CLXXXVII.—*Experiments on the Synthetic Preparation and Isolation of Some of the Simpler Amino-acids.*

By Wesley Cocker and Arthur Lapworth.

Section I. Introductory.

Some difficulties usually met with in applying the familiar synthetic methods for preparing and isolating the more soluble amino-acids may be overcome by adopting certain general modes of procedure, based partly on theoretical considerations and partly on empirical observations made during the course of recent investigations in these laboratories.

It may be stated at the outset that, in the experience of the present authors, the first essential to uniform success is the rigid exclusion, from first to last, of even small quantities of compounds of the alkali metals. Thus the use of potassium or sodium cyanide with an ammonium salt in the Strecker synthesis, while suitable enough for the preparation of a sparingly soluble amino-acid, is in other cases strongly to be deprecated, as it introduces at later stages complications quite out of proportion to the extra initial trouble or cost involved in using hydrogen cyanide and ammonia.

For similar though less cogent reasons, great care should be taken that all reagents used are carefully prepared and tested.

The main synthetic method studied was the Strecker synthesis (*Annalen*, 1850, **75**, 29) involving the formation and hydrolysis of the α-amino-nitriles from a variety of aliphatic aldehydes and ketones, as well as that from ethyl β-aminocrotonate as leading to an amino-dicarboxylic acid. Special attention was paid to the possibility of working out general methods, avoiding (1) the use of pressure vessels and (2) highly exact measurements or precipitations at any stage. A fair measure of success can be claimed and the general procedure worked out for isolating soluble amino-acids was extended with little modification to the preparation of an amino-acid (glycine) by the second well-known synthetic method, due to Kolbe (*Annalen*, 1860, **113**, 220), namely, that of replacement of halogen in a substituted acid by the amino-group.

In using either of the two general synthetic methods, conditions have been imposed unfavourable to the formation of imino-compounds. In the case of the Strecker synthesis, the equation

$$2R_2C(CN)\cdot NH_2 \longleftrightarrow (R_2C\cdot CN)_2NH + NH_3$$

ndicates that excess of ammonia should be helpful if, as is almost certainly the case, the reaction is a reversible one. Eschweiler (*Annalen*, 1894, **279**, 40) has shown that with methylamine and formaldehyde cyanohydrin, iminodinitrile and the still more complex trinitrile are formed in large quantity unless the amine is used in great excess. The authors have used twice the theoretical quantities of ammonia and hydrogen cyanide; this may prove in some cases to be excessive, but the view of the authors has been that the working out of easily applied general methods for the quantitative hydrolysis of the amino-nitriles and for securing with certainty the bulk of the resulting amino-acid in nearly pure condition would make it easy to investigate empirically the question of the more economical proportions of initial reactants in any given case.

The tendency to formation of imino-compounds and other complex by-products in the synthesis of amino-acids from halogeno-acids is much more pronounced than in the Strecker synthesis, and Robertson (*J. Amer. Chem. Soc.*, 1927, **49**, 2889) has shown that with chloroacetic acid 5% of the latter is converted into these more complex products even when more than 200 times the theoretical quantity of ammonia is used.

Section II. Notes on the Purity and Uses of Materials recommended.

Sulphuric acid, aqueous ammonia, and hydrochloric acid should be free from salts of alkali metals. A little lead in the sulphuric

acid, however, is not likely to interfere and would be eliminated toward the end of the operation recommended.

The hydrogen cyanide required for the Strecker synthesis was always used in liquid form, in measured quantities by volume. But concentrated aqueous solutions, free from mineral residue, would probably lead in most cases to results nearly or quite as satisfactory, especially when starting from an aldehyde. When employing aqueous solutions of hydrogen cyanide, gaseous ammonia might be absorbed with cooling, prior to addition of aldehyde or ketone, and accidental introduction of considerably larger quantities of ammonia than that recommended in Section III would not be harmful.

