

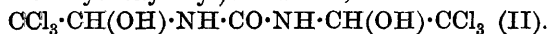
IV.—*The Condensation of Chloral Hydrate and Carbamide.*

By NOEL GUILBERT STEVENSON COPPIN and
ARTHUR WALSH TITHERLEY.

THE study of the condensation between chloral and carbamide, described in the present paper, was made in order to facilitate the investigation now being undertaken of the mechanism of condensation of glyoxylic acid and carbamide, which it is hoped will eventually lead to the synthesis and proof of constitution of certain degradation products of allantoin and uric acid, such as allanturic acid and oxonic acid, the chemical nature of which is still obscure.

Jacobsen (*Annalen*, 1871, **157**, 246), by adding chloral hydrate or alcoholate to a nearly saturated solution of carbamide, obtained a crystalline solid (m. p. 150°), which he regarded as the double compound, $\text{CCl}_3\cdot\text{CH}\cdot\text{O}\cdot\text{CO}(\text{NH}_2)_2$, and also obtained a second compound (m. p. 190°) in smaller amount, which on analysis corresponded with the formula $2\text{CCl}_3\cdot\text{CH}\cdot\text{O}\cdot\text{CO}(\text{NH}_2)_2$.

The nature and conditions of formation of these two derivatives have been examined by the authors, who find that they are normal condensation derivatives, analogous in constitution to the methylol derivatives obtained by Einhorn (*Annalen*, 1905, **343**, 207; 1908, **361**, 131) in the condensation of formaldehyde and amides. That is, the solid of lower melting point is β -trichloro- α -hydroxyethyl-carbamide, $\text{CCl}_3\cdot\text{CH}(\text{OH})\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$ (I), whilst the other is di(β -trichloro- α -hydroxyethyl)carbamide,



Although the reactions leading to their formation are reversible, owing to the ease with which they crystallise out under suitable conditions, no difficulty is experienced in their isolation and purification. Both these substances, which are sparingly soluble in water, are interesting in showing phenolic properties, by readily dissolving in aqueous alkali, owing to the negative influence of the CCl_3 group on the neighbouring hydroxyl. Whilst, however, they may be recovered unchanged from the alkaline solution by acidification, they are unstable towards alkali on warming, and readily yield chloroform and other products.

It has been found that whilst in concentrated aqueous solutions equivalent quantities of chloral hydrate and carbamide react slowly at the ordinary temperature to give mainly the simple condensation derivative (I), small quantities of the compound (II), derived from two molecules of chloral hydrate and one of carbamide, were always formed, and that this secondary reaction is best prevented by using

two molecular proportions of carbamide to one of chloral hydrate in the condensation. When hydrochloric acid is present as catalyst, the velocity of the condensation is greatly accelerated, especially that leading to the formation of the compound (II) melting at 196° , which results even when two molecular proportions of carbamide to one of chloral hydrate are used. The same compound is found in considerable quantity without an acid catalyst when chloral hydrate and an excess of carbamide are heated at 80° without solvent; and it is also slowly formed from the compound (I) and chloral hydrate in aqueous solution in the absence or presence of hydrochloric acid. The yield, however, by this method is much less than in its direct formation in the wet way from carbamide. In no case was any evidence obtained of the formation of trichloroethylidenedicarbamide, $\text{CCl}_3\cdot\text{CH}(\text{NH}\cdot\text{CO}\cdot\text{NH}_2)_2$, in the wet condensation of chloral hydrate and carbamide, with or without acid catalyst. This substance has already been described by Pinner and Lifschütz (*Ber.*, 1887, **20**, 2346), who obtained it by heating a mixture of chloral cyanohydrin and carbamide at 90° . It was finally obtained by the present authors by the condensation of β -trichloro- α -hydroxyethylcarbamide and carbamide (in excess) in presence of acetic anhydride at 100° . The unsaturated compound, trichloroethylidenecarbamide, $\text{CCl}_3\cdot\text{CH}:\text{N}\cdot\text{CO}\cdot\text{NH}_2$, was obtained in a pure form, as silky needles of high melting point, by a similar method to that employed by Diels and Seib (*Ber.*, 1909, **42**, 4065) in the dehydration of chloralurethane, namely, by the action of acetic anhydride on β -trichloro- α -hydroxyethylcarbamide (I) in the presence of aqueous alkali.

