide for potassium cyanide would have in the preparation of dichloro-acetic acid according to Wallach's method a series of experiments was made as described above but with varying proportions of sodium cyanide. The amount of cyanide employed was calculated on the basis of the actual cyanogen content of the commercial product and the chloral

used was always dissolved in a definite amount of water. The results obtained in a series of 5 experiments are recorded in Table I.

TABLE I.
50 G. of Chloral Hydrate Dissolved in 150 Cc. of Water.

| Expt. | Sodium cyanide dissolved in 60 cc. of water. G. | Yield of $\text{Cl}_2\text{CH}_2\text{COOH}$. % |
|--------|--|---|
| 1..... | 7 | 36 |
| 2..... | 12 | 53 |
| 3..... | 15 | 55 |
| 4..... | 20 | 67 |
| 5..... | 25 | 61.5 |

These results show very conclusively that sodium cyanide can be substituted in this reaction for potassium cyanide. A theoretical proportion of sodium cyanide is productive of a 55% yield of the acid, but this yield diminishes decidedly when less than a molecular proportion of cyanide is used. An increase of about 20% over the calculated amount gives the maximum yield of the dichloro-acetic acid. These results are represented graphically in Fig. 1.

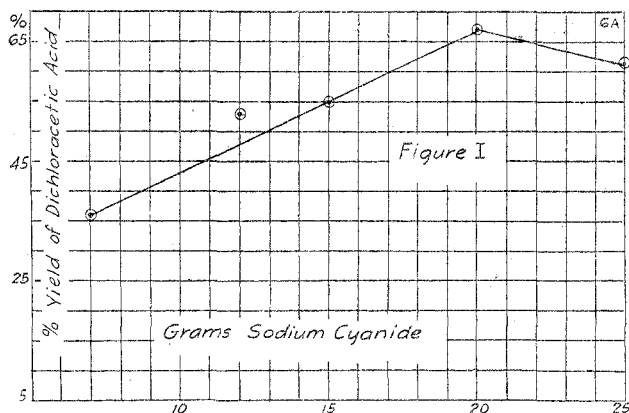


Fig. 1.

The Effect of Dilution on the Yield of Dichloro-acetic Acid.

In order to determine the best concentration for producing a maximum yield of dichloro-acetic acid, a series of experiments was performed in which the proportion of water was varied within wide limits, but the proportion of sodium cyanide was kept constant. A definite quantity of chloral hydrate was taken in each case and the series was operated at the beginning with water just sufficient to dissolve the sodium cyanide. The results of these experiments are recorded in Table II and represented graphically in Fig. 2.

TABLE II.
20 G. of NaOH in 60 Cc. of H₂O and 50 G. of Chloral Hydrate.

| Expt. | Water added to chloral. Cc. | Yield of C ₂ HCl ₂ COOH. %. |
|--------|-----------------------------|---|
| 1..... | 0 | 12 |
| 2..... | 50 | 46 |
| 3..... | 100 | 59 |
| 4..... | 150 | 67 |
| 5..... | 200 | 66 |

It was observed that this reaction is very violent and almost uncontrollable when molten chloral is used, and is productive of a very low yield of the acid. Dilution of the solution with water leads to an increase in the yield which reaches its maximum when about 150 cc. of water is used for every 50 g. of chloral hydrate.

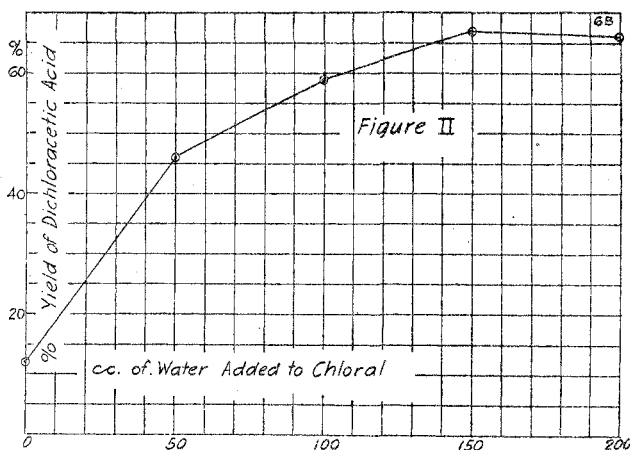


Fig. 2.

