CCLVI.—*A Preparation of Sarcosine.*

By Wesley Cocker and Arthur Lapworth.

The literature dealing with the synthetic preparation of sarcosine (*N*-methylglycine) is voluminous. Eschweiler (*Annalen*, 1894, **279**, 40 *et seq.*) and Staudt (*Z. physiol. Chem.*, 1925, **146**, 286) obtained sarcosine from methylamine and formaldehyde by the Strecker synthesis. Volhard (*Annalen*, 1862, **263**, 261) used ethyl chloroacetate and methylamine. Scheibler and Neef (*Ber.*, 1926, **59**, 2) reduced a methyleneglycine ester and also methyleneaminoacetonitrile. Décombe (*Compt. rend.*, 1930, **191**, 945) made *N*-alkylated amino-acids by catalytic reduction of the esters of simple amino-acids in presence of aldehydes. In all these cases the methods were somewhat awkward and the yields of pure product often very unsatisfactory.

Fischer and Bergmann (*Annalen*, 1913, **398**, 117) investigated the methylation of arylsulphonyl derivatives of glycine by means of dilute alkali and methyl iodide at 67° in closed vessels. They hydrolysed the alkylated products by means of hydrochloric acid at 100°, again using closed vessels. Good yields of sarcosine were obtained by hydrolysis of its *p*-toluenesulphonyl derivative in this way, without further complications, as most of the toluenesulphonic acid formed crystallised on cooling. When the benzenesulphonyl derivative was used, the isolation of sarcosine was accomplished only by use of phosphotungstic acid as precipitant.

Johnson and Ambler (*J. Amer. Chem. Soc.*, 1914, **36**, 371) evaded the difficulties inherent in separation of sarcosine and sulphonic acid by synthesising the *N*-ω-toluenesulphonyl derivative; on hydrolysis of this compound by hot mineral acid, the ω-toluenesulphonic acid,

which accompanied the sarcosine formed, broke down readily with evolution of sulphur dioxide and products easy to separate from the accompanying sarcosine.

The present authors have worked out a scheme for the preparation of sarcosine from glycine which is very simple in operation, obviates the use of closed vessels at any stage, and gives satisfactory yields.

The glycine is first converted into its *N*-benzenesulphonyl derivative by means of benzenesulphonic chloride in cold dilute alkali. As the presence of a considerable proportion of impurities, such as salts of the alkali metals or calcium, does not interfere seriously with this conversion, or with purification of the product, special precautions to exclude traces of these during the preparation of the glycine (compare this vol., p. 1392) are not necessary. The sulphonyl derivative is very readily methylated in cold dilute alkaline solution by means of methyl sulphate. Ullmann (*Annalen*, 1903, **327**, 110) methylated the *p*-toluenesulphonyl derivative of aniline under similar conditions, but the authors have not found in the literature any reference to a successful application of the method to sulphonyl derivatives of the simpler amino-acids.

The resulting *N*-benzenesulphonyl derivative of sarcosine is hydrolysed by heating for 3 hours at 125° with 60% aqueous sulphuric acid. The method of removing the benzenesulphonic acid formed is apparently quite novel and is based on the fact that many salts of sulphonic acids, especially those with bivalent metals, are very sparingly soluble in 30—50% sulphonic acid (Lapworth and Morris, B.P., 1915, 14,402), if excess of the sulphate of the metal be present. In the patent, the objective was the salt of a sulphonic acid. In the present instance the objective is a second compound which is very difficult to isolate until the sulphonic acid has been removed from the system. The sulphate selected in the present instance was that of zinc, as it was found that the excess of zinc remaining in the solution after separation of the zinc benzenesulphonate, can be quantitatively removed by means of barium carbonate, which is also the most suitable agent for removing the sulphuric acid.

Owing to complications likely to arise in the application of ferrous or magnesium sulphate as precipitants, the possibility of using either of these in place of zinc sulphate has not yet been explored.

Experimental.*

A. *Preparation of* N-*Benzenesulphonylglycine.*—(1) *From pure glycine.* Glycine (1 mol.), dissolved in excess of cold *N*-sodium

* Melting points were taken as described in a previous paper (this vol., p. 1398).

hydroxide, is shaken with benzenesulphonyl chloride (1¼ mols.) until the odour of the latter has disappeared, and the solution, filtered if necessary, is then acidified with dilute hydrochloric acid. The benzenesulphonyl derivative is at once precipitated, separated by filtration, and washed with water. The yield of dry product is 2·8 g. from 1 g. of glycine (93%). Once recrystallised from water it has m. p. 165° (compare Ihrfelt, *Ber.*, 1889, **22**, 692), and the material, at least when prepared from high-grade glycine, need not be further purified before proceeding as in Section B.

