XXVII. THE OXIDATION OF AMINO-ACIDS TO CYANIDES.

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The oxidation of α-amino-acids to aldehydes may be effected with a variety of reagents including hydrogen peroxide [Dakin, 1906], lead dioxide and dilute sulphuric acid [Liebig, 1849], alloxan [Strecker, 1862; Hurtley and Wootton, 1911], glyoxals [Dakin, 1914], and also with sodium hypochlorite [Langheld, 1909]. In all of these and many similar reactions, the nitrogen of amino-acids seems very easily removed by oxidation. The action of sodium hypochlorite on amino-acids was carefully studied by Langheld who showed that in all probability the first stage in the reaction was conditioned by the formation of a monochloroamino-acid, which subsequently underwent decomposition as follows:

$$R \cdot CH(NH_2) \cdot COOH \xrightarrow{+NaClO} R \cdot CH(NHCl) \cdot COONa \xrightarrow{+H_2O} R \cdot CHO + NH_3 + NaCl + CO_2.$$

In the case of leucine Langheld isolated the monochloroamino-acid as an unstable solid and obtained good evidence for the formation of a dichloroamino-acid when excess of hypochlorite was used. Apparently he did not investigate the decomposition products of the dichloroamino-acids.

Recently the writer has been engaged with the investigation of the properties of sulphochloroamides such as sodio-*p*-toluenesulphochloroamide, a substance prepared by the combination of sodium hypochlorite and toluene-sulphonamide, and now used to some extent as an antiseptic under the name chloramine-T. It has already been shown that though a solution of this substance contains no free hypochlorite, it reacts with α-amino-acids much in the same way as hypochlorite, yielding aldehydes, carbon dioxide

and ammonia [Dakin, Cohen, Daufresne and Kenyon, 1916]. The corresponding aldehydes were prepared from glycine, alanine, leucine, aminophenylacetic acid and methylaminophenylacetic acid.

Now sodio-*p*-toluenesulphochloroamide gives a practically neutral solution and the products of its decomposition are neutral. It appeared therefore that this substance might prove to be a useful neutral oxidising agent suitable for the oxidation of rather unstable substances. Langheld believed that he had obtained a small amount of glyoxaline acetaldehyde from histidine by oxidation with hypochlorite but the characterisation of the substance left much to be desired. It was decided, therefore, to try the action of sodio-*p*-toluenesulphochloroamide on histidine in the hope of obtaining more favourable results. A considerable yield of a crystalline product was obtained which was at first thought to be the aldehyde but which on investigation proved to be cyanomethyl-glyoxaline, a substance already prepared by Pyman [1911]. At first this appeared to be an anomalous result but it now appears that the reaction is of a fairly general character and that cyanides may be obtained by the oxidation of a variety of amino-acids. Apparently the cyanides are produced by the decomposition of previously formed dichloroamino-acids:

$$R \cdot CH(NH_2) \cdot COOH \rightarrow R \cdot CH(NCl_2) \cdot COOH \rightarrow R \cdot CN + 2HCl + CO_2.$$

On applying the reaction to other amino-acids, traces of hydrocyanic acid were obtained from glycine, acetonitrile from alanine, isobutyl cyanide (isovaleronitrile) from leucine and cyanobenzene (benzonitrile) from aminophenylacetic acid. The yields of cyanide in the case of the last three amino-acids were large.

As a matter of fact the reaction is not entirely novel, for Langheld apparently overlooked the fact that Schwanert [1857] many years ago before the constitution of leucine was settled had obtained clear proof of the formation of isobutyl cyanide when alkaline solutions of leucine were treated with chlorine. Liebig [1849] also stated that leucine on treatment with manganese dioxide and sulphuric acid gave isobutyl cyanide, while glycine gave hydrocyanic acid.

In this connection Plimmer's [1904, 1, 2] observation of the formation of hydrocyanic acid from glycine and other amino-acids on oxidation with nitric acid may be recalled; also the production of isobutyl cyanide from gelatin and caseinogen on oxidation with chromic acid recorded by Schlieper [1846] and Guckelberger [1847].

The oxidation of α-amino-acids to cyanides may have more than a theoretical interest in certain cases since it affords an additional method for the preparation of amines from amino-acids. Histidine for example may be oxidised to cyanomethyl-glyoxaline and then reduced to β-aminoethyl-glyoxaline without much difficulty and with relatively good yields.

Experimental.

