CCCIX.—*A New Synthesis of Creatine and Alacreatine.*

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ONE of the most convenient methods for the preparation of alkylated guanidines was worked out by Wheeler and Jamieson (*J. Biol. Chem.*, 1908, **4**, 111), who allowed primary or secondary amines to react with the alkyl iodide addition products of thiocarbamide.

$$NH{:}C(NH_2)\cdot SMe,HI + NHMe_2 \longrightarrow NH{:}C(NH_2)\cdot NMe_2 + MeSH.$$

With one exception, which seems to have been generally overlooked, this reaction has apparently never been applied to the naturally occurring amino-acids. In an earlier paper Wheeler and Merriam (*Amer. Chem. J.*, 1903, **29**, 478) had shown that glycine and methyl*iso*thiocarbamide hydriodide reacted in the presence of a molecular proportion of alkali to give glycocyamine (guanidinoacetic acid):

$$NH_2\cdot CH_2\cdot CO_2H + NH{:}C(NH_2)\cdot SMe,HI \longrightarrow NH_2\cdot C(:NH)\cdot NH\cdot CH_2\cdot CO_2H.$$

The reaction may in fact be regarded as an improved modification of Strecker's synthesis of glycocyamine from glycine and cyanamide, since methyl*iso*thiocarbamide when liberated from its salts breaks down into methyl mercaptan and nascent cyanamide.

The value of Wheeler and Merriam's synthesis has been confirmed by the author by the isolation of guanidinoacetic acid in 90% yield. The reaction has now been applied to *N*-methylaminoacetic acid (sarcosine) and to *dl*-α-aminopropionic acid (alanine) with the production of the corresponding guanidino-acids, namely, creatine and alacreatine respectively. These three biologically important nitrogenous compounds have been converted by suitable cyclisation methods into the corresponding anhydrides, namely, glycocyamidine, creatinine, and alacreatinine. The six substituted guanidines so obtained have been characterised by preparation of hydrochlorides and picrates, since, as often happens with materials of biological origin, there are great discrepancies in the literature of these compounds.

Two points only need further discussion. According to Wörner (*Z. physiol. Chem.*, 1899, **27**, 7) creatine and picric acid solutions when mixed give creatinine picrate, and Folin (*J. Biol. Chem.*, 1914, **17**, 463) reports that contrary to the statements in the literature creatine and creatinine are easily precipitated by picric acid. The cause of the uncertainty which has hitherto existed with regard to

creatine picrate arose, no doubt, from the observation, now apparently put on record for the first time, that creatine and creatinine picrates melt at almost the same temperature and that a mixture of the two shows no depression. The crystalline appearance of the two picrates, their solubilities and analytical figures, however, leave no uncertainty as to their difference.

The second point concerns some observations made by Söll and Stutzer (*Ber.*, 1909, **42**, 4539), who claimed to have prepared a bimolecular guanidinoacetic acid by the action of guanylcarbamide on chloroacetic acid. The only evidence adduced in support of this so-called bimolecular acid was that it decomposed at about 300°, that is, higher than the m. p. at that time attributed to guanidinoacetic acid, that it gave a half-picrate, m. p. 235—237°, whereas normal guanidinoacetic acid picrate is stated to melt at 201°, and that it was converted into ordinary guanidinoacetic acid by boiling with concentrated hydrochloric acid. According to the present author's observations, postulation of a bimolecular acid is unnecessary, since guanidinoacetic acid is unmelted at 300° and forms two picrates, a half-picrate, m. p. 242°, and a normal picrate, m. p. 210°.

EXPERIMENTAL.

Glycocyamine.—Glycine (7·5 g.) was dissolved in 100 c.c. of *N*-potassium hydroxide (1 mol.), and methyl*iso*thiocarbamide hydriodide (21·7 g.; 1 mol.) added. The solution was slowly evaporated under reduced pressure, the temperature of the external bath being regulated at 50°, and the evolved methyl mercaptan being absorbed by alkaline permanganate solution. A succession of crystalline crops of glycocyamine was collected amounting to 10·55 g. (90% of the theoretical yield). They were recrystallised from the minimum volume (330 c.c.) of boiling water. The pure material crystallised in small rectangular plates (10·2 g.). It was unmelted at 300°, in agreement with Nicola (*Giorn. Farm. Chim.*, **51**, 241); Wheeler and Merriam (*loc. cit.*), however, give m. p. 250—260° (decomp.) (Found: N, 35·9. Calc.: N, 35·9%).

The hydrochloride crystallises from concentrated hydrochloric acid in large plates, m. p. 200° (with efferv.) (Korndorfer, *Arch. Pharm.*, 1905, **242**, 622, gives m. p. 191°).

On mixing glycocyamine and picric acid (1·05 mols.) in hot water and allowing the solution to cool, needles of glycocyamine picrate, m. p. 210° (decomp.), separated (Wheeler and Merriam give m. p. 202°) (Found: picric acid as nitron picrate, 67·1. Calc.: 66·2%). When recrystallised from 25 volumes of boiling water, this picrate gave the ***half picrate***, crystallising in plates, and later the normal picrate, crystallising in needles. The half picrate is more readily

obtained by using half a molecular proportion of picric acid in its preparation. It then crystallises homogeneously in laminated plates, m. p. 242° (decomp.) (Söll and Stutzer, *loc. cit.*, give m. p. 235—237°) [Found: picric acid as nitron picrate, 49·6. $(C_3H_7O_2N_3)_2$, $C_6H_3O_7N_3$ requires picric acid, 49·4%].