Barium carbonate is usually to be recommended, (*a*) whenever the object is to eliminate all ammonia from ammonium salts present or/and (*b*) to remove from solution, in the first instance, considerable proportions of sulphuric acid, free or in combination with ammonia or amino-acid. Barium carbonate in a suitable state of purity can be obtained from British Drug Houses, Ltd., or may be prepared from barium chloride solution by precipitation with ammonium carbonate. In the latter case, any trace of ammonium salt in the product should be entirely eliminated, and this is readily effected by blowing steam through the suspension in hot water. The presence of a little barium chloride as impurity is not objectionable when working as hereinafter described (compare p. 1401 for a method for economising in pure barium carbonate).

Litharge, in very small proportion, though never necessary, can be employed to accelerate complete conversion of sulphuric acid and hydrochloric acid into lead salts. In using this compound it is always necessary to remember that with more than a very small excess, indicated by alkaline reaction of the solution towards Congo paper, there is the possibility of forming sparingly soluble basic lead salts of the amino-acids; however, providing the excess is not large, it is very easy to return to the correct point by cautious addition of dilute sulphuric acid (compare p. 1401). Strecker himself and other workers since have used lead hydroxide for elimination of ammonia from ammonium salts in solution; but the present authors much prefer barium carbonate for this purpose, as excess is necessary for rapid working in either case, and this in the case of barium carbonate leads to no complications. Commercial litharge, finely powdered, is as a rule quite suitable for use without special purification.

Lead carbonate is recommended for use after all ammonium salts have been eliminated by means of barium carbonate and the barium salts in solution and excess of barium carbonate have then been converted into sulphate by addition of an appreciable excess of

sulphuric acid. In these circumstances it precipitates the whole of the sulphate ion present and, in the conditions hereafter described, all but traces of halide ion. It has the advantage over litharge that, when it is necessary to use either compound in large quantities, the cessation of effervescence gives a rough guide to the point where enough agent has been added; moreover, when used in excess in aqueous solutions of the amino-acids examined, the carbonate shows no appreciable tendency to form insoluble basic lead salts of the amino-acids even after, say, ½ hour's boiling. As it decomposes ammonium salts in boiling aqueous solution only very slowly, it is not suitable for use in place of barium carbonate (or litharge) for this purpose. Lead carbonate may be obtained in a pure form from Kahlbaum, or may be specially prepared. Material made by exhaustive treatment of elutriated litharge in aqueous suspension with carbon dioxide would probably be very suitable: but, until they found that Kahlbaum sold a sufficiently pure product, the authors made their lead carbonate from aqueous lead acetate by means of ammonium carbonate, taking special pains to eliminate the last traces of ammonium salts. Steaming an aqueous suspension of the carbonate seems to accelerate the purification.

Each of the above agents, at various times, has previously been used by other workers in isolating amino-acids, but it does not appear that their properties have been applied to the greatest advantage.

The activated charcoal used was " norite," of which all specimens examined were tested and found suitable for use without further treatment.

Section III. Preparation of Crude Amino-nitriles from Aldehydes and Ketones.

(A) *General Remarks.*—A number of workers, including the discoverer, Strecker (*Annalen*, 1850, **75**, 29 *et seq.*), Zelinski, Fischer, Slimmer, and others, have thought it desirable to heat aldehydes and ketones with ammonia and hydrogen cyanide in closed vessels in order to obtain the amino-nitrile. This, however, demands the use of pressure vessels, and the present authors have found that equally good or better yields are obtained in all the cases tried, at laboratory temperature, though a longer period of reaction (up to 1½ days in extreme cases) is necessary.

In the examples dealt with in the present paper, there would be no gain in simplicity, yield, or cost by attempting to separate the amino-nitrile as hydrochloride or other salt.

(B) *Procedure recommended in preparing an Amino-nitrile.*—The aldehyde or ketone (1 mol.) is added, with cooling, to a mixture of

ammonia (*d* 0·880; 2 mols.) and hydrogen cyanide (2 mols.).* Alternatively, an aldehyde-ammonia (1 mol.) may be added to a mixture of aqueous ammonia (1 mol.) and hydrogen cyanide (2 mols.). The results, in the cases actually compared, were not appreciably different.

In any case the mixture is left at laboratory temperature to attain equilibrium in a closed vessel for a period depending on the particular type of carbonyl compound used (compare p. 1399) and is then treated in one or other of the modes described under Section IV below.

