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NOVEL SYNTHESIS OF N-IMIDAZOLE-BENZYL-HISTIDINE DERIVATIVES WITHOUT THE USE OF SODIUM LIQUID AMMONIA.

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Since the introduction of the benzyl group for the protection of the imidazole side chain of histidine by Du Vigneaud and Behrens (1), a very large number of peptide syntheses have been carried out using this group. The imidazole benzyl group can be removed elegantly by catalytic hydrogenolysis or by treatment with sodium in liquid ammonia. The classical synthesis (1) of imidazole-benzyl-histidine involves the use of large amounts of sodium in liquid ammonia, a potentially hazardous reagent. We would like to report a new procedure for the synthesis of N-α-carbobenzoxy-imidazole-benzyl-L-histidine which bypasses the use of sodium in liquid ammonia.

N-α-Cbz-im-benzyl-L-histidine-benzyl ester was obtained in a few hours at room temperature by treating N-α-Cbz-L-histidine with two equivalents of benzyl bromide and dicyclohexylamine, each in dimethylformamide (DMF) solution. After evaporation of DMF in vacuo, the residue was triturated with ethyl acetate and the solution of Cbz-im-benzyl-L-histidine benzyl ester was separated from dicyclohexylamine-hydrobromide by filtration. The ethyl acetate solution containing the benzyl ester was evaporated to dryness. The residue was dissolved in a mixture of DMF and 95% ethanol (1:1) and was saponified by adding a slight excess of 1 Normal NaOH and allowing to stand for two hours at room temperature. Analytically pure Cbz-imidazole-benzyl-L-histidine (33% yield) was obtained by dilution of this mixture with water, precipitation of the product with acetic acid, filtration, and washings with H_2O and ether. m.p. 216-218°C. Lit. 210-213°C. (1,2) $[\alpha]_D$ -17.2° C=2 in 1N HCl, Lit. $[\alpha]_D^{20}$ -17.6 ± 0.5° C=2 in 1N HCl (2)

Anal. for $C_{21}H_{21}N_3O_4$

	C	H	N	O
Calcd	66.48	5.58	11.08	16.87
Found	66.23	5.52	11.14	16.87

Thin layer chromatography (silica, THF 93: cyclohexane 7: H_2O 5) of the material showed a single spot comparable with the known standard. The above preparation after acid hydrolysis (6N HCl 110° for 24 hours) yielded imidazole-benzyl-histidine. This was identified by using an amino acid analyzer* and a standard preparation for comparison. Crude yields up to 55% have been obtained. N-imidazole-benzyl-histidine may conceivably be obtained from N-α-Cbz-imidazole-benzyl-histidine by treatment with HBr/AcOH.

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REFERENCES

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2. E. Bricas and C. Nicot-Gutton, Bull. Soc. Chim. France, p. 466 (1960).

*Imidazole-benzyl histidine: Retention time, 92 minutes while using Beckman Spinco amino acid analyzer model 120B, PA35 resin column (0.9 x 5 cm.), 0.7 molar sodium citrate buffer pH 5.28, temperature 50°C with a buffer flow rate of 55 ml/hr.