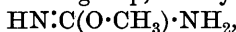


LXXXVIII.—*The Constitution of Carbamides. Part I.*
The Preparation of isoCarbamides by the Action
of Methyl Sulphate on Carbamides.

By EMIL ALPHONSE WERNER.

HITHERTO, carbamide, in contrast to its sulphur analogue, has not been found to yield by any direct reaction derivatives of the so-called *iso*- or ψ -carbamides; thus, whilst thiocarbamide and the alkyl haloids interact readily to form compounds of the type $\text{HN}:\text{C}(\text{SR})\cdot\text{NH}_2$, the corresponding oxygen derivatives have, so

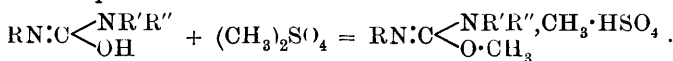
far, been obtained from the direct union of cyanamides and alcohols. The simplest member of the group, methylisocarbamide,



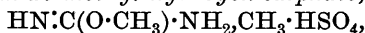
was originally prepared by Stieglitz and McKee (*Ber.*, 1900, **33**, 1518) from the union of cyanamide and methyl alcohol in the presence of hydrogen chloride; several derivatives of the types $\text{HN:C(OR)}\cdot\text{NH}_2$, $\text{RN:C(OR)}\cdot\text{NH}_2$, and $\text{RN:C(OR)}\cdot\text{NHR}$ have since been obtained by analogous reactions, sodium ethoxide being used in some cases to bring about the changes (Stieglitz and Noble, *Ber.*, 1905, **38**, 2243; Bruce, *J. Amer. Chem. Soc.*, 1904, **26**, 419, 449).

It has recently been suggested by the author (T., 1913, **103**, 2281) that carbamide, during its decomposition by heat, probably does assume the isocarbamide configuration; in the hope of obtaining direct evidence on this point the experiments described below were carried out, and the results have furnished strong support in favour of the author's views on the constitution of carbamide and its immediate derivatives.

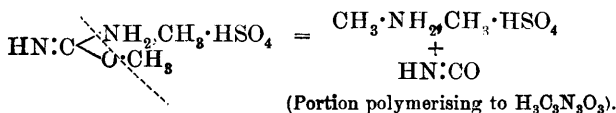
It is now shown that methylisocarbamide and its *N*-alkyl derivatives of the different types may be readily obtained by the direct action of methyl sulphate on carbamide and its alkyl substituted derivatives; the change which takes place may be represented by the general equation:



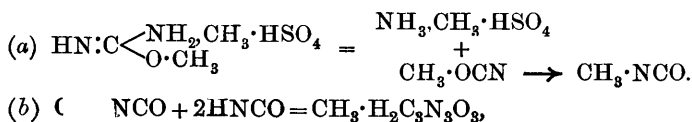
Methylisocarbamide methyl hydrogen sulphate,



is formed from carbamide and methyl sulphate at 112°; if the reaction is allowed to become violent (see experimental part), the isocarbamide salt is decomposed, with the production of methylammonium hydrogen sulphate, methylammonium methyl sulphate, cyanuric acid, and *N*-methylcyanuric acid. Whilst the main change may be represented by the equation:



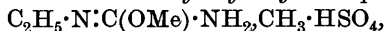
the formation, in relatively large quantity, of *N*-methylcyanuric acid must originate either from the production of methyl cyanate, which condenses with cyanic acid, thus:



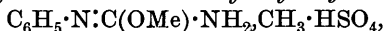
or an interchange in position may occur between the methyl group and the imide hydrogen atom of the *isocarbamide* salt, which then decomposes, with the direct formation of methyl cyanate (keto-form) and ammonium methyl sulphate. Since no ammonium salt could be detected, the latter must undergo isomeric change* into the more stable methylammonium hydrogen sulphate.

The yield of methylamine in the above decomposition was so satisfactory, that the method may be recommended for the rapid preparation of the amine on a small scale; two-thirds of the total methyl content of the ester can be obtained as methylamine.