Section IV. Hydrolysis of Crude Amino-nitriles.

(A) *General Remarks.*—Anslow and King (J., 1929, 2463) have used aqueous barium hydroxide for the hydrolysis of the amino-nitrile from formaldehyde. The majority of α-amino-nitriles, however, revert too readily to cyanide, ammonia or amine (compare J., 1930, 449, 453) in presence of alkalis and cannot therefore satisfactorily be converted into the amino-acids except by means of acid reagents.

While the free α-amino-nitriles as a class are among the most unstable nitriles known, and readily lose, or exchange, their CN (as cyanidion), their salts with mineral acids are much more stable, and show no tendency to behave in this manner even at 125° provided that a sufficient concentration of mineral acid is maintained in the system. This is in accord with the view that the radicals NR_2 and $NR_3 \oplus$ (where R = H or Alk) lie nearly at opposite extremes in the scale of primary effects, as they have long been known to do in the related scale of ortho-para-directive effects (Flürscheim, J., 1909, **95**, 726; compare also J., 1930, 449).

(B) *Hydrolysis by Means of Aqueous Sulphuric Acid.*—This method is applicable to all the amino-nitriles dealt with in the present paper.

Procedure. The product obtained as in III B is mixed with 40% aqueous sulphuric acid (5—7 mols.), and preferably by slow addition thereto with constant agitation. The whole is then heated † at 125° for 3 hours, by which time a test portion of the solution, heated with excess of sodium hydroxide and ferrous hydroxide, usually

* A larger proportion of either hydrogen cyanide or ammonia is not disadvantageous though wasteful.

† Where the amino-nitrile has been prepared from a saturated aliphatic aldehyde or ketone it is usually quite safe to boil under reflux without exercising special control over the temperature. It has been observed, however, that amino-nitriles obtained from cyclic ketones require more cautious treatment and 125° is therefore mentioned as a temperature which is suitable even in these cases.

gives no reaction for ferrocyanide, indicating complete hydrolysis of amino-nitrile as well as hydrolysis or elimination of hydroxy-nitrile (compare V A) and hydrogen cyanide. The whole is then diluted with several times its own bulk of water and worked up as described in Section V B.

(C) *Hydrolysis by Means of Hydrochloric Acid.—General remarks.* This agent may also be used in open vessels instead of dilute sulphuric acid throughout the above operations, but is convenient only when one of the lower aldehydes is used as starting material; the amino-nitriles derived from ketones hydrolyse too slowly. There is also the disadvantage that much larger quantities of lead carbonate or litharge must be employed owing to the need of eliminating the considerable amount of chloridion present. The only case worked out in full detail was that of the preparation of *dl*-alanine from acetaldehyde, where the yield obtained was 70% as compared with 71·8% when dilute sulphuric acid was employed.

Procedure. The product obtained as in III B (p. 1394) is poured into several times its bulk of concentrated hydrochloric acid, left over-night, and finally heated on the water-bath for several hours until a test portion, boiled with excess of alkali and ferrous hydroxide, gives no indication of formation of ferrocyanide. The whole is then evaporated (in the last stages on the steam-bath), and the residue is dissolved in several times its bulk of hot water and treated as described in V B (p. 1397).

Section V. Isolation of Amino-acid from the Solutions specified in Sections IV B and IV C.

(A) *General Remarks.*—It has been found that impurities, such as hydrogen cyanide, formic acid, hydroxy-acids, imino-di- and -tri-carboxylic acids which might be expected to be present or to arise in the Strecker synthesis, do not, in the cases examined, seriously affect the isolation of the amino-acids if all the operations are carried out as recommended in the present paper. This is due in part to deliberate adoption of conditions unfavourable to formation of imino-dinitriles, or imino-dicarboxylic acids. Other favourable factors are (*a*) the high ratio of amino-nitrile to hydroxy-nitrile in those cases where hydrochloric acid in open vessels can be used as hydrolyst, (*b*) the molecular stability of amino-nitriles and amino-acids to hot 40% sulphuric acid at 125° and the comparative instability of the corresponding hydroxy-nitriles and hydroxy-acids, some of which are broken down by the agent into very volatile products (such as the original ketone) which readily escape in the later evaporation processes. Appreciable quantities of hydroxy-acids have never been found in the final solutions, obtained in the

authors' adaptation of the Strecker synthesis, and, in fact, there is usually little but amino-acid present.