Effect of Substituting Certain Salts in Place of Sodium Cyanide.

In order to determine whether the cyanide radical is a necessary factor in this transformation of chloral hydrate into dichloro-acetic acid, a series of experiments was run in which various salts were incorporated. The salts investigated were sodium carbonate, sodium sulfite, sodium hydrogen sulfite and sodium acetate, and the operation was carried out in a manner similar to that employed when sodium cyanide was used. No dichloro-acetic acid was formed; in all cases chloroform was the normal product of reaction. On the other hand, when some sodium cyanide was introduced with any one of these salts, dichloro-acetic acid was formed immediately. These results are in accord with the original assumption made by Wallach,¹ namely, that the cyanide radical functions in this reaction, and that the reaction cannot be brought about in its absence. The results of our experiments are recorded in Table III.

¹ Wallach, *Ann.*, 173, 288 (1874).

TABLE III.
Fifty G. of Chloral Hydrate Dissolved in 150 Cc. of Water.

| Salt (sodium). | Weight used; dissolved in 45 cc. of water. G. | Sodium cyanide dissolved in 15 cc. of water. G. | Yield of $\text{C}_2\text{H}_3\text{COOH}$. %. |
|-----------------------|---|---|---|
| Acetate..... | 40 | .. | 0 |
| Carbonate..... | 16 | .. | 0 |
| Hydrogen sulfite..... | 32 | .. | 0 |
| Sulfite..... | 19 | .. | 0 |
| Acetate..... | 40 | 7 | 55 |
| Carbonate..... | 16 | 7 | 53 |
| Hydrogen sulfite..... | 32 | 7 | 38 |
| Sulfite..... | 19 | 7 | 51 |

In the application of this reaction, dichloro-acetic acid is always obtained in the form of its sodium salt by evaporation of the solution. To prepare the free acid from this salt, our first procedure was to dry the latter and then treat it with a slight excess of hydrochloric acid; finally, the liberated acid was extracted with benzene. This method of operation was never productive of yields over 50%. In the next modification of the procedure the aqueous solution was acidified with hydrochloric acid after completion of the reaction and then evaporated to dryness under diminished pressure. The dichloro-acetic acid was removed from the solid residue by extraction with benzene. This method of operation proved unsatisfactory, because a large amount of tar was always formed and, furthermore, the quality of the dichloro-acetic acid obtained was very poor. The use of sodium hydrogen sulfate to liberate the dichloro-acetic acid was not successful. The method finally chosen was that originally employed by Johnson and Cretcher¹ which involves the suspension of the crude sodium salt of dichloro-acetic acid in dry benzene and subsequent decomposition of it by hydrogen chloride passed through the benzene. Dichloro-acetic acid is purified best by distillation under diminished pressure. During the purification, a small amount of tarry residue is always obtained which is decomposed violently by treatment with nitric acid. This reaction is productive of a substance having the odor of chloropicrin which indicates that, very probably, some unaltered chloral-cyanohydrin is present in the dichloro-acetic acid before distillation.

The following procedure, based on the results of many preliminary experiments and already employed by us with success, is recommended for the preparation of pure dichloro-acetic acid in kilogram quantities.

