CCCXXVI.—*The Synthesis of Glycine.*

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SIMPLE and economical methods for the preparation of the naturally occurring amino-acids are much to be desired. The authors have described such a method for the isolation of *d*-glutamic acid hydrochloride from gluten (*Biochem. J.*, 1927, **21**, 1172), and one is now described for the synthesis of glycine, the simplest of the amino-acids.

In most of the recent syntheses of glycine the initial material has been methyleneaminoacetonitrile, $(CH_2{:}N{\cdot}CH_2{\cdot}CN)_3$, prepared by the elegant method of Klages (*Ber.*, 1903, **36**, 1506; compare Adams and Langley, *Organic Syntheses*, 1925, **4**, 47) from formalin, ammonium chloride, and alkali cyanide. When boiled with a relatively large volume of alcoholic hydrogen chloride, this substance gives glycine ester hydrochloride in 90% yield (Klages, *loc. cit.*), but the satisfactory conversion into free glycine involves the use of silver at some stage. When aqueous hydrochloric acid is used for the hydrolysis of the nitrile, glycine hydrochloride is formed mixed with ammonium chloride (Jay and Curtius, *Ber.*, 1894, **27**, 60) and the separation of these substances is difficult. To overcome this, Clarke and Taylor (*Organic Syntheses*, 1925, **4**, 31) used hydrobromic acid and utilised the solubility of ammonium bromide in methyl alcohol for separating the two hydrobromides, the simultaneous presence of pyridine allowing free glycine to separate in 31—37% yield. To surmount the difficulty presented by the formation of ammonium salts by hydrolysis, Ling and Nanji (*Biochem. J.*, 1922, **16**, 703) boiled the nitrile with 40% barium hydroxide solution for 3 hours to remove ammonia formed by hydrolysis of the nitrile group and then with 3% sulphuric acid for 4 hours to remove formaldehyde formed by acid hydrolysis of methyleneglycine postulated by these authors as an intermediate product. In this way a 90% yield of glycine was said to have been obtained.

On exact repetition of Ling and Nanji's process, the yields of crude glycine obtained in different experiments were 57, 50, 42, and 52%. To throw some light on this discrepancy in yields, an attempt was made to isolate the barium salt of the supposed intermediate product, methyleneglycine. Such a barium methyleneglycine had already been obtained as a crystalline substance stable to carbon dioxide by the action of formaldehyde on barium glycine by Franzen and Fellmer (*J. pr. Chem.*, 1917, **95**, 299) and by Bergmann, Jacobsohn, and Schotte (*Z. physiol. Chem.*, 1923, **131**, 18), but on removal of free barium hydroxide by carbon dioxide after the hydrolysis of

methyleneaminoacetonitrile, we found no evidence for the presence of barium methyleneglycine. Instead, crude glycine was isolated in three different experiments in 71, 62, and 62% yield, so that omission of the 4 hours' hydrolysis with 3% sulphuric acid recommended by Ling and Nanji effected a distinct improvement in the yield of glycine. The residual mother-liquors when exactly freed from barium or sulphate ions in Ling and Nanji's process consisted of a thick brown syrup with slight reducing properties on Fehling's solution; its production is compatible with the polymerising action of boiling barium hydroxide on the formaldehyde split off by hydrolysis.

The 40% barium hydroxide used for the hydrolysis of methyleneaminoacetonitrile is not without destructive action on the methyleneamino portion of the molecule, for we found in two experiments that the glycine liquors after the barium hydroxide and sulphuric acid hydrolysis contained only 76 and 74% of the theoretical amount of nitrogen, and therefore the failure to isolate larger amounts of glycine than those recorded in this communication is not surprising.

All these difficulties may be surmounted by the following simple process. Methyleneaminoacetonitrile, when treated with a small volume of warm alcoholic sulphuric acid, is rapidly converted into aminoacetonitrile (Klages, *loc. cit.*), which separates as a beautifully crystalline hydrogen sulphate, and by the addition of a large excess of ether Klages obtained a 91% yield of this salt. On repetition of this experiment, we obtained an 87·3% yield, and the same yield by keeping the mixture for a few days below 0° and avoiding the use of ether. When aminoacetonitrile hydrogen sulphate was boiled with 27% barium hydroxide solution until evolution of ammonia had ceased, a practically quantitative yield of glycine was obtained and this on recrystallisation from water gave pure glycine in 83% yield calculated on the methyleneaminoacetonitrile used.