While these considerations may not cover all the factors concerned, it has been found empirically that the solutions obtained as in IV B and IV C readily afford good yields of the amino-acids which they contain if they are treated as follows. It will be evident that the procedure recommended is nothing more than a rational application of barium and lead carbonates (and litharge) on the assumption that ammonia, sulphuric acid, and hydrochloric acid, free or as salts, are the only impurities which must deliberately be removed.

(B) *Procedure.*—The liquid is heated by boiling while a rapid current of steam (best superheated) is passed through it, and barium carbonate (compare p. 1393) is added in quantity more than sufficient, not only to neutralise any free mineral acid, but also to decompose all ammonium salts present; the minimum quantity required can readily be calculated in many cases. When no more ammonia is evolved (Nessler test) even after a small further addition of carbonate, enough dilute sulphuric acid is added to the boiling liquid to destroy excess of barium carbonate, and precipitate all barium from solution; as the precipitate settles very quickly, it is easy to ascertain whether the solution now contains sulphate ions, as should be the case. The precipitate is removed by filtration and thoroughly washed, and the combined filtrates and washings are concentrated to a small bulk and treated, while still hot, with pure lead carbonate * in small successive quantities until effervescence ceases. If the solution still shows an acid reaction towards Congo-paper after a few minutes, finely powdered litharge may be added in very small quantity until a negative result is obtained with the indicator. If chloridion is present, but not otherwise, the whole should be cooled to 0°† or below and left over-night to ensure the almost complete deposition of lead halide salt. After filtration, the clear solution and washings (ice-cold water is necessary for washing when chloride is present in the precipitate) are treated with hydrogen sulphide to precipitate lead, next with activated charcoal (p. 1394), and finally filtered and evaporated. The amino-acid is obtained by cooling and filtering at suitable stages and washing with methyl or ethyl alcohol.

* When halide is absent, the quantity of lead carbonate required will be quite small unless a lavish excess of sulphuric acid was previously used in removing barium.

† Alternatively, when chloridion is present, the liquid, cooled to the ordinary temperature and filtered, may be stirred with a little silver hydroxide (about 1 g. per 100 c.c.) and refiltered, preparatory to treatment with hydrogen sulphide. The authors have used this method only when preparing glycine from chloroacetic acid (p. 1402).

Section VI D may be consulted for a modification of the above procedure by which a saving in the amount of barium carbonate required may be effected. The modification has only been applied, so far, to the isolation of glycine.

Section VI.

(A) In this section are given the results obtained in special cases by using the procedure described in previous sections.

The yields refer to quantities obtained of colourless crystalline product, free from stickiness and practically free from SO_4'', Cl', and ash and yielding, on recrystallisation, material of correct melting point without appreciable loss. Usually only a part was recrystallised as check on the substantial purity of the main bulk of product, the remainder being used for the preparation of derivatives.

Small quantities of the lower monoamino-carboxylic acids, when obtained in such a nearly pure state as by the authors' procedure, are most conveniently recrystallised as follows. The acid is suspended in hot 95% spirit, and water added drop by drop until solution is complete; the whole is then cooled, and a mixture of equal volumes of anhydrous alcohol and ether added. A proportion of the acid is soon deposited in crystalline form and is separated by filtration and washed with a little absolute alcohol. The mother-liquors may be evaporated nearly to dryness and the residues treated in the same way, these processes being repeated so long as more than a negligible amount of solution remains.

"*Melting points.*" A large proportion of the compounds examined decompose more or less rapidly when slowly heated even in the solid state, so that observations on their apparent temperatures of fusion have little significance unless the precise conditions are known. The melting points given in the present paper for the authors' own products are temperatures defined as follows.

