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XXXIII.—*The Synthesis of 3-β-Aminoethylindole.*

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A VERY considerable amount of interest has of late centred round a number of amines which may be considered to belong to a special group in that they are derived from the amino-acids of proteins by the removal of carbon dioxide (loss of the carboxyl group). Such bases are often produced by the action of putrefactive organisms on the amino-acids.

The earliest examples of this class of bases were discovered by Brieger in the ptomaines, putrescine and cadaverine. Their formation by the action of putrefactive organisms on the corresponding amino-acids was first established by Ellinger (*Ber.*, 1899, **32**, 3542). Since then amines derived from almost all the known amino-acids have been obtained either by putrefactive processes or by chemical means. The interest attaching to these bases lies in the fact that certain of the more complex amines are possessed of considerable physiological activity, and have been the subject of several recent communications (Barger and Walpole, *J. Physiol.*, 1909, **38**, 343; Dale and Dixon, *J. Physiol.*, 1909, **39**, 25; Acker-

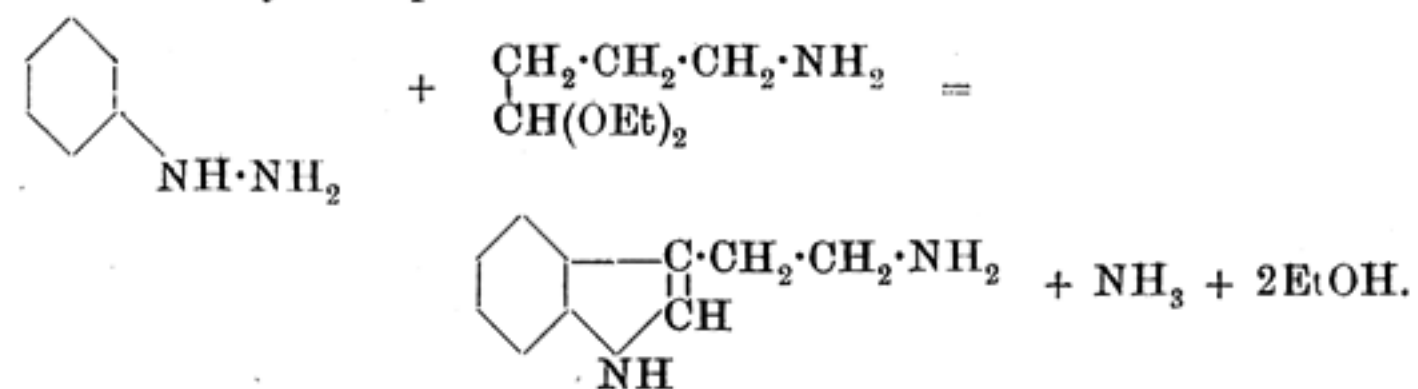
* Since writing the above the author has received a private communication from Dr. M. Freund stating that the melting point previously ascribed to the methylimide of cotarnic acid is incorrect. A specimen of this substance kindly sent by Dr. Freund, to whom the author desires to express his sincere thanks, melted at 199° and was identical with the compound described in this investigation.

mann and Kutscher, *Zeitsch. Biol.*, 1910, **54**, 387; Barger and Dale, *Trans.*, 1910, **97**, 2592; Dale and Laidlaw, *J. Physiol.*, 1910, **41**, 318).

Of the amino-acids known to occur in proteins for which the corresponding amine remained unknown, tryptophan is the most important. This amino-acid was first isolated by Hopkins and Cole (*J. Physiol.*, 1901-1902, **27**, 418), and afterwards synthesised by Ellinger and Flamand (*Ber.*, 1907, **40**, 3029). The amine derived from this amino-acid has now been obtained both synthetically and by the action of putrefactive bacteria on tryptophan itself (Ewins and Laidlaw, *Proc.*, 1910, **26**, 343), and the method of synthesis forms the subject of the present communication. (The action of putrefactive bacteria on tryptophan had previously been studied, but the isolation of the base was achieved only when its synthesis had revealed the properties of the amine.)

It was at first hoped that by heating tryptophan under very greatly diminished pressure, carbon dioxide might be split off, as in the case of tyrosine. This experiment was carried out at Dr. G. Barger's suggestion but the only product that could be isolated from the sublimate was a very small quantity of unchanged tryptophan. The method employed by Windaus and Vogt (*loc. cit.*) in the synthesis of 4-β-aminoethylglyoxaline from β-glyoxaline-4-propionic acid derived from histidine cannot here be employed, owing to the action of nitrous acid on the indole nucleus.