Glycine and Alanine. The production of formaldehyde and acetaldehyde from glycine and alanine (1 mol) when their aqueous solutions are warmed with sodio-*p*-toluenesulphochloroamide (1 mol) has already been recorded [Dakin and colleagues, 1916]. When two molecular proportions of the sulphochloroamide are used to one of glycine and the mixture distilled, the distillate contains traces of hydrocyanic acid which are easily recognisable by the customary tests. In the case of alanine the first portion of the distillate contains oily drops of acetonitrile which subsequently dissolve as the distillate becomes more dilute. A trace of chloroamine, NH_2Cl, is also usually present and is easily recognised by its irritating odour. It disappears on standing owing to decomposition. The acetonitrile is readily shaken out with ether and gives a crystalline hydrobromide sparingly soluble in dry ether. On hydrolysis with sulphuric acid the formation of acetic acid can easily be recognised.

Leucine. The synthetic amino-acid (3·6 g.) was gently warmed with a solution of sodio-*p*-toluenesulphochloroamide (13 g.) in 100 cc. of water and the mixture was then distilled. The oily layer consisting largely of isobutyl cyanide was separated and shaken with sodium bisulphite solution to remove a little isovaleric aldehyde. The cyanide was then taken up in a little ether and distilled from a small distilling flask. 1·8 g. of isobutyl cyanide were obtained corresponding to a yield of about 70 per cent. of the theoretical amount. The cyanide was hydrolysed by boiling under a reflux condenser with excess of fifty per cent. sulphuric acid, the mixture diluted with water and the isovaleric acid recovered by distillation. It was converted into the silver salt which was analysed.

0·5944 g. gave 0·3081 g. silver = 51·8 per cent. Ag

$C_5H_9O_2Ag$ requires 51·7 „ „ „

α-Amino-phenylacetic acid. This acid was oxidised with two molecular proportions of the sulphochloroamide in the same fashion as in the preceding

experiment with leucine. The oily distillate consisting of cyanobenzene mixed with some benzaldehyde was dissolved in a little ether, shaken vigorously with sodium bisulphite to remove benzaldehyde and then the ether layer washed successively with sodium carbonate solution and water. On evaporation of the ether a 60 per cent. yield of crude cyanobenzene was obtained. Part of this was hydrolysed with sulphuric acid to benzoic acid, M.P. 120°, and another portion was converted into benzamide by cautious treatment with alkali. The most satisfactory identification was effected by dissolving 0·5 g. of the oil in 3 cc. absolute alcohol, then adding 3 cc. of concentrated ammonia and saturating the mixture with sulphuretted hydrogen. The solution was then heated in a sealed tube at 100° for an hour, the alcohol evaporated off and the solid residue of thiobenzamide crystallised from boiling water. The yield of thiobenzamide was practically quantitative as stated by Gabriel [1890] and the substance crystallised from water in long fine felted needles melting at 117°.

Histidine. The material for the experiments with histidine was kindly furnished by Dr Ewins. The dihydrochloride (1 g.) was dissolved in 20 cc. of water, neutralised with 0·5 g. of sodium carbonate, and 2·6 g. of sodio-toluenesulphochloroamide was then added. After standing for some time the solution was filtered to remove toluenesulphonamide and the filtrate shaken a few times with ether to remove the bulk of any dissolved sulphonamide. This procedure involves some loss of the nitrile but this can be recovered by washing the extracted sulphonamide with a little water. The main filtrate was then concentrated, preferably under reduced pressure, and before taking to complete dryness excess of dry sodium carbonate was added. The dry residue was then extracted with boiling ethyl acetate. It was found most convenient to do this in a Soxhlet apparatus after mixing the residue with plaster of Paris. The ethyl acetate extracts the cyanomethyl-glyoxaline almost exclusively and on evaporation of the solvent the substance readily crystallises, but it is usually somewhat pigmented As much as 0·4 g. of the cyanomethyl-glyoxaline can be obtained from 1 g. of histidine dihydrochloride corresponding to about eighty per cent. of the theoretical amount.

The cyanomethyl-glyoxaline was purified either by direct crystallisation from water, or from a mixture of methyl alcohol and toluene, or it was converted into the sparingly soluble picrate or finally it was sublimed at a temperature just below its melting point under the very low pressure obtained with the Gaede pump. However obtained the substance melts sharply at 138° and has all the properties described by Pyman [1911].

A mixed melting point with material kindly supplied by Dr Pyman showed no change.

Part of the substance was converted into the picrate which melted sharply at 167° after recrystallisation from water. It was analysed for picric acid by means of Busch's "nitron" method [1905].

0·6148 g. picrate gave 0·9891 g. precipitate = 68·1 per cent. picric acid

$C_5H_5N_3 \cdot C_6H_2(NO_2)_3OH$ requires 68·1 „ „ „

The cyanomethyl-glyoxaline gave the abnormal diazo-reaction and yielded a very soluble hydrochloride agreeing exactly with Pyman's description.

A portion of the cyanomethyl-glyoxaline was reduced to aminoethyl-glyoxaline with sodium and alcohol. The physiologically active base gave the characteristic dipicrate melting at 238°.

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