NEW SYNTHESIS OF DESTHIOBIOTIN

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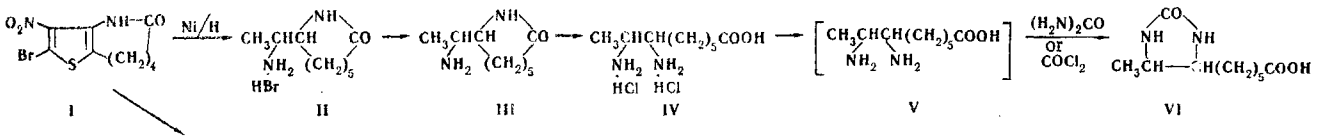
A method for the synthesis of desthiobiotin was developed. It is based on the reductive desulfurization of the lactam of δ-(5-bromo-4-nitro-3-amino-2-thienyl)valeric acid, saponification of the resulting ε-(1-aminoethyl-ε-enantholactam to 7,8-diaminopelargonic acid, and condensation of the latter with phosgene or urea.

We have previously [1] demonstrated the possibility of obtaining 2,3,4,5-tetradehydrobiotin from the lactam of δ-(4-nitro-3-amino-2-thienyl)valeric acid. The reductive desulfurization of 2,3,4,5-tetradehydrobiotin by means of Raney nickel gave a mixture of the diastereomers of ε-(4-methyl-2-oxo-5-imidazolidinyl)-caproic acid (VI) (desthiobiotin). It was subsequently found that one can proceed directly from the lactam of δ-(5-bromo-4-nitro-3-amino-2-thienyl)valeric acid (I) to obtain this mixture. When this is done, a number of steps that cannot be avoided in the synthesis of 2,3,4,5-tetradehydrobiotin become unnecessary, and this simplifies the process considerably.

The reductive desulfurization of I was carried out with Raney nickel in aqueous media in the presence of ammonia. In this case, we isolated hydrobromide II, from which free aminolactam III was obtained by the action of alkali. Refluxing III with hydrochloric acid gave 7,8-diaminopelargonic acid dihydrochloride (IV)



[2], and the sodium salt of 7,8-diaminopelargonic acid (V), which was obtained from it, gave desthiobiotin (VI) on reaction with phosgene or when heated with urea in the presence of alkali and ethylene glycol. The same product (VI) can also be obtained from I without isolation of the pure intermediates. The preparations of the lactams, which are the starting compounds for the synthesis of bromonitrolactam I are given in [3,4]. The method that we are proposing is suitable not only for the synthesis of VI but also for the preparation of diverse homologs of desthiobiotin [5], the individual representatives of which have antibiotic activity. A study of the effect of VI on the growth of yeast-like fungi used in the manufacture of feed protein [6] demonstrated that it is an active growth stimulator.

EXPERIMENTAL

Desthiobiotin (VI) from 2,3,4,5-Tetradehydrobiotin. About 50 g of Raney nickel that had been stored under water was added gradually at 65-70° C with vigorous stirring to a solution of 3.1 g of tetradehydrobiotin and 1.2 g of sodium bicarbonate in 150 ml of water, and the mixture was stirred for 4 h (until it gave a negative reaction for sulfur when tested with sodium nitroprusside [7]). The nickel was removed by filtration and washed several times with warm water. The filtrates were vacuum-evaporated, the residue was dissolved in 25 ml of warm water, and the precipitated aluminum hydroxide was removed by filtration. The filtrate was acidified with hydrochloric acid, and the warm solution was treated with activated charcoal. The solution was then allowed to stand in a refrigerator. The resulting precipitate was removed by filtration and washed with ice water to give 0.9 g (32.5%) of colorless VI with mp 126-130° C. Recrystallization from water

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gave a product with mp 130-132° C (mp 166 [8] and 130-136° [9]). This disparity in the melting points is explained by the fact that the different investigators obtained VI as mixtures with differing percentages of the diastereoisomers. Found: N 13.07%. $C_{10}H_{18}N_2O_3$. Calculated: N 13.08%.