One thousand g. of chloral hydrate is dissolved in 3000 cc. of water and the solution is heated to 40° in a large enameled pail, or stock pot. A stirrer is introduced before beginning the next operation. When the temperature reaches 40°, the flame is removed, the stirrer started, and a solution of 400 g. of commercial sodium cyanide dissolved in 1100 cc. of

¹ Johnson and Cretcher, *THIS JOURNAL*, 37, 2149 (1915).

water is added to the solution. This solution should be added through a separatory funnel just rapidly enough to prevent the temperature of the mixture from rising above 50° . No application of heat is necessary since the heat of reaction is sufficient to maintain this temperature. After all of the cyanide is added the mixture is kept at 50° for an hour. At this stage the clear yellow solution is transferred to a large porcelain evaporating dish and the water evaporated over a steam-bath until a viscous, pasty mass is obtained. This crude mass of salt is then transferred to a saponification vessel where it is suspended in 2.5 liters of commercial benzene. The vessel used by us for this operation was an ordinary 4-liter wide-mouth bottle, which was equipped with a cork containing a stirrer operated through a mercury seal, as well as inlet and exit tubes for the passage of hydrogen chloride. While the hydrogen chloride is bubbled through the benzene the bottle is surrounded with ice water and the stirrer is run continually. The reaction is generally complete at the end of 4-5 hours, when the benzene solution is filtered and dried over sodium sulfate, and the solvent finally recovered by distillation from an oil-bath heated at 160° . The recovered solvent can be used for the next preparation. The dichloro-acetic acid is obtained as a heavy liquid which is purified by distillation under diminished pressure. It boiled, practically constant, at 102° (uncorr.) at 20 mm. On account of the large quantities of prussic acid evolved, special precautions must be taken to carry out the entire operation in a well-ventilated hood. The method of procedure requires only ordinary laboratory apparatus, and, in a few days, several kilograms of the acid can be prepared with a yield of 60-65% of the calculated amount.

Reversal of the order of addition, namely, chloral hydrate to the sodium cyanide solution, did not lead to an improvement in the yield of dichloro-acetic acid. When sodium cyanide is added to the chloral solution the reaction proceeds very smoothly and a gradual rise in temperature is observed. At first the mixture is almost neutral to litmus, but finally becomes strongly acid during the addition of the cyanide, and at the close of the reaction, the solution is colored slightly yellow. No odor of chloroform is detected during this operation. On the other hand, when the chloral hydrate is added to the sodium cyanide solution, there is no apparent reaction until about half of the chloral has been added, when the temperature rises suddenly to 60° and in a short time the entire mixture assumes a dark red color. Chloroform was produced, and the basicity of the original cyanide solution gradually decreased until about two-thirds of the chloral had been added, when it became distinctly acid. After evaporation of the solution a residue was formed which was black and gummy in appearance. This material gave a yield of dichloro-acetic acid amounting to only 45% of that calculated.

Corrosion Tests with Dichloro-acetic Acid.

In order to determine whether other vessels besides those constructed of glass could be used in reactions where dichloro-acetic acid is employed, the corrosive effect of this reagent on different metals was studied. Weighed strips of the different metals were immersed completely in acid of different concentrations and the loss by corrosion at different temperatures was determined quantitatively. The results obtained are recorded in Table IV where the losses in weight are expressed in terms of percentage of the original weight of metal taken. At 20°, the 4 metals investigated are not readily attacked by the acid, while the corrosion increased with dilution and with rise in temperature. Aluminum appears to be the most resistant to the action of the pure acid at high temperature, while the diluted acid fails to attack copper and lead appreciably.

TABLE IV.
Action of Dichloro-acetic Acid on Metals. Time of Action, 48 Hours.

| Metal. | Temp. ° C. | Loss in weight in pure acid. %. | Loss in weight in 10% aqueous acid. %. | Loss in 10% ben- zene sat. with HCl dichloro-acetic acid. %. |
|---------------|---------------|--|---|---|
| Iron..... | 20 | 0.55 | 3.5 | 2.53 |
| Iron..... | 90 | 2.78 | .. | .. |
| Copper..... | 20 | 0.00 | 1.1 | 0.02 |
| Copper..... | 90 | 4.85 | .. | .. |
| Aluminum..... | 20 | 0.14 | 17.7 | 0.19 |
| Aluminum..... | 90 | 0.66 | .. | .. |
| Lead..... | 20 | 1.51 | 1.5 | .. |
| Lead..... | 90 | 9.30 | .. | .. |
| Aluminum..... | 190 | 0.31 | .. | .. |

Methyl Diethoxy Acetate, $(C_2H_5O)_2CHCOOCH_3$.