(*a*) Below 240°. Here a bath of sulphuric acid was used and the m. p. given in each case is the lowest temperature of the bath at which complete fusion occurs within one second when a thin-walled tube containing the compound and not previously heated is plunged into the sulphuric acid.

(*b*) Above 240°. Here an air-bath was used and the maximum interval allowed to elapse before fusion was 10 seconds.

In some cases the temperature so defined was the same as that of the melting point taken in the usual way, but in others was higher by several degrees.

The thermometer readings were checked against those given by a standard instrument used in the same manner. Its stem was

exposed from 20° upwards, no correction being applied for this exposed portion.

(B) *Examples of Applications to the Strecker Synthesis of Amino-acids from Open-chain Aldehydes and Ketones.*—In the cases within this category, the time required for interaction of the aldehyde or ketone with hydrogen cyanide at the ordinary temperature need be no longer than ½ hour in the cases of aldehydes and acetone, but should be considerably longer, say 24 hours, in the case of methyl ethyl ketone.

The hydrolyst throughout was dilute sulphuric acid (IV B) and in each example the name of the carbonyl compound used is given.

Acetaldehyde. Product: *dl*-Alanine in 71·8% yield; m. p. 295° (decomp.), identical with that of purest authentic specimens (Found: N, 15·5. Calc. for $C_3H_7O_2N$: N, 15·7%).

Zelinski and Stadnikoff (*Ber.*, 1908, **41**, 2061), applying the Strecker synthesis in a different manner, obtained a yield of 63%. Other workers do not record their yields.

The phenylcarbamido-derivative formed flat prisms, m. p. 180·5° (decomp.). Kühn (*Ber.*, 1884, **17**, 2884) gives m. p. 170° (Found: C, 57·9; H, 6·1. Calc. for $C_{10}H_{12}O_3N_2$: C, 57·7; H, 5·8%).

Propaldehyde. Product: *dl*-α-Amino-*n*-butyric acid in 60·8% yield, which may be regarded as a minimum one, as the preparation was carried out before the methods described in Sections IV and V were worked out in detail. The product had m. p. 304° (decomp.) in an open tube and 307° (decomp.) in a closed one (compare Fischer and Mounerat, *Ber.*, 1900, **33**, 2388) (Found: N, 13·4. Calc. for $C_4H_9O_2N$: N, 13·6%). The phenylcarbamido-derivative had m. p. 169·5—170° (decomp.); Mounerat (*Ber.*, 1900, **33**, 2395) gives m. p. 170° (Found: N, 12·9. Calc. for $C_{11}H_{14}O_3N_2$: N, 12·6%).

n-*Butaldehyde.* Product: *dl*-α-Amino-*n*-valeric acid in 68·4% yield; m. p. 291° (decomp.) in a closed tube. The purest specimens melt only 0·5° higher in the same circumstances (Found: N, 12·0. Calc. for $C_5H_{11}O_2N$: N, 12·0%).

Lipp (*Annalen*, 1882, **211**, 359) made this acid by the Strecker synthesis but does not record his yield.

The phenylcarbamido-derivative formed colourless plates, m. p. 125°. Slimmer (*Ber.*, 1902, **35**, 401) gives m. p. 119° (Found: N, 12·0. Calc. for $C_{12}H_{16}O_3N_2$: N, 11·9%).

Acetone. Product: *dl*-α-Amino*iso*butyric acid in 72·7% yield (Found: C, 46·4; H, 8·6; N, 14·0. Calc. for $C_4H_9O_2N$: C, 46·6; H, 8·9; N, 13·6%). The acid crystallises readily from boiling glycol in large transparent prisms. Zelinski and Stadnikoff (*Ber.*, 1906, **39**, 1726), by a somewhat complicated process involving the use of closed vessels at 50—60°, obtained this acid in 72·8% yield and gave

280—281° as the temperature at which the compound sublimes. The acid obtained by the present authors, if slowly heated to 270°, partly sublimes; if the temperature is then raised quickly, there is decrepitation at 294° and melting at 315° (decomp.); only when suddenly heated to 337° does it melt at once (decomp.).