Glycocyamidine.—Glycocyamine (6 g.) was converted into glycocyamidine by heating under pressure with 45 c.c. of concentrated hydrochloric acid for 6·5 hours at 150°. It was isolated in 74% yield as the hydrochloride by crystallisation from alcohol, and on recrystallisation gave a 66% yield of pure glycocyamidine hydrochloride, m. p. 213° (Pyman and Fargher, J., 1919, **115**, 242, give m. p. 211—213° corr.) (Found: Cl, 26·0. Calc.: Cl, 26·2%).

The base liberated by ice-cold aqueous ammonia is very soluble in water. It turns brown near 240° and chars gradually up to 300°. The picrate is readily soluble in hot water and crystallises in long silky needles, m. p. 214—215° (decomp.) (Fargher and Pyman give m. p. 215—216° corr.) (Found: picric acid as nitron picrate, 69·9. Calc.: 69·8%). It also crystallises in a more stable form, on long keeping of its solution, as orange plates which melt at the same temperature as the needles. This is apparently the form obtained by Abderhalden and Sickel (*Z. physiol. Chem.*, 1928, **173**, 54).

Alacreatine.—This base, prepared in the same way as glycocyamine from 8·9 g. of alanine, was obtained in 65% yield. The mother-liquors contain some unchanged alanine. On crystallisation of the crude alacreatine from 4 volumes of boiling water, it separated in narrow rectangular plates, m. p. 246—247° (efferv.) (Baumann, *Ber.*, 1873, **6**, 1371, gives m. p. 180°, and Ramsay, *Ber.*, 1908, **41**, 4388, gives m. p. 226° corr.) (Found: N, 32·2. Calc.: N, 32·1%). The *picrate* is soluble in 9 volumes of boiling water and crystallises in glistening yellow needles, m. p. 187° (decomp.) (Found: picric acid as nitron picrate, 63·5. $C_4H_9O_2N_3$,$C_6H_3O_7N_3$ requires picric acid, 63·6%).

Alacreatinine.—Alacreatine was evaporated to dryness twice with concentrated hydrochloric acid and the crystalline alacreatinine hydrochloride formed was crystallised from 3 volumes of boiling absolute alcohol. Alacreatinine hydrochloride separated in clear glassy crystals, m. p. 203—204° (Fargher and Pyman give 202—203° corr.). The picrate is soluble in 14 volumes of boiling water and crystallises in needles, m. p. 214—215° to a red liquid which soon decomposes (Fargher and Pyman give 212° corr.). The base is obtained by the action either of the calculated amount of silver oxide or of excess of ice-cold 2*N*-ammonia on the hydrochloride. Crystallised from water, it separates in clear spiked prisms, m. p

221—222° (efferv.) (Fargher and Pyman give 222—223° corr.). A mixed m. p. with a sample made by Fargher and Pyman from an azoglyoxaline and for which I am indebted to Dr. Henry, Director of the Wellcome Chemical Research Laboratories, showed no depression of m. p. (Found: H_2O, 12·2; N in anhydrous material, 36·8. Calc.: H_2O, 13·7; N, 37·1%). Alacreatinine is gradually changed by boiling with water, probably through formation of alacreatine.

Creatine.—Sarcosine hydrochloride (18·8 g.) was treated with 300 c.c. of *N*-potassium hydroxide, and methyl*iso*thiocarbamide hydriodide (32·7 g.) added. The solution was evaporated under reduced pressure at 50°. The crude creatine (yield 8·75 g. or 40%) was recrystallised from the minimum volume of boiling water (50 c.c.) and separated in large rectangular tablets, m. p. 303° (Found: H_2O, 12·6, 12·3; N in anhydrous material, 32·1. Calc.: H_2O, 12·1; N, 32·1%). The *picrate*, prepared from the components in hot aqueous solution, was recrystallised from the minimum volume (17 parts) of boiling water and separated as a felt of woolly needles, m. p. 218—220° to a red liquid with decomp. (Found: picric acid as nitron picrate, 64·2. $C_4H_9O_2N_3,C_6H_3O_7N_3$ requires picric acid, 63·6%).

Creatinine.—Pure creatine was evaporated to dryness with 4 volumes of concentrated hydrochloric acid and the residue was dissolved in a small volume of water and cooled in ice. On addition of excess of concentrated aqueous ammonia creatinine separated in small prisms, m. p. 305° (decomp.) (Found: N, 36·7. Calc.: N, 37·1%). The picrate is slightly less soluble than creatine picrate and requires 23 volumes of boiling water to effect its solution. It separates in long, silky, yellow needles, m. p. 220—221° (decomp.) (Found: picric acid as nitron picrate, 67·4. Calc.: 67·0%).

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