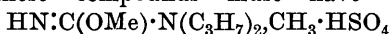
Methylethylisocarbamide methyl hydrogen sulphate,



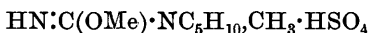
and *phenylmethylisocarbamide methyl hydrogen sulphate,*



prepared from ethylcarbamide and phenylcarbamide respectively, did not yield a trace of either cyanuric acid or its *N*-methyl derivative when decomposed by heat, thus proving the absence of the group $\text{HN}:\overset{|}{\text{C}}\cdot\text{O}\cdot\text{CH}_3$ in the products from these two carbamides. The production of methylaniline from the phenyl derivative indicates a migration of the methyl group from oxygen to nitrogen, as already suggested in the case of methylisocarbamide itself. The isocarbamide salts prepared from *as*-dipropylcarbamide and from piperidine-1-carboxylamide ($\text{C}_5\text{H}_{10}\text{N}\cdot\text{CO}\cdot\text{NH}_2$, usually, although incorrectly, called piperidylcarbamide) both yielded cyanuric acid and its *N*-methyl derivative when decomposed by heat, from which it follows that these compounds must have the constitution



and



respectively. The action of methyl sulphate on several other carbamides has been examined qualitatively, and in every case evidence was obtained of the formation of an *isocarbamide*. The experimental results just described have supplied sufficient material to discuss their theoretical bearing on the main problem under consideration.

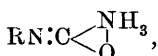
Theoretical Discussion of the Results.

The view that the carbamide molecule may possibly assume a tautomeric form corresponding with the *isocarbamide* structure $\text{HN}:\text{C}(\text{OH})\cdot\text{NH}_2$ has hitherto been considered little more than a theoretical speculation, based, perhaps, mainly on the analogy of

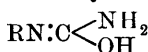
* This change has been confirmed with a specimen of ammonium methyl sulphate which, after heating to fusion for a short time, gave methylamine in quantity on boiling with sodium hydroxide solution.

the compound to thiocarbamide. The theory that carbamide when heated must, in addition to dissociation, be capable of assuming the *isocarbamide* configuration, has already been suggested by the author (*loc cit.*) in explaining the mechanism of the formation of biuret; * this theory has now been brought within the domain of experimental fact, since carbamide and the substituted derivatives examined must have assumed the *isocarbamide* structure in their reactions with methyl sulphate. The constitutions of the *iso*-carbamides obtained from the two monosubstituted carbamides prove that the latter assume the configuration $\text{RN}:\text{C} \begin{smallmatrix} \text{NH}_2 \\ \text{OH} \end{smallmatrix}$, and not

$\text{HN}:\text{C} \begin{smallmatrix} \text{NHR} \\ \text{OH} \end{smallmatrix}$, a fact which supports the cyclic formula

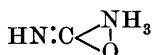


now suggested by the author for the constitution of such carbamides in the static condition. If the change in structure is considered to be derived from a carbamide having the constitution $\text{RHN}\cdot\text{CO}\cdot\text{NH}_2$, there appears no a priori reason why the configuration



should be assumed rather than $\text{RHN}\cdot\text{C} \begin{smallmatrix} \text{NH} \\ \text{OH} \end{smallmatrix}$, particularly when the carbamides examined, $\text{R}'_2\text{N}\cdot\text{CO}\cdot\text{NH}_2$ and $\text{R}''\text{N}\cdot\text{CO}\cdot\text{NH}_2$, which can only change in one direction, assume the configurations $\text{R}'_2\text{N}\cdot\text{C} \begin{smallmatrix} \text{NH} \\ \text{OH} \end{smallmatrix}$ and $\text{R}''\text{N}\cdot\text{C} \begin{smallmatrix} \text{NH} \\ \text{OH} \end{smallmatrix}$, just as easily as the monosubstituted derivatives.

So far, only one form of monosubstituted carbamides are known in which the radicle is in direct union with nitrogen; to this fact is to be ascribed one of the chief reasons for the general use of the otherwise unsatisfactory "diamide" formula to explain the constitution of carbamide. That such isomerides have not hitherto been obtained would appear to be a serious objection to the acceptance of either the formula $\text{HN}:\text{C} \begin{smallmatrix} \text{NH}_2 \\ \text{OH} \end{smallmatrix}$ or the cyclic formula



proposed by the author (*loc. cit.*).

