XVII.—2-*Thiol*-4(5)-β-*aminoethylglyoxaline* (2-*Thiolhistamine*).

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IN view of the physiological activity of histamine, and of the natural occurrence of ergothioneine, the synthesis of 2-thiolhistamine appeared to be of interest. This has now been effected by using as the starting material, αδ-dibenzamido-β-ketobutane (I) which Windaus, Dörries, and Jensen (*Ber.*, 1921, **54**, 2745) prepared from the tribenzamidobutene resulting from the benzoylation of histamine. When αδ-dibenzamido-β-ketobutane was hydrolysed with

(I.) $COPh{\cdot}NH{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NH{\cdot}COPh \longrightarrow$

$HCl,NH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2,HCl$ (II.) $\longrightarrow$

$NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}C(CH{=}NH)=N{>}C{\cdot}SH$ (III.)

alcoholic hydrochloric acid at 150°, αδ-*diamino*-β-*ketobutane dihydrochloride* (II) was obtained, and on condensation of this with 1 mol.

of sodium thiocyanate 2-*thiolhistamine* (III) resulted. Its constitution follows from the results of analysis combined with the fact that it yields histamine on oxidation.

Dr. Dale, Sec. R.S., and Mr. J. H. Gaddum, M.A., of the National Institute for Medical Research, to whom the author wishes to express his thanks, found that 50 mg. of 2-thiolhistamine hydrochloride produced a smaller fall in the blood pressure of a cat under ether than 0·001 mg. of histamine when injected intravenously, and also that 50 mg. of 2-thiolhistamine hydrochloride appeared to have no effect upon a 20 g. mouse when injected subcutaneously. Mr. W. A. Broom, B.Sc., of Boots' Pharmacological Department found that 2-thiolhistamine hydrochloride had only one/two-thousandth part of the activity of histamine in causing contraction of the isolated uterus of a virgin guinea-pig, and did not reduce the blood sugar of the rabbit when injected subcutaneously. It appears, therefore, that the substance has no significant histamine-like action.

EXPERIMENTAL.

αδ-Dibenzamido-β-ketobutane was prepared by the method of Windaus, Dörries, and Jensen (*loc. cit.*), the yield being 80 to 90% of the theoretical. It melts at 158—159° (corr.) and is not easily soluble in alcohol, requiring about 7 parts by weight of boiling alcohol for solution, and being much less soluble in cold alcohol. Windaus, Dörries, and Jensen give m. p. 151° and state that the substance is easily soluble in alcohol.

αδ-*Diamino*-β-*ketobutane*.—αδ-Dibenzamido-β-ketobutane (10 g.), alcohol (50 c.c.), and concentrated hydrochloric acid (50 c.c.) were heated under pressure for 2 hours at 150°. The solution was evaporated to low bulk, extracted with ether to remove benzoic acid, digested with charcoal, filtered, concentrated to low bulk, and mixed with alcohol; αδ-*diamino*-β-*ketobutane dihydrochloride* then crystallised, and further crops were obtained on concentration, the total yield being 73% of the theoretical. This salt crystallises from water in colourless diamond-shaped plates, m. p. 221° (decomp.; corr.). It is anhydrous and is very easily soluble in water, but sparingly soluble in alcohol (Found : C, 27·5; H, 7·4; Cl, 40·3. $C_4H_{10}ON_2,2HCl$ requires C, 27·4; H, 6·9; Cl, 40·5%). On the addition of cold saturated aqueous picric acid it gives a sparingly soluble picrate, crystallising from water in long, yellow, prismatic needles, m. p. 212° (decomp.; corr.).

2-*Thiol*-4(5)-β-*aminoethylglyoxaline*.—αδ-Diamino-β-ketobutane dihydrochloride (7·0 g.) and sodium thiocyanate (3·24 g.) were dissolved in 20 c.c. of water. The solution was evaporated to a syrup and heated for another hour at 100°, and just enough water was

added to dissolve the sodium chloride which had separated. On keeping, 2-thiolhistamine hydrochloride crystallised; it was purified by recrystallisation from water (yield, 3·7 g. = 52% of the theoretical).

2-*Thiol*-4(5)-β-*aminoethylglyoxaline hydrochloride* crystallises from water in clusters of colourless prismatic needles, m. p. 248—249° (corr.). It is anhydrous, very easily soluble in water, giving a neutral solution, and almost insoluble in hot absolute alcohol (Found: C, 33·0; H, 6·1; Cl, 19·8; S, 17·9. $C_5H_9N_3S,HCl$ requires C, 33·4; H, 5·6; Cl, 19·8; S, 17·8%). When cold aqueous solutions of this salt and picric acid are mixed, no immediate precipitate is formed, but a picrate crystallises on keeping in dense, golden, bevelled tablets, m. p. 225° (decomp.; corr.). Aqueous solutions of the hydrochloride give with diazobenzene-*p*-sulphonic acid (a) in the presence of sodium carbonate, an orange colour; (b) under Hunter's conditions (*Biochem. J.*, 1928, **22**, 4), in the presence of sodium carbonate and acetate, a yellow solution, which changes to red with a faint purple fluorescence on addition of sodium hydroxide.

Oxidation. 2-Thiolhistamine hydrochloride (0·18 g.) was boiled with hydrated ferric chloride (1·6 g.) in water (30 c.c.) for ½ hour. The solution was partly neutralised with sodium carbonate, mixed with a hot saturated aqueous solution of picric acid (0·46 g.), filtered, and kept. Histamine dipicrate (0·38 g.; yield, 67%) then separated in a pure state, having m. p. 238° (decomp.; corr.) when heated quickly, alone or mixed with an authentic specimen.

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