LII.—*The Constitution of Carbamides. Part VI.
The Mechanism of the Synthesis of Urea from
Urethane.*

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THE formation of urea from the interaction of ammonia and urethane (ethyl carbamate) has always been considered to afford conclusive evidence in support of the 'carbamide' structure, and is commonly represented by the equation:

This synthesis of urea is invariably assumed to be analogous to the formation of acetamide from ethyl acetate, urethane being merely recognised as the normal intermediate product.

As a matter of fact, it is nothing of the kind.

When the true mechanism of the change is brought to light, it is seen to be nothing more than a modification of Wöhler's synthesis, namely, the formation of urea from the union of ammonia and cyanic acid in the keto-form.

Properties of Urethane, and the Conditions under which Urea is formed from the Ester.

The vapour density of urethane (b. p. 182°) at $202\cdot8^\circ$ (b. p. of *m*-cresol) was found to be $43\cdot22$, whilst theory requires $44\cdot5$; on the other hand, when the ester was boiled under reflux, it was gradually dissociated in accordance with the equation

thus, after two hours, 16 per cent. of the theoretical yield of cyanuric acid was obtained.

The decomposition of the ester by alkali in aqueous solution was found to proceed on the same lines: the change is not a direct hydrolysis, as commonly stated in the literature, and may be represented thus:

The following results were obtained when urethane and sodium hydroxide (both in *N*/5-solution) were heated at 100°:

Time in minutes.	Urethane decomposed, per cent.	Sodium cyanate formed, per cent.	Sodium carbonate formed, per cent.
5	50.9	32.9	18.0
15	62.5	37.25	25.25
30	63.95	29.70	34.25
60	66.80	28.80	38.0
90	71.0	17.0	54.0

At 15°, after three days, 18 per cent. of urethane was decomposed, with the formation of 5.5 per cent. of sodium cyanate and 12.5 per cent. of sodium carbonate. The change was therefore independent of dissociation of the ester (compare decomposition of urea, this vol., p. 88).

When urethane was heated in a current of hydrogen chloride, it was decomposed, thus:

This decomposition of urethane in two different directions may be represented thus:

Since urea is formed from the hydrolysis of cyanic acid, thus,

(this vol., p. 95), it is necessary to reach the temperature of the dissociation of urethane in solution in order to obtain urea from it; thus, when the ester was heated in aqueous solution in a sealed tube for two hours at 130°, 5.94 per cent. of the theoretical yield of urea was obtained; after six hours, the yield was 16.62 per cent. (Expts. II and III). Whilst the presence of ammonia would obviously promote the change, the origin of urea in this synthesis is clearly revealed by these results, and is properly represented thus:

A comparative study of the formation of urethane and ammonia from the interaction of urea and ethyl alcohol (a change which is also regarded from a false point of view) has brought to light evidence in support of the above explanations; thus, when a 5*N*-alcoholic solution of urea was heated for two hours at 150°, 41.66 per cent. of the theoretical yield of urethane was formed, as against 33.3 per cent. yield of urea from the interaction of urethane and ammonia under similar conditions (Expts. V and VI).

The greater facility with which urea dissociates explains the higher result in the former case, which otherwise appears abnormal, since the formation of an amide from an ester and ammonia takes place with ease, as compared with the reverse reaction.

Urea is a relatively stable substance, and if it has the 'carbamide' constitution, the question may be asked why it is not formed from ethyl carbonate (or carbamate) with the same ease as undoubted diamides are formed from esters and ammonia; for example, no urea was produced after urethane had remained in contact with a considerable excess of ammonia solution for ten months at the ordinary temperature.

It has been generally accepted as an axiom that the system :C(OH)_2 cannot form part of a stable molecule; the author now ventures to maintain that the evidence all round is no less convincing as regards the system $\text{:C(NH}_2)_2$, and herein lies the true answer to the question just stated. Urea, thiourea, and guanidine are the only known stable substances that have been assumed to contain this system, and in the case of thiourea it is well known that when the thiocarbamic esters $\text{H}_2\text{N}\cdot\text{CS}\cdot\text{OEt}$ and $\text{H}_2\text{N}\cdot\text{CS}\cdot\text{SEt}$ respectively are heated with ammonia in alcoholic solution, ammonium thiocyanate is formed. Since the reaction is effected below the temperature at which this salt dissociates (a necessary preliminary for the formation of the isomeride), no thiourea is produced, a fact for which no explanation can be offered when the erroneous 'thiocarbamide' structure is assumed.

As regards guanidine (free base), its constitution has yet to be proved (compare Krall, T., 1915, 107, 1398).

EXPERIMENTAL.