A consideration of the mechanism which, according to the author's theory (T., 1913, 103, 1010), underlies the isomeric trans-

* An interesting confirmation of this view is supplied by some results obtained by Bruce (*loc. cit.*), who has shown that methyl*isocarbamide* cyanate readily undergoes transformation into a methylbiuret, a fact of which the present author was not aware when the suggestion referred to above was made.

formation of ammonium and all amine cyanates into carbamides, shows that the above objection is more apparent than real. It may be taken as a fundamental principle that when two (or more) groups of atoms unite to form a more or less complex molecule, the tendency will be ultimately to produce that configuration which represents the most stable state of equilibrium. If this principle be applied to the isomeric transformation of an amine cyanate, the mechanism of the change will be as follows: when ethylamine and cyanic acid ($\text{HO}\cdot\text{CN}$) unite at a low temperature, a very unstable salt is formed, which has the constitution $\text{C}_2\text{H}_5\cdot\text{NH}_3\cdot\text{OCN}$. The first step which marks its transformation into ethylcarbamide is dissociation, and since this is a change towards the attainment of more stable equilibrium, the products of dissociation will be ammonia and ethyl cyanate (which changes at once to the stable form $\text{C}_2\text{H}_5\cdot\text{NCO}$) rather than ethylamine (less stable than ammonia) and the very unstable cyanic acid. Ethylcarbamide then results from the union of ammonia and the cyanic ester (keto-form), and will therefore have the constitution $\text{C}_2\text{H}_5\cdot\text{N}:\text{C} \begin{smallmatrix} \text{NH}_3 \\ \diagup \\ \text{O} \end{smallmatrix}$ in the static condition, and capable of readily changing to the isocarbamide configuration $\text{C}_2\text{H}_5\cdot\text{N}:\text{C} \begin{smallmatrix} \text{NH}_2 \\ \diagup \\ \text{OH} \end{smallmatrix}$. The decomposition of ethylcarbamide by heat, with the production of ammonia and diethyl cyanurate, and only a trace of ethylamine (Würtz, *Rep. Chim. Pure*, 1862, 199; Leuckart, *J. pr. Chem.*, 1880, [ii], 21, 1), is in perfect agreement with this structure.

EXPERIMENTAL.

The general plan adopted in all the experiments was as follows: A mixture in equal molecular proportions of methyl sulphate, and the particular carbamide in fine powder, was gradually heated in a wide-mouthed test-tube (12 cm. long by 3 cm. wide) immersed in a bath of glycerol to such an extent that the surface of the mixture was just level with the glycerol outside. The mixture was occasionally stirred with a thermometer held in the tube by means of a loosely fitting cork. The heating was maintained at such a rate that the thermometer did not show an average rise of more than about 4—5° per minute; by this means the first reaction, that is, the formation of an isocarbamide, was not liable to be overstepped.

I. Carbamide and Methyl Sulphate.

A mixture of carbamide (6 grams) and methyl sulphate (12·6 grams) was heated as described above. At 80° the carbamide melted rapidly, but did not mix with the ester; at 112° the liquids

became suddenly miscible, and the temperature rose rapidly to about 170° , when the tube containing the reaction product was quickly removed from the source of heat and cooled under a stream of cold water. The viscous product was soluble in water or alcohol in all proportions. The aqueous solution gave an immediate precipitate with picric acid; this was purified by crystallisation from a solution in hot water, from which it separated in thin, glistening yellow needles, melting and decomposing at 184° :

0.15 gave 28.2 c.c. N_2 at 9° and 770 mm. $N=22.92$.

$C_2H_6ON_2 \cdot C_6H_3O_7N$ requires $N=23.10$ per cent.

A *platinichloride* separated in small, orange-red cubes on adding chloroplatinic acid to the aqueous solution of the reaction product:

0.165 * gave 0.0576 Pt. $Pt=34.90$.

$(C_2H_6ON_2)_2 \cdot H_2PtCl_6$ requires $Pt=34.94$ per cent.

A specimen of methylisocarbamide prepared from the interaction of cyanamide and methyl alcohol according to the method of Stieglitz and McKee (*loc. cit.*) gave a crystalline picrate which melted and decomposed at the same temperature as that mentioned above.

In order to realise the production of the isocarbamide only, it was necessary to check the rise in temperature, and this could only be done with certainty when the amounts of carbamide and methyl sulphate used were not greater than those specified above. If the source of heat was maintained while the first change was in progress a violent reaction occurred, quickly followed with considerable rise of temperature (to about 220°), and the isocarbamide salt was decomposed.

Examination of the Products of Decomposition of Methylisocarbamide Methyl Hydrogen Sulphate.

The united product from three experiments, in which the reaction was allowed to become violent, was dissolved in 60 c.c. of boiling water; the presence of cyanuric acid in the crystalline material which separated on cooling was readily proved by the preparation of the characteristic violet-red copper salt. The accompanying acid, which constituted the chief product, was easily purified and freed from cyanuric acid by two crystallisations from hot water, in which it is much more freely soluble:

0.1888 * gave 46.7 c.c. N_2 at 9° and 758 mm. $N=29.68$.