EXPERIMENTAL.

Hydrolysis of Methyleneaminoacetonitrile by Barium Hydroxide and Sulphuric Acid in Succession.—Throughout these experiments the methyleneaminoacetonitrile was prepared by Klages's method. It contained a trace of chloride, was almost completely soluble in boiling absolute alcohol, and melted between 128° and 129° (Found: N, 39·7. Calc.: N, 41·2%). Of this nitrile, 13·7 g. were hydrolysed by barium hydroxide and sulphuric acid exactly as described by Ling and Nanji. On concentration of the hydrolysis liquor after exact removal of barium and sulphate ions, 8·6 g. of glycine were obtained corresponding to a 57% yield. The brown syrupy mother-

liquor still contained nitrogen equivalent to 2·9 g. of glycine, which could not be isolated either by careful addition of alcohol or by prolonged keeping at 0°. Only traces could be isolated by conversion into the copper salt. The crude glycine could be freed from adhering brown mother-liquor by washing with 50% alcohol.

In another experiment using 10 g. of methyleneaminoacetonitrile, the hydrolysis liquor was made up to a known volume, an aliquot portion taken, and the nitrogen determined by Kjeldahl's method. This corresponded to 8·1 g. of glycine or 74%. On crystallisation, however, only 52% could be isolated.

Hydrolysis of Methyleneaminoacetonitrile by Barium Hydroxide Alone.—The nitrile (13·7 g.) was hydrolysed by boiling with 54·8 g. of barium hydroxide octahydrate in 137 c.c. of water for 2·5 hours; ammonia evolution had then ceased. Carbon dioxide was passed into the solution until this was no longer alkaline, and after removal of barium carbonate the liquor on concentration gave 8·95 g. of crude glycine. On exact removal of barium ions from the final liquor with sulphuric acid and concentration, a further 1·75 g. of glycine were obtained (total yield, 71%). The mother-liquor still contained nitrogen equivalent to 2·75 g. of glycine, but more glycine could not be isolated.

Hydrolysis of Methyleneaminoacetonitrile by Sulphuric Acid and Barium Hydroxide in Succession.—The nitrile (34 g. = 0·5 mol.) was added all at once to a warm solution of 48·0 g. of sulphuric acid in 125 c.c. of spirit contained in a wide-stoppered glass bottle. On shaking, the nitrile dissolved immediately with evolution of formaldehyde, and, when the contents had cooled, aminoacetonitrile hydrogen sulphate separated in large rectangular plates. (Occasionally the solution separates into two liquid layers, but the lower layer readily crystallises on rubbing.) During crystallisation the contents of the bottle were shaken vigorously at intervals to avoid formation of a hard cake. After being kept for some hours below 0°, the salt was collected and washed with ice-cold spirit. The yield was 67·2 g. or 87% of the theoretical.

Barium hydroxide octahydrate (270 g. = 2 mols.) was added to 500 c.c. of water in an open dish, and the liquid brought almost to boiling. Aminoacetonitrile hydrogen sulphate (67·2 g.) was then added, and the solution boiled at constant volume until the odour of ammonia had gone. This usually requires 2·5—3 hours. The barium ions were removed quantitatively by addition of 50% sulphuric acid, the filtrate concentrated, and the successive crops of crude glycine collected. There was no residual syrup such as occurs in Ling and Nanji's process. The combined crops were recrystallised once more from water and gave, when collected in

six crops, 31·5 g. of glycine, or an 84% yield on the original methyleneaminoacetonitrile (Found : N, 18·7. Calc. : N, 18·7%). The penultimate crop melted at the same temperature as purest glycine (King and Palmer, *Biochem. J.*, 1920, **14**, 582). Both melted when taken side by side in the same bath at 262° with effervescence. Washing of the successive crops with small quantities of 50% alcohol is of great value for obtaining products free from mother-liquor and of the highest m. p. The use of alcohol for crystallisation of glycine, recommended by Ling and Nanji, is impracticable, as glycine is almost insoluble in boiling spirit.

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