KRATKA SAOPĆENJA SHORT COMMUNICATIONS

A Synthesis of DL-α-Amino-β-hydroxy-valeric Acid. (Hydroxynorvaline)

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By applying the method used by Pfister et al.[1] for the synthesis of threonine we prepared DL-α-amino-β-hydroxy-valeric acid (hydroxynorvaline) starting from ethyl β-keto-valerate. This amino acid was prepared earlier by different methods by Osterberg[2], Abderhalden and Heyns[3], Botvinnik et al[4], Buston et al.[5], and by Izumiya[6].

The melting points of hydorxynorvaline and of its N-benzoyl derivate indicate that the product obtained consists mainly of the threo-isomer.

EXPERIMENTAL*

Ethyl β-keto-valerate

The ester was prepared according to Brändström[7] from propionyl chloride and ethyl ethoxymagnesium-malonate in 70% yield.

α-Amino-β-hydroxy-valeric Acid

A solution of phenyldiazonium chloride (from 6.14 g. of aniline and 6.27 g. of sodium nitrite) was added slowly and with stirring to a mixture consisting of ethyl β-keto-valerate (12.7 g., 0.089 mole), 96% ethanol (269 ml.), cryst. sodium acetate (65.5 g.) and water (44 ml.). During the addition the temperature was held at 10°. After standing on ice for two days the separation of the oily product was completed by the addition of water (300 ml.). The aqueous layer was separated and extracted with ether. After evaporating the solvent in vacuo at 30° the residual oil was combined with the main part of the product. Thus, 20.3 g. (92%) of crude *ethyl α-phenylazo-β-keto-valerate* were obtained. The dark yellow colored oil could not be induced to crystallization.

The azo-compound was dissolved in glacial acetic acid (21 ml.) and added in the course of one hour to a vigorously stirred mixture of zinc powder (34.1 g.), glacial acetic acid (45 ml.), and acetic anhydride (22.5 ml.); by means of external cooling the temperature was held at 10—15°. The stirring was continued for additional three hours at 25—30°. After standing for two hours at room temperature the mixture was filtered and the cake on the filter washed with glacial acetic acid. The combined filtrates were evaporated in vacuo, the rasidue diluted with 10 ml. of warm water, cooled to 10°, and the excess of acetic acid neutralized with sodium hydrogen carbonate. After standing for two hours in an ice-box the separated acetanilide was removed by filtration. The filtrate was extracted with chloroform, and the solvent evaporated in vacuo. The crude *ethyl α-acetamido-β-keto-valerate* (13.1 g., 80%) solidified upon standing in an ice-box.

The crude ester was dissolved in water (111 ml.) and ethanol (40 ml.) and reduced at room temperature and ordinary pressure in the presence of W-4 Raney

* All melting points are uncorrected

nickel catalyst. After removing the catalyst, the solution was evaporated in vacuo and the oily residue dried azeotropically with benzene. *Ethyl α-acetamido-β-hydroxy-valerate* thus obtained (9.88 g., 75.2%) was dissolved in benzene (11 ml.) and treated with thionyl chloride (7 ml.) in benzene (5 ml.) in the course of 1.5 hour — the temperature being held at 4°. The stirring was continued for one hour at room temperature, and the mixture was then poured into 265 ml. of dry ether. After standing for three days at 0° ether was decanted and the oil remaining at the bottom refluxed for 15 hours with 100 ml. of diluted hydrochloric acid (1 : 1). After cooling, the solution was extracted with ether, and the aqueous layer evaporated to dryness in vacuo giving 4.92 g (59.8%) of hydroxynorvaline hydrochloride. The free acid was obtained by passing the aqueous solution of the hydrochloride through an Amberlite IR-45 column. The resulting solution was evaporated to dryness, and the residue recrystallized from 80% ethanol. The pure *α-Amino-β-hydroxy-valeric acid* melted at 221—223°. Recorded m. p. 215° (threo) and 236° (erytho)[5]. According to Izumiya[6] the m. p.'s are 227—228°, and 257—259° respectively.

Anal. 6.865 mg. subst.: 0.625 ml. N_2 (21°C, 750 mm.)
$C_5H_{11}NO_3$ (133.15) calc'd.: N 10.52%
found: N 10.43%

α-Benzamido-β-hydroxy-valeric Acid

A sample of hydroxynorvaline was benzoylated according to Carter and Stevens[8], and recrystallized from hot water. M. p. 143—144.5°. Recorded m. p. 149° (threo), and 181° (erythro)[5].

Anal. 5.930 mg. subst.: 0.303 ml. N_2 (22.5°C, 761 mm.)
$C_{12}H_{15}NO_4$ (237.25) calc'd.: N 5.90%
found: N 5.91%

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IZVOD

Sinteza DL-α-amino-β-hidroksi-valerijanske kiseline (Hidroksinorvalin)

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Primjenom metode Pfistera i suradnika[1] izvedena je jedna nova sinteza DL-α-amino-β-hidroksi-valerijanske kiseline (hidroksinorvalina). Ta sinteza polazi od etilnog estera β-keto-valerijanske kiseline, a usporedba tališta slobodne kiseline i N-benzoil derivata pokazuje, da na taj način pretežno nastaje treo-oblik recemičkog hidroksinorvalina.

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