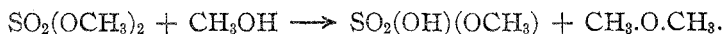
This ester can be prepared by the action of dimethyl sulfate on the sodium salt of diethoxy-acetic acid. Thirty g. of metallic sodium is dissolved in 400 cc. of absolute alcohol. If a molecular proportion (50 g.) of dichloro-acetic acid is added to this solution slowly the corresponding sodium salt of diethoxy-acetate is formed. The reaction is completed by heating the mixture on the steam-bath for 2 hours. At this stage the solution is cooled and filtered to remove sodium chloride. After the excess of alcohol is removed by distillation under diminished pressure the residue is mixed with 75 g. of dimethyl sulfate and the mixture heated on the water bath for 3 hours to complete the esterification. To isolate the ester the product is poured into water and extracted with ether. After removal of the ether, the ester was obtained in about 44% yield as a colorless oil with an agreeable odor. It boiled at 184-5°.

Calc. for $C_7H_{14}O_4$: C, 51.8; H, 8.7. Found: C, 51.7; H, 8.8.

Molecular weight (ebullioscopic method, benzene as solvent). Calc. value: 162. Found: 158.

The ester does not solidify at -81°; d^{25} is 1.0049.

In a second experiment, the sodium salt of diethoxy-acetate, dissolved in methyl alcohol, was heated with dimethyl sulfate. The yield of ester, however, was less than that obtained by the former procedure, since it amounted to only 20% of the calculated value. The low yield here is accounted for by the fact that dimethyl sulfate was partially destroyed by the action of methyl alcohol with formation of dimethyl ether and methyl sulfuric acid. Baulin and Simon¹ showed that this is the case.



It was shown that unaltered sodium salt of diethoxy-acetic acid was present in the aqueous solution in both of the above experiments. After extraction of methyl diethoxy-acetate with ether, barium hydroxide was added to remove sulfates. After the excess of barium had been removed as carbonate by saturating the solution with carbon dioxide, silver nitrate was added to precipitate the silver salt of diethoxy-acetate. This salt dried and subjected to the action of ethyl iodide in ether solution gave ethyl diethoxy-acetate.² From the aqueous solution which remained in Expt. 1 we recovered 15 g. of this ester and in Expt. 2, 25 g. These results show conclusively that only a part of the sodium salt of diethoxy-acetic acid interacted with dimethyl sulfate during esterification. Dimethyl sulfate does not interact with the copper salt of diethoxy-acetate.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS.]

A STUDY OF THE POSSIBLE ASYMMETRY OF THE ALIPHATIC DIAZO COMPOUNDS.³

BY C. S. MARVEL, WITH W. A. NOYES.

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During the last 20 years a large number of papers on the electron theory of valence have appeared in the literature. Most of the papers are of a speculative nature and the applications of the theory have been developed farther than the experimental evidence seems to justify. For some time one of us has been attempting to isolate some of the isomers which, according to this theory, should logically exist and, in that way, to obtain evidence to substantiate the theory.

A study of the aliphatic diazo compounds has been undertaken, since in these compounds, according to the structure usually accepted, 2 nitrogen atoms are combined with one carbon atom. The method of preparation of this class of compounds is such that one of the nitrogen atoms comes

¹ Baulin and Simon, *Compt. rend.*, 170, 392 (1920).

² Johnson and Cretcher, *J. Biol. Chem.*, 26, 99 (1916).

³ An abstract of a thesis submitted by C. S. Marvel in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the University of Illinois.