The *phenylcarbamido*-derivative, which is soluble in alcohol and in hot water but insoluble in light petroleum, crystallises from hot water in small transparent prisms, m. p. 187—188° (decomp.) (Found : N, 12·8. $C_{11}H_{14}O_3N_2$ requires N, 12·6%).

Methyl ethyl ketone. Product : *dl*-α-Amino-*sec.*-butylacetic acid in 73·8% yield (Found : N, 11·7. Calc. for $C_5H_{11}O_2N$: N, 12·0%). The acid had m. p. 317—318° (decomp.). Slimmer (*Ber.*, 1902, **35**, 406) found m. p. 307·5° (decomp.) in a closed tube.

Slimmer (*loc. cit.*) heated methyl ethyl ketone with anhydrous hydrogen cyanide in a closed vessel at 80°, the resulting cyanohydrin being heated with alcoholic ammonia in a closed vessel at 45°. He used hydrochloric acid to hydrolyse the amino-nitrile and obtained the amino-acid in 60% yield.

The phenylcarbamido-derivative had m. p. 180° (decomp.) as recorded by Slimmer (*loc. cit.*, p. 407) (Found : N, 12·2. Calc. for $C_{12}H_{16}O_3N_2$: N, 11·9%).

(C) *Preparation of* dl-*Methylaspartic Acid from Ethyl* β-*Aminocrotonate.*—Hydrogen cyanide (17 c.c.) was added to ethyl β-aminocrotonate (19 g.) suspended in well-cooled ether, the solid ester passing very quickly into solution. After being kept for 4 days at the ordinary temperature, the solution was filtered from the black product, added to a cooled mixture of sulphuric acid (30 c.c.) and water (80 c.c.), and the whole well shaken. After the ether had been removed on the water-bath, the residual solution was heated at 115° for 3—4 hours and then diluted with water and treated with barium carbonate, sulphuric acid, and lead carbonate in succession as recommended in Section V B.

The resulting *dl*-methylaspartic acid was obtained in 51% yield as needles of the monohydrate form, m. p. 229—230° (decomp.) (Found : N, 8·7. Calc. for $C_5H_9O_4N,H_2O$: N, 8·5%). Piutti (*Ber.*, 1898, **31**, 2044) gives m. p. 232—234° (decomp.) for the monohydrate.

The corresponding *hydantoin*,

$$C_6H_5\cdot N\begin{<}CO\cdot NH\\CO\end{>}C(CH_3)\cdot CH_2\cdot CO_2H,$$

was made by shaking an aqueous solution of *dl*-methylaspartic acid with phenylcarbimide, and filtering off carbanilide when reaction was complete. When the liquid was acidified with hydrochloric acid, very little precipitate was formed (for behaviour of aspartic acid in similar circumstances, compare *Ber.*, 1903, **36**, 3339). The

whole was kept at the ordinary temperature for 24 hours and then heated for 10 minutes on the water-bath, and cooled. The hydantoin, which was deposited in solid form, separated from water in long prisms or needles containing water of crystallisation (Found : C, 54·2; H, 5·3; N, 10·5. $C_{12}H_{12}O_4N_2,H_2O$ requires C, 54·1; H, 5·3; N, 10·5%). The crystals have m. p. 146° (efferv.). After the crystals have been heated at 130° for 15 minutes, the solid residue obtained (Found : N, 11·3. $C_{12}H_{12}O_4N_2$ requires N, 11·3%) has m. p. 197° (decomp.), but on recrystallisation from water yields, once more, crystals having the m. p. 146° (decomp.).

(D) *Preparation of Glycine by Acid Hydrolysis of Aminoacetonitrile Hydrogen Sulphate.*—(i) Anslow and King (J., 1929, 2463) showed that the readily accessible hydrogen sulphate of aminoacetonitrile gives an 84% yield of pure glycine on hydrolysis with aqueous baryta.