The results of the decomposition of urethane by sodium hydroxide in aqueous solution were obtained as follows. A mixture of 0.89 gram of urethane, 10 c.c. of *N*-sodium hydroxide, and 40 c.c. of distilled water was heated to the boiling point under reflux for the stated periods. After the solution had been rapidly cooled,

the 'carbonate' was precipitated by barium nitrate and barium hydroxide; the filtrate, after careful neutralisation with dilute nitric acid, was precipitated with *N*/10-silver nitrate, the excess of which was titrated by Volhard's method. Each experiment was made in duplicate.

The results were calculated on the basis:

0.89 Gram of urethane $\rightarrow$ $\text{BaCO}_3 = 20$ c.c. *N*-HCl.

$\text{NaOCN} = 100$ c.c. *N*/10- AgNO_3 .

Example.—After one hour, BaCO_3 precipitated required for neutralisation 7.6 c.c. *N*-HCl, = 38.0 per cent. of the theoretical; NaOCN formed required for precipitation 28.8 c.c. *N*/10- AgNO_3 , = 28.8 per cent. of the theoretical.

Decomposition of Urethane by Hydrochloric Acid.

Expt. I.—Twenty grams of urethane were heated to 150—160° in a distillation flask, while hydrogen chloride was passed through the liquid; after a short time crystals began to separate, and the heating was maintained for half an hour. The gas which was evolved (1) burned with a green flame (ethyl chloride), and (2) gave a copious precipitate with excess of barium hydroxide solution (carbon dioxide). The product was treated with ether to remove all unchanged urethane, and the residue, which was readily and completely soluble in cold water, contained $\text{Cl} = 66.24$ (NH_4Cl requires $\text{Cl} = 66.35$ per cent.), and gave no reaction for cyanuric acid.

The evolved gas, when collected over warm water, was reduced to almost half its volume after treatment with sodium hydroxide, and the residual gas burnt more freely than before with a green flame. The decomposition was therefore in accordance with the equation given.

Formation of Urea when Urethane was Heated with Water.

Expt. II.—2.5 Grams of urethane and 7.5 c.c. of water were heated in a sealed tube for two hours at 130°. After evaporation of the solution to dryness at 100°, the residue was extracted with ether, when there remained 0.05 gram, which was proved to be urea by the urease test and other reactions.

Expt. III.—As before, but the heating was maintained for six hours. Half of the final residue gave, when decomposed by

alkaline sodium hypobromite, 24.28 c.c. N_2 at *N.T.P.*, equal to 0.14 gram of urea, or 16.62 per cent. of the theoretical. Urea nitrate was readily prepared for identification from the remainder.

Formation of Ethyl Allophanate from Urethane.

Expt. IV.—A solution of 5 grams of urethane in 20 c.c. of alcohol was heated in a sealed tube for three hours at 150° . After evaporation of the alcohol, the residue was extracted with ether, and the insoluble product (0.065 gram) crystallised from hot water in colourless needles melting at 191° , which was the melting point of a specimen of ethyl allophanate used for comparison. When heated with barium hydroxide solution, a copious precipitate of barium carbonate was formed after a few moments, a reaction characteristic of the ester. Whilst the yield was small, the result proves that dissociation of urethane must have taken place.

*Quantitative Comparison of (a) Interaction of Urea and Alcohol,
(b) Interaction of Urethane and Ammonia.*

Expt. V.—A solution of 3 grams of urea in 10 c.c. of alcohol (urea=5*N*) was heated in a sealed tube for two hours at 150° ; from the product, after evaporation of the alcohol and extraction with ether, 1.75 grams of urea were recovered, whilst 1.85 grams of urethane were obtained from the ethereal extract. As 3 grams of urea are equivalent to 4.45 grams of urethane, the yield of the latter was 41.6 per cent. of the theoretical.

Expt. VI.—A solution of 4.45 grams of urethane in 10 c.c. of alcohol (urethane=5*N*) which contained 0.85 gram of ammonia was heated as in the last experiment. One gram of urea was obtained after extraction of the residue with ether. Hence the yield was equal to 33.3 per cent. of the theoretical.

A determination of the vapour density of urethane by V. Meyer's method at 202.8° gave the following result: 0.0763 gram gave 21.2 c.c. at 14.5° and 741.45 mm. (corrected), whence $V.D. = 43.22$. Hence there was no dissociation under this condition.

Summary.

(1) Urethane is not directly hydrolysed when heated with sodium hydroxide in aqueous solution, as commonly stated; alkali cyanate is first formed, and then hydrolysed.

(2) The formation of urea when urethane (or ethyl carbonate) is heated in solution with ammonia is solely dependent on the dissociation of urethane, and is no more than a repetition of Wöhler's synthesis in a modified form.

(3) A comparison of the reaction with the formation of urethane from urea and alcohol supplies evidence which is opposed to the 'carbamide' formula.

(4) Attention is directed to a rational inference from the facts, namely, that the system $\text{:C(NH}_2\text{)}_2$ cannot form part of a stable molecule.

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