$C_4H_5O_3N_3$ requires $N=29.37$ per cent.

0.2554 * required for neutralisation 17.9 c.c. $N/10-NaOH$ (phenolphthalein as indicator).

* Dried at 110° .

Assuming the compound to behave like cyanuric acid, as a mono-basic acid, this result gives $M.W. = 143.05$.

$C_4H_5O_3N_3$ requires $M.W. = 143$.

0.5 Gram, when heated in a sealed tube with concentrated hydrochloric acid to 100° , remained unchanged; at 170° , after four hours it was almost completely hydrolysed, with the production of carbon dioxide, ammonia, and methylamine, thus proving the acid to be an *N*-methyl derivative. It crystallises from water in thin, semi-transparent, rhomboidal prisms, which have the composition $CH_3 \cdot H_2C_3N_3O_3, 2H_2O$:

0.1904 * lost 0.0378 at 110° . $H_2O = 19.85$.

$C_4H_5O_3N_3, 2H_2O$ requires $H_2O = 20.11$ per cent.

A characteristic reaction of the acid is the production of a very gelatinous precipitate on addition of ammoniacal silver nitrate solution. The aqueous solution, from which the mixture of acids had separated, was distilled with excess of sodium hydroxide solution; the evolved gas was absorbed in an excess of hydrochloric acid; on evaporation of the latter to dryness, methylamine hydrochloride was obtained in considerable quantity. The presence of some dimethylamine hydrochloride was indicated by the analysis of the products when fractionally crystallised from alcohol, but no ammonium chloride could be detected.

II. Ethylcarbamide and Methyl Sulphate.

A mixture of ethylcarbamide (m. p. 92° ; 4.4 grams) and methyl sulphate (6.3 grams) was gradually heated; at about 70° the carbamide dissolved rapidly in the ester; at 80° there was a brisk evolution of gas, and the temperature rose quickly to 120° ; the product was at once removed from the source of heat and rapidly cooled.

The colourless and odourless viscous liquid obtained was readily and completely soluble in water; the solution gave no precipitate on the addition of barium chloride.

A *picrate* prepared from the solution was obtained in thin, glistening, deep yellow needles, melting at 147° :

0.1802 gave 32.2 c.c. N_2 at 16° and 759 mm. $N = 20.94$.

$C_4H_{10}ON_2, C_6H_5O_7N_3$ requires $N = 21.14$ per cent.

A *platinichloride* was prepared in the form of stout, tetragonal, deep orange-red, anhydrous prisms, melting at 142° :

0.31 gave 0.098 Pt. $Pt = 31.61$.

$(C_4H_{10}ON_2)_2, H_2PtCl_6$ requires $Pt = 31.75$ per cent.

* Air-dried.

Examination of the Products of Decomposition of Methyl ethylisocarbamide Methyl Hydrogen Sulphate.

At 170° the isocarbamide salt decomposed, with sudden evolution of much pungent vapour of methyl cyanate (keto-form), and the temperature rose rapidly to 220°; there was no very violent reaction as in the case of ordinary carbamide. The viscous product was readily dissolved in a small quantity of warm water, from which solution not a trace of either cyanuric acid or its *N*-methyl derivative could be obtained.

The solution was boiled in an excess of sodium hydroxide, and the evolved gases were absorbed in hydrochloric acid; on evaporation of the latter, a crystalline residue of amine hydrochloride was obtained, which was very deliquescent:

0.0968 required 11.3 c.c. *N*/10-AgNO₃. Cl=41.44.

C₂H₇N.HCl requires Cl=43.55 per cent.

The low result obtained was probably due to the presence of some methylethylammonium chloride, as the portion analysed was previously heated to 120° for more than an hour to expel all moisture.

III. *Phenylcarbamide and Methyl Sulphate.*

A mixture of phenylcarbamide (6.8 grams) and methyl sulphate (6.3 grams) was gradually heated; at 85° the carbamide melted and dissolved in the ester, whilst the temperature rose rapidly to 110°. The product was an almost colourless and odourless viscous liquid, which dissolved completely in water; the solution gave no precipitate on addition of barium chloride.

A *platinichloride* was prepared from the solution; it separated in clusters of fine, orange-red, elongated prisms, which decomposed at 180° without melting:

0.2054 * gave 0.056 Pt. Pt=27.26.

(C₈H₁₀ON₂)₂.H₂PtCl₆ requires Pt=27.46 per cent.

A *picrate* was obtained in microscopic, yellow needles, melting at 162°, but was not analysed.

