The Synthesis of 3, 6-Bis(α-hydroxyethyl)-2, 5-diketopiperazine

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It is well known that diketopiperazine derivatives of the usual amino acids are readily obtained from the methyl or ethyl ester of the corresponding amino acid.[1] However, there has been no report concerning the synthesis of 3, 6-bis(α-hydroxyethyl)-2, 5-diketopiperazine, although other diketopiperazine derivatives of many hydroxy amino acids have already been synthesized.[2]

The authors obtained 3, 6-bis(α-hydroxyethyl)-2, 5-diketopiperazine from the product of the reaction, and then the catalytic hydrogenation, of carbobenzoxy-L-threonine and dicyclohexylcarbodiimide, it could also be obtained by the thermal condensation of the crystalline L-threonine methyl ester.* The infrared spectra of the products prepared by the two methods were identical, and both exhibited characteristic peaks at 3390 cm^{-1} (OH), 1680 cm^{-1} (amide I) and 1470 cm^{-1} (amide II).

The structure of the product was confirmed by the elemental analysis and molecular weight measurements by the cryosocopic method of Schwyzer.[3]

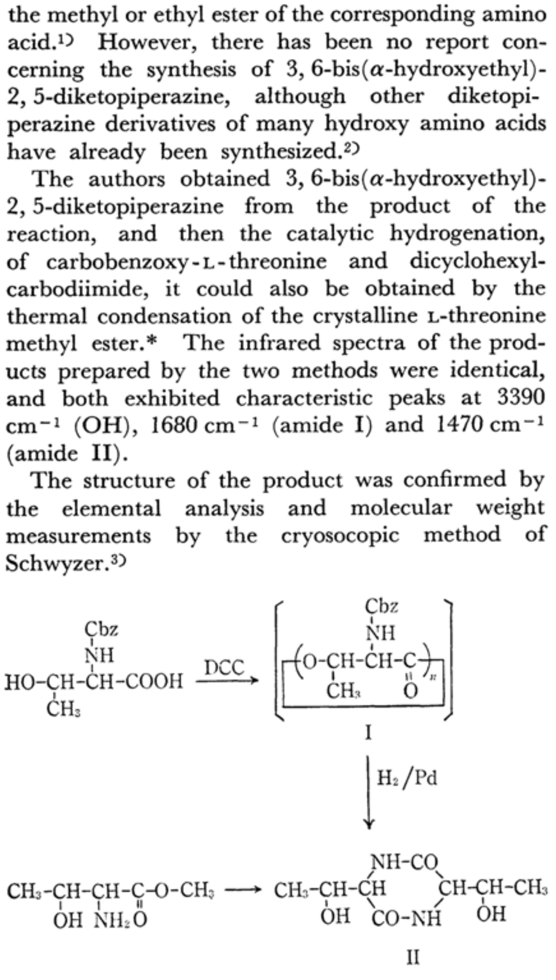

Fig. 1.

Experimental

The Synthesis of the Lacton Derivative (I).—A solution of 10.5 g. (0.054 mol.) of dicyclohexylcarbodiimide in 50 ml. of methylene chloride was added, drop by drop, into a solution of 13 g. of carbobenzoxy-L-threonine in 100 ml. of methylene chloride at room temperature.

After the addition had been completed, the stirring was continued for 1 hr. at room temperature. The reaction mixture was then allowed to stand overnight, the urea produced was filtered off (11.3 g., 100%), and the filtrate was washed with a N sodium bicarbonate solution and water and finally dried over anhydrous sodium sulfate. The filtrate was then concentrated in vacuo to give an oily product (12 g.) (I).

3, 6-Bis(α-hydroxyethyl)-2, 5-diketopiperazine (II).—To a 180 ml. methanol solution of 8 g. of I, 5 g. of palladium-charcoal was added, the mixture was then hydrogenated at room temperature for 5 hr. After the catalyst and the solvent had been removed, the product was dissolved in methanol.

Crystals were gradually separated. The yield was 625 mg. M. p. 254—256°C (decomp.). $[\alpha]_D^{23.5}$ $-87.0°$ (c 1.01, water).

Found. C, 47.51; H, 7.09; N, 13.53; Mol. wt., 208.** Calcd. for $C_8H_{14}N_2O_4$: C, 47.56; H, 6.99; N, 13.87%; Mol. wt., 202.

The L-Threonine Methyl Ester.—Into a suspension of 5.95 g. (0.05 mol.) of L-threonine in 60 ml. of absolute methanol, 6.5 g. of thionyl chloride was added, drop by drop, under cooling at about -5°C, the stirring was then continued for 1.5 hr. at room temperature. After the reaction product had been allowed to stand at room temperature for 24 hr., the solvent was removed under reduced pressure at 30°C, an oily product (L-threonine methylester hydrochloride) was thus obtained (8.4 g. (99%)).

Three grams of triethylamine were added, drop by drop, into a solution of 5 g. of the above ester hydrochloride under cooling. After the addition was over, 150 ml. of ether was added to the resulting mixture, and it was stored in a refrigerator for 1 hr. The triethylamine hydrochloride was then filtered off, the solvent was removed, the resulting partly-crystallized oily material was dissolved in a small amount of ether, and the insoluble material was filtered off. The filtrate was then concentrated under reduced pressure until crystals appeared.

From the mother solution, other crops of crystals were obtained. The total yield was 2 g. (32%).

Recrystallization from ether gave 1 g. of fine crystals. M. p. 63—65°C $[\alpha]_D^{23.5}$ $-21.0°$ (c 0.999, N HCl).

Found. C, 45.08; H, 8.22; N, 10.75. Calcd. for $C_5H_{11}NO_3$. C, 45.15; H, 8.34; N, 10.53%.

The Synthesis of 3, 6-Bis(α-hydroxyethyl)-2, 5-diketopiperazine (III) from the L-threonine Methyl Ester.—In a small vessel connected with a vacuum system there was placed 316 mg. of a free ester, after

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[1] J. P. Greenstein, "Chemistry of the Amino Acids," John Wiley & Sons, New York (1961), p. 797.

[2] T. Sherdsky, Y. Knobler and Max Franknel, *J. Org. Chem.*, **26**, 1482 (1961).

* No attempts to crystalize this free ester have been made previously.

[3] R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **41**, 2190 (1958).

** The molecular weight was determined by the cryoscopic method of Schwyzer.[3]

the bath temperature had then been gradually raised until the crystals melted (about 75°C), the temperature was kept at 75°C for 3 hr. After cooling, the reaction mixture was dissolved in 3 ml. of methanol and allowed to stand in a refrigerator until crystals appeared. The crystals were then filtered and dried (30 mg.). Recrystallization from methanol gave 21 mg. (12%) of material. M. p. 254—256°C (decomp.). No depression in melting point was observed upon the admixture of II and III.

Found. C, 47.41; H, 7.33; N, 13.64. Calcd: for $C_8H_{14}N_2O_4$. C, 47.56; H, 6.99; N, 13.87%.