EXPERIMENTAL.

β -Trichloro- α -hydroxyethylcarbamide, $\text{CCl}_3\cdot\text{CH}(\text{OH})\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$.

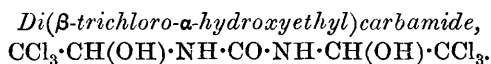
The best conditions for the preparation of this substance were as follow: Twelve grams of carbamide (2 mols.) in 10 c.c. of water and 16.5 grams of chloral hydrate (1 mol.) in 10 c.c. of water were mixed and left in a corked flask at the ordinary temperature. Transparent crystals began to separate in a few hours, and at the end of three days, when no more was deposited, the crystals, consisting of nearly pure β -trichloro- α -hydroxyethylcarbamide, weighed 14.8 grams (66 per cent. of the theoretical) and melted at 146° . After slow recrystallisation from a mixture of methyl alcohol and benzene it was obtained in large, transparent pyramids, melting at 150° . (Found, $\text{Cl}=51.16$; $\text{N}=13.65$. $\text{C}_3\text{H}_5\text{O}_2\text{N}_2\text{Cl}_3$ requires $\text{C}=51.33$; $\text{N}=13.49$ per cent.).

When, instead of using the above proportions, equimolecular

quantities of chloral hydrate (16.5 grams) and carbamide (6 grams) are taken, after two days a mixture (12 grams) is obtained, consisting essentially of β -trichloro- α -hydroxyethylcarbamide, but containing 3 per cent. of di(β -trichloro- α -hydroxyethyl)carbamide. It is possible to separate the two by cautious, rapid, fractional crystallisation from warm water.

β -Trichloro- α -hydroxyethylcarbamide is soluble in 25 parts of water at 15°; it is very readily soluble in methyl and ethyl alcohols, or acetone, somewhat sparingly so in ether, and almost insoluble in chloroform or benzene. It is easily soluble in hot water, and on rapidly cooling separates out again without appreciable loss, but owing to slow hydrolysis into chloral and carbamide the amount which separates out on cooling decreases with the length of time of heating. Moreover, owing to the gradual appearance in the solution of free chloral hydrate and carbamide in equimolecular proportions, di(β -trichloro- α -hydroxyethyl)carbamide is slowly formed. By weighing the crystals of impure β -trichloro- α -hydroxyethylcarbamide which separated, and allowing for solubility, it was found that whilst in 50 per cent. aqueous solution at 70° no appreciable hydrolysis occurs in thirty seconds, in fifteen minutes about 25 per cent. of the substance becomes hydrolysed into chloral and carbamide. On continued heating at 70° (in 50 per cent. aqueous solution) di(β -trichloro- α -hydroxyethyl)carbamide, which is sparingly soluble in hot water and apparently less easily hydrolysed than the mono-derivative, continually separates and disturbs the equilibrium. After an hour the solid mixture, which was isolated after cooling, weighed 50 per cent. of the original β -trichloro- α -hydroxyethylcarbamide, and consisted of about 70 per cent. of the mono- and 30 per cent. of the di-derivative. After three hours' heating at 70° the solid mixture obtained by cooling (51 per cent. of the original weight) was richer in the di-derivative (53 per cent.).

β -Trichloro- α -hydroxyethylcarbamide readily dissolves in aqueous sodium hydroxide, and is precipitated again in not too dilute solution by acids. On warming the alkaline solution rapid decomposition occurs, with the formation of chloroform.



Six grams of carbamide in 5 c.c. of water were mixed with 33 grams of chloral hydrate in 10 c.c. of water, and 20 c.c. of concentrated hydrochloric acid were added. In a short time a fine, white, insoluble, micro-crystalline powder separated, and increased until finally the whole mass became largely solid. After three days

the insoluble solid was collected, and found to be pure di(β -trichloro- α -hydroxyethyl)carbamide (25 grams, or 71 per cent. of theory). The mother liquor deposited a further 0.5 gram on keeping. The substance after recrystallisation from aqueous alcohol separated in small, pearly flakes, melting at 196°. (Found, Cl=59.58; N=7.99. $C_5H_6O_3N_2Cl_6$ requires Cl=60.0; N=7.9 per cent.)