The free base, *phenylmethylisocarbamide*, was precipitated from the solution of the reaction product by sodium hydroxide as a viscous oil.

* Dried at 110°.

Examination of the Products of Decomposition of Phenylmethylisocarbamide Methyl Hydrogen Sulphate.

The isocarbamide salt decomposed at 175° , a gas being evolved, having the pungent odour of phenyl cyanate (keto-form), and the temperature rose rapidly to 205° .

A clear, glass-like solid of a pale garnet-red colour was formed, which was completely soluble in a small quantity of warm water. No trace of cyanuric acid or its methyl derivative could be detected. The solution on distillation with sodium hydroxide gave some aniline, but chiefly methylamine and methylaniline, the latter being identified by the preparation of the nitroso-derivative.

IV. *Piperidine-1-carboxylamide and Methyl Sulphate.*

A mixture of piperidine-1-carboxylamide (6.4 grams) and methyl sulphate (6.3 grams) was heated gradually; at 55° the carbamide melted; at 65° it dissolved rapidly in the ester, and the temperature rose to 115° without any visible change in the liquid; after a few moments the temperature commenced to fall. The clear, viscous product was readily soluble in water, and the solution gave no precipitate with barium chloride.

A *platinichloride* was prepared from the solution; it separated in stout, orange-red prisms, which melted at 144° :

0.348 gave 0.0982 Pt. $\text{Pt} = 28.21$.

$(\text{C}_7\text{H}_{14}\text{ON}_2)_2, \text{H}_2\text{PtCl}_6$ requires $\text{Pt} = 28.09$ per cent.

A *picrate*, melting at 158° , was prepared, but not analysed.

The free base was obtained in the usual manner as a clear, nearly colourless oil, which did not solidify at -10° .

The action of heat on *piperidyliminomethyl methyl ether methyl hydrogen sulphate*, $\text{HN}:\text{C}(\text{O}\cdot\text{CH}_3)\cdot\text{NC}_5\text{H}_{10}\cdot\text{CH}_3\cdot\text{HSO}_4$, showed this salt to be much more stable than those already examined. At about 130° the evolution of the vapour of methyl cyanate (keto-form) commenced, and the temperature was raised to 210° without any evidence of sudden decomposition; a quiet evolution of gas was noticeable throughout the process, whilst the liquid became dark brown. The product, when treated with water, gave a micro-crystalline precipitate, which was proved, by the tests already referred to, to be a mixture of cyanuric acid and its *N*-methyl derivative. The basic products formed were not examined so far.

Note on Piperidine-1-carboxylamide.

When preparing this substance by the interaction of potassium cyanate and piperidine sulphate, it was found advisable to heat the

crude product to about 130° , to ensure complete isomeric transformation of the piperidine cyanate. The substance was best purified by crystallisation from chloroform, from which solvent it separated in large, transparent, oblong, rectangular prisms containing one molecule of chloroform of crystallisation; the crystals are quite stable when kept in a closed vessel. For analysis the crystals were quickly drained and pressed between bibulous paper, and then heated for one hour at 90° :

0.574 lost 0.274 $\text{CHCl}_3 = 47.72$.

$\text{C}_6\text{H}_{12}\text{ON}_2$ requires $\text{CHCl}_3 = 48.28$ per cent.

V. *as-Dipropylcarbamide and Methyl Sulphate.*

A mixture of *as*-dipropylcarbamide (7.2 grams) and methyl sulphate (6.3 grams) was heated gradually; the carbamide dissolved rapidly in the ester; at 80° gas was slowly evolved, and there was a slight rise in temperature. As the chief object was to examine the decomposition products of the *isocarbamide* salt formed, the heating was continued; at 140° there was sudden evolution of the vapour of methyl cyanate (keto-form), and the temperature rose very rapidly to 270° . The viscous residue obtained after cooling was dissolved in a small quantity of hot water, and after a short time a crystalline precipitate separated, which consisted of a mixture of cyanuric acid and its *N*-methyl derivative, as proved by the tests already mentioned.

A portion of the product obtained at 80° was used for the preparation of a *platinichloride*, which crystallised in deep orange-red, quadratic prisms:

0.144 gave 0.0379 Pt. Pt = 26.32.

$(\text{C}_3\text{H}_7\text{ON})_2, \text{H}_2\text{PtCl}_6$ requires Pt = 26.85 per cent.

The basic products of the decomposition of the *isocarbamide* methyl hydrogen sulphate have not yet been examined, for want of material.

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