(2) *From aminoacetonitrile hydrogen sulphate.* "Aminoacetonitrile hydrogen sulphate" (1 mol.) is hydrolysed by 40% aqueous sulphuric acid at 125°, the product being treated with lime and calcium carbonate as described elsewhere (this vol., p. 1395). In the present instance, however, the presence of salts of alkali metals in any of the agents used has no objectionable effect. The filtrate and washings from the sludge of calcium sulphate and carbonate are evaporated to a small bulk, filtered, and shaken with alkali and benzenesulphonyl chloride (1¼ mols.). When the sulphonyl chloride has disappeared, the resulting solution is saturated with common salt and either strongly acidified with hydrochloric acid or poured into excess of the dilute acid. In these circumstances, all the calcium normally remains in solution and nearly pure *N*-benzenesulphonylglycine (m. p. 165°) is precipitated; it is separated by filtration and washed thoroughly with water. In case the product proves still to contain a trace of calcium, it may be dissolved in a little spirit containing hydrochloric acid and reprecipitated by water. The crude product may be purified by recrystallisation from hot water prior to methylation (Section B). The yield of nearly pure *N*-benzenesulphonylglycine obtainable by this method is at least 88% of the theoretical.

B. *Preparation of* N-*Benzenesulphonylsarcosine.*—The *N*-benzenesulphonylglycine is dissolved in 3*N*-sodium hydroxide (3 mols.), and to the cold clear solution is then added, in about 6 portions and with constant agitation, methyl sulphate (2 mols.). The temperature rises somewhat, but when working with quantities of sulphonyl derivative not larger than about 40 g., cooling is not necessary. When the whole of the ester has disappeared (5—10 minutes), the clear liquid is cooled and acidified with hydrochloric acid, and the precipitated solid collected and washed with water. The crude *N*-benzenesulphonylsarcosine, thus obtained in 95% yield, has m. p. 173—174°, and appears quite homogeneous. Recrystallisation from hot water yields a product of correct m. p. (179°) (compare Johnson and McCollum, *Amer. Chem. J.*, 1906, **35**, 59, who

prepared this compound by quite a different process) (Found : N, 6·3. Calc. for $C_9H_{11}O_4N_5$: N, 6·1%).

C. *Hydrolysis of* N-*Benzenesulphonylsarcosine and Isolation of Sarcosine.*—The *N*-benzenesulphonyl derivative (35 g.; 1 mol.) is suspended in a mixture of 45 c.c. of concentrated sulphuric acid (5½ mols.) and 53 c.c. of water, and the whole heated under reflux at 125—130° with frequent agitation during the first hour. After about 4 hours' heating, a clear solution is obtained, and this is thoroughly mixed with a solution of hydrated zinc sulphate (37 g. = 1¾ equivs.) in the minimum amount of cold water. The whole is cooled to 0°, and after a few hours is filtered through glass wool contained in a well-cooled funnel. The residue of zinc benzenesulphonate is well pressed, and washed with 5—10 c.c. of 40% aqueous sulphuric acid saturated with zinc sulphate. The united filtrate and washings are diluted with water, *nearly* neutralised (Congo-red paper) with barium carbonate or aqueous barium hydroxide, then heated to boiling for about 10 minutes with addition of pure barium carbonate (about 50 g.), the precipitate being separated by filtration and washed thoroughly.

The clear filtrate and washings contain a little barium but no appreciable quantity of zinc. The barium may be removed by addition of the requisite amount of dilute sulphuric acid, or by treatment with excess of this acid, then with lead carbonate, and finally with hydrogen sulphide (compare this vol., p. 1397).

Little but sarcosine remains in solution, and this may be obtained by evaporation (if desired, after treatment with "norite") and collection in successive crops, each of which is washed with alcohol; the last mother-liquors are concentrated and stirred with alcohol, whereupon further deposits are obtained. In this manner 10·0 g. (74% of theory) of crude crystalline sarcosine, free from mineral residue or acidity, are isolated, and by careful recrystallisation of this product from 95% alcohol, at least 8·9—9·0 g. of material having the properties (m. p. 212—213°, decomp.) of the best authentic samples of sarcosine can be obtained (Found : N, 15·75. Calc. for $C_3H_7O_2N$: N, 15·75%).

N-Benzoylsarcosine (*N*-methylhippuric acid) was obtained by Paulmann (*Arch. Pharm.*, 1894, **232**, 601) only as an oil. It may be prepared in crystalline form by the following process. A solution of sarcosine (3·85 g.) in water (30 c.c.) is warmed to 40° and shaken with benzoyl chloride (20 g.) and sodium hydrogen carbonate (40 g.) for about an hour. After cooling, addition of excess of hydrochloric acid, and filtration from benzoic acid, the liquid is extracted with chloroform, the extract being freed from benzoic acid by means of

light petroleum. On recrystallisation from benzene–light petroleum, the benzoyl derivative separates as short prisms which are freely soluble in ether, alcohol, and water and melt at 103·5—104° (decomp.); yield *ca.* 50% (Found : N, 7·2. Calc. for $C_{10}H_{11}O_3N$: N, 7·25%). The product had the same properties whether made from sarcosine prepared in the manner above described or from sarcosine purchased from Schuchardt. No depression in m. p. was observed on admixture of the two specimens.

THE UNIVERSITY, MANCHESTER. [*Received, June 16th,* 1931.]