Experiments made by the present authors indicate that even larger yields can be obtained by hydrolysing the compound with 40% sulphuric acid for 3 hours at 125°. Thus in one experiment, 24 g. of aminoacetonitrile hydrogen sulphate yielded 10·8 g. (92% of the theoretical amount) of colourless glycine, m. p. 256—257° (decomp.), free from mineral residue, ammonium salts or other detectable impurities. By one recrystallisation from water of part of this product, the melting point was raised to 263°, the loss being inappreciable. In earlier trials, smaller quantities of starting material (4—6 g.) were used, probably entailing greater loss in manipulation, and yields were about 84—86%.

It is worthy of note that the highest yield (92%) was obtained during the course of a series of trials made with the object of reducing the quantity of pure barium carbonate required in working according to the procedure described in V B. As the results obtained with glycine have been so wholly satisfactory and likely to be of general application for the isolation of an amino-acid obtained by hydrolysis of an amino-nitrile by means of sulphuric acid, the following procedure may be recommended whenever, for the sake of economy or other reason, it may be desirable to reduce the amount of pure barium carbonate employed to a minimum.

(ii) The acid liquor remaining after hydrolysis of the aminonitrile with aqueous sulphuric acid is diluted and treated at the boiling point with successive small quantities of milk of lime until ammonia begins to be evolved; excess of pure calcium carbonate is now added and the boiling continued, but only until the evolution of ammonia sensibly slackens; the liquid is then filtered, the residual solids are washed thoroughly, and the united filtrates and washings treated while hot with more than enough solid ammonium oxalate

to precipitate the whole of the dissolved calcium. The quantity of oxalate required is small, its presence in the solution is easily and quickly detectable, and even a considerable excess is harmless. After filtration from precipitated calcium oxalate the liquid (which should be free from cloudiness) is treated with a little barium carbonate and a current of steam as described in Section V B, the further procedure being precisely as there detailed.

(E) *A Preparation of Glycine from Chloroacetic Acid.*—A simple method for preparing pure glycine is the following, which is based on Robertson's experiments (*J. Amer. Chem. Soc.*, 1927, **49**, 2889).

Chloroacetic acid (47 g.) is dissolved in aqueous ammonia (*d* 0·880, 1½ litres), the whole kept in a stoppered bottle at laboratory temperture for 3 days, and the ammonia then driven off and collected in water; the residue is evaporated to about 500 c.c., and barium carbonate (60 g.) added. The subsequent treatment with steam, sulphuric acid (about 33 g. of conc. acid diluted with water), and lead carbonate (about 70 g.) in succession is as described in Section V A. The solution should be evaporated to about 50 c.c. before being cooled, and lead chloride separated.

The filtrate, if treated directly with hydrogen sulphide, filtered, and evaporated in stages, yields several batches of quite colourless glycine, which, after being washed with methyl alcohol and dried, has m. p. 259° (decomp.), identical with that of the best samples obtainable. The product is almost free from ash and from chloridion if evaporation of the mother-liquors has not been carried too far. The yield is about 17·5 g. or 50% of the theoretical amount (Found : N, 18·5. Calc. for $C_2H_5O_2N$: N, 18·65%).

If the filtrate, before treatment with hydrogen sulphide, is first stirred with a little silver hydroxide (about 0·5 g.) and refiltered, the yield of practically pure glycine is about 21 g. or 58% of the theoretical.

Robertson (*loc. cit.*, p. 2892), starting with similar proportions of ammonia and chloroacetic acid and then using a whole mol. of silver hydroxide, followed by treatment with permutite to remove some ammonia, obtained pure glycine in 50% yield. Boutwell and Kuick (*J. Amer. Chem. Soc.*, 1930, **52**, 4166), starting with a still larger proportion of ammonia and then using a pyridine–methyl alcohol mixture to induce separation of glycine in the crystalline state, subsequently treating the product with permutite, obtained a 54% yield of pure glycine.

Summary.

General modes of procedure have been worked out for the isolation of a number of the more soluble amino-carboxylic acids obtainable by the application of known synthetic methods.

In the preparation of α-amino-nitriles from open-chain aldehydes and ketones by means of ammonia and hydrogen cyanide, heating is not necessary and hydrolysis of the nitriles is readily effected by means of dilute sulphuric acid at about 125° at atmospheric pressure.

THE UNIVERSITY, MANCHESTER. [*Received, May 1st,* 1931.]