The method ultimately adopted was a modification of Fischer's method of synthesising indole derivatives, in which the phenylhydrazone of the suitable aldehyde is heated with zinc chloride. In this instance, the requisite aldehyde cannot be isolated in the free state on account of the readiness with which condensation takes place with formation of cyclic compounds (Wohl and Schäfer, *Ber.*, 1905, **38**, 4157). It was found, however, that the corresponding acetal (γ-aminobutyryl acetal) could be employed in place of the aldehyde, and that by heating with zinc chloride and phenylhydrazine, condensation was effected, alcohol and ammonia being eliminated, and a good yield of the desired base thus obtained. The reaction may be represented thus:

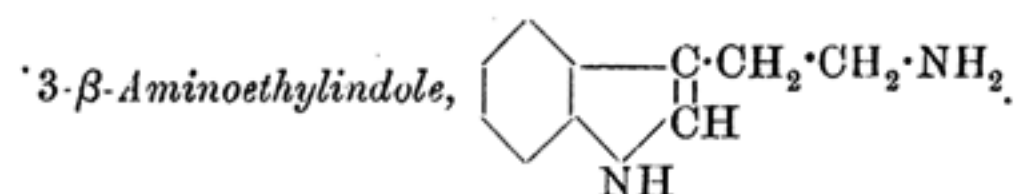


The picrate of the base was found to be identical in all respects,

chemical and physiological, with that of the base obtained by the action of putrefactive bacteria on tryptophan. This fact, the method of formation, and the analytical results leave no doubt as to the constitution of the base. As might be expected, the base gives the glyoxylic (Adamkiewicz) reaction described in detail by Hopkins and Cole (*Proc. Roy. Soc.*, 1901, **68**, 21) as a reaction for tryptophan. With bromine, however, which with tryptophan gives a pink colour, no reaction is obtainable.

As was expected, the base proved to be physiologically active. Dr. P. P. Laidlaw, who is undertaking its physiological examination, and by whom a full account of its action will be communicated elsewhere, has found that among other effects it produces a rapid and marked rise of blood pressure.

EXPERIMENTAL.



Four grams of γ -aminobutyrylacetal (b. p. 104—106°/18 mm.), obtained according to the method employed by Wohl and Schäfer (*Ber.*, 1901, **34**, 1914), were heated to 180° for three hours with 2.6 grams of phenylhydrazine and 3.6 grams of anhydrous zinc chloride in an open vessel. The product was dissolved in dilute acetic acid; the solution extracted with ether, and the zinc removed from the acetic acid solution as sulphide. The filtrate was then concentrated under diminished pressure to about 10 c.c. On cooling, a crystalline precipitate separated, which was collected. The crude hydrochloride thus obtained was dissolved in a small quantity of water, and an excess of an aqueous solution of sodium hydroxide added. An oil separated which, on keeping, crystallised to a mass of fine needles. The base thus obtained was recrystallised from a mixture of alcohol and benzene, and separated in long, colourless needles, melting at 145—146°. Yield, 45 per cent. of the theoretical:

0.1400 gave 0.3862 CO₂ and 0.0960 H₂O. C=75.2; H=7.6.

C₁₀H₁₂N₂ requires C=75.0; H=7.5 per cent.

3- β -Aminoethylindole is readily soluble in alcohol or acetone, and almost insoluble in water, ether, benzene, or chloroform. The base decomposes on heating under the ordinary pressure, yielding volatile products having an indole-like odour.

The free base (as well as its salts) gives the bluish-violet coloration with glyoxylic acid and concentrated sulphuric acid described by Hopkins and Cole (*loc. cit.*) as a characteristic reaction of tryptophan. The reaction may be obtained with a solution of one part of the base in about 300,000 parts. With bromine, however,

no coloration is obtained, the base differing in this respect from tryptophan, which gives a pink colour.

3- β -Aminoethylindole Hydrochloride, C₁₀H₁₂N₂·HCl.

The crude hydrochloride of 3- β -aminoethylindole, obtained as described above, was recrystallised from 95 per cent. alcohol by careful addition of ether. The salt was thus obtained in colourless, thin prisms, melting at 246°:

0.1444 gave 0.1058 AgCl. Cl=18.1.

C₁₀H₁₂N₂·HCl requires Cl=18.1 per cent.

The hydrochloride is soluble in about 12 parts by weight of water at 18°, and very soluble in hot water, from which it may be recrystallised.

3- β -Aminoethylindole Picrate, C₁₀H₁₂N₂·C₆H₂(NO₂)₃·OH.

This salt, the most characteristic of the base, is readily obtained by addition of a cold saturated aqueous solution of picric acid to a solution of the hydrochloride in water. The mixture immediately becomes turbid and orange-red in colour, and dark red crystals, consisting of fern-like aggregates of needles or prisms (very similar in form to that of ammonium chloride), rapidly separate. The picrate is characterised by its general insolubility. It is almost insoluble in water, very sparingly soluble in alcohol, ethyl acetate, chloroform, and most organic solvents except acetone, in which it is readily soluble.

For analysis, the salt was recrystallised from dilute acetone. The pure picrate melted and decomposed at 242—243°:

0.1286 gave 0.2338 CO₂ and 0.0452 H₂O. C=49.6; H=3.9.

C₁₆H₁₅O₇N₅ requires C=49.3; H=3.85 per cent.

3- β -Aminoethylindole picrolonate was prepared by adding rather more than one molecular proportion of picrolonic acid in dilute alcoholic solution to an aqueous solution of the hydrochloride. On concentrating the mixture, a crystalline solid separated, which was readily recrystallised from hot water, and separated in bundles of short, stout, deep chrome-yellow prisms, melting and decomposing at 231°.

The *benzoyl* derivative, obtained by the Schotten-Baumann method, or by heating the base with benzoic anhydride, is not readily obtained crystalline. It may be crystallised by very slow evaporation of the alcoholic solution of the compound, or by very careful addition of light petroleum to its solution in dry ether or ethyl acetate, and is then obtained in stout prisms, melting at 137—138°.

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