The formation of this compound has been observed whenever aqueous chloral hydrate and carbamide are present in equimolecular proportions, or even in the ratio of 1 mol. : 2 mols. in the presence of hydrochloric acid; thus 16.5 grams of chloral hydrate and 12 grams of carbamide dissolved in 120 c.c. of water and 5 c.c. of concentrated hydrochloric acid gave, after twelve hours, 2.8 grams, and in a week 3.6 grams of pure di(β -trichloro- α -hydroxyethyl)carbamide. The aqueous filtrate contained β -trichloro- α -hydroxyethylcarbamide (12 grams). A much larger yield of the di-derivative (15.5 grams) was obtained from the above quantities of chloral hydrate and carbamide when dissolved in only 15 c.c. of water and 27 c.c. of concentrated hydrochloric acid, the mixture being allowed to remain for several days.

Di(β -trichloro- α -hydroxyethyl)carbamide is practically insoluble in water, chloroform, or benzene, somewhat sparingly soluble in ether, and moderately easily soluble in alcohol or acetone. It dissolves at once in aqueous sodium hydroxide, and is precipitated unchanged by acids, but if the alkaline solution is kept or heated, slow or rapid decomposition occurs, with the formation of chloroform.

Trichloroethylidenecarbamide, $CCl_3 \cdot CH:N \cdot CO \cdot NH_2$.

Ten grams of β -trichloro- α -hydroxyethylcarbamide, dissolved in 100 c.c. of ice-cold *N*-sodium hydroxide (2 mols. NaOH), were treated gradually, and with continual agitation, with 5 grams of acetic anhydride. The temperature was kept low by surrounding the vessel with ice, and the addition of acetic anhydride, which immediately produced a white precipitate, occupied ten minutes. After a further ten minutes the mass was made distinctly alkaline by stirring with a little aqueous sodium hydroxide, and the snow-white, solid powder was collected and washed. It consisted of pure trichloroethylidenecarbamide, and the yield (9.3 grams) was practically theoretical. It was obtained in fine, silky needles by cautious recrystallisation from a mixture of alcohol and benzene, and melted at 234°:

0.1330, by Kjeldahl's method, required 13.9 c.c. *N*/10-HCl.
N=14.63.

0.1534 gave 0.3482 AgCl. Cl=56.1.

$C_3H_3ON_2Cl_3$ requires N=14.78; Cl=56.2 per cent.

The substance is readily soluble in alcohol or acetone, sparingly so in ether, and practically insoluble in chloroform, benzene, or water.

Trichloroethylidenedicarbamide, $CCl_3 \cdot CH(NH \cdot CO \cdot NH_2)_2$.

Twelve grams of carbamide (2 mols.) and 20.8 grams of β -trichloro- α -hydroxyethylcarbamide (1 mol.), both very finely powdered, were heated on the water-bath with 12 grams (1 mol.) of acetic anhydride for six hours. The clear liquid began to deposit a white solid after about half-an-hour, and ultimately the contents of the flask became largely solid. The mass was extracted with alcohol, and after washing with the latter the insoluble white powder was digested with 10 per cent. sodium hydroxide and washed. The residual crude trichloroethylidenedicarbamide (7 grams) gave low values (between 20 and 21 per cent.) for nitrogen on analysis; it was purified by dissolving in warm concentrated sulphuric acid, and after cooling cautiously precipitating by water and digesting with aqueous alkali. It was obtained in this way in fine needles (with considerable loss), sparingly soluble in boiling acetic acid, and practically insoluble in all the usual solvents. (Found, Cl=42.70; N=22.0. $C_4H_7O_2N_4Cl_3$ requires Cl=42.69; N=22.45 per cent.)

ORGANIC LABORATORY,
UNIVERSITY OF LIVERPOOL.