ε-(1-Aminoethyl)-ε-enantholactam Hydrobromide (II). A 6-g sample of bromonitrolactam I was added gradually to a suspension of 70 g of Raney nickel in 250 ml of water and 50 ml of concentrated ammonium hydroxide heated to 55° C, and the mixture was stirred at 65-70° C for 7 h. (A small amount of foaming occurred at the start of the process.) The nickel was removed by filtration and washed with warm water. The water was then vacuum-evaporated, and the green residue was dissolved in 35 ml of warm water. The aqueous solution was filtered, and the filtrate was vacuum evaporated. The residue (3.34 g of crude hydrobromide II) was recrystallized from absolute alcohol to give II with mp 239-241° C (dec.). Found: C 43.01; H 7.60; Br 31.93%. Calculated: C 43.93; H 7.62; Br 31.82%.

ε-(1-Aminoethyl-ε-enantholactam (III). A 10-g sample of bromonitrolactam I was subjected to reductive desulfurization under the conditions described above. Removal of the nickel and water gave 7.4 g of crude hydrobromide II, which was dissolved in 45 ml of water. The solution was filtered, and the filtrate was saturated with potassium carbonate. The resulting oil was extracted with chloroform, and the extract was dried with potassium carbonate, filtered, and distilled to give 3.6 g (64%) of aminolactam III as a viscous oil with bp 196-201° C (10 mm) that crystallized on standing to give a product with mp 71-73° C (from heptane). Found: C 63.21; H 10.65%. $C_9H_{18}N_2O$. Calculated: C 63.49; H 10.66%.

7,8-Diaminopelargonic Acid Dihydrochloride (IV). A 3.6-g sample of distilled aminolactam III was dissolved in 40 ml of dilute (1 : 1) hydrochloric acid, and the solution was refluxed for 5 h. The resulting dark-red solution was decolorized with activated charcoal, and the filtrate was vacuum-evaporated. The residue was vacuum-dried over phosphorus pentoxide to give 4.7 g (85%) of crude dihydrochloride IV with mp 162-172° C (dec.). Recrystallization from absolute alcohol gave a product with mp 176-182° C (dec.) (mp 180-182° C, 206, and 217° C [10-12]). Found: C 41.36; H 8.38; Cl 27.40%. $C_9H_{22}Cl_2N_2O_2$. Calculated: C 41.38; H 8.49; Cl 27.15%.

Desthiobiotin (VI). A) From Phosgene. A 4.67-g sample of crude hydrobromide III (obtained by the reductive desulfurization of 6.0 g of I under the conditions presented above) was dissolved in 60 ml of dilute (1 : 1) hydrochloric acid, and the solution was refluxed for 5 h. The solution was then diluted with 50 ml of water and decolorized with charcoal. The filtrate was vacuum-evaporated, and the viscous residue (the crude hydrochloride–hydrobromide of diamino acid V) was dissolved in 30 ml of warm water. The solution was made slightly alkaline with 10% sodium hydroxide solution, 1.5 g of sodium carbonate was added, and the mixture was filtered. Phosgene was passed through the filtrate until it was acid to Congo red, and it was then allowed to stand overnight in a refrigerator. The resulting crystals were removed by filtration and washed with ice water to give 1.57 g of a product with mp 129-132° C. Storage of the mother liquor in a refrigerator gave another 0.17 g of product with mp 134-145° C to give an overall yield of 1.74 g (41.5%) of crude VI. One recrystallization from water (with activated charcoal) gave a product with mp 132-134° C. Found C 56.12; H 8.33%. $C_{10}H_{18}N_2O_3$. Calculated: C 56.05; H 8.47%.

B) From Urea (see [13]). A 6.4-g sample of the crude hydrochloride–hydrobromide of 7,8-diaminopelargonic acid (obtained by the reductive desulfurization of 7.3 g of I with subsequent hydrolysis of hydrobromide II under the conditions presented above) was treated with 30% sodium hydroxide solution to pH 8-9. Urea (2.5 g) and 25 ml of ethylene glycol were added to the mixture, which contains the precipitated salts, and it was refluxed for 4 h. (The temperature in the liquid was 130-135° C.) The condenser was set for distillation, and the water and a portion of the ethylene glycol were removed by distillation until the temperature in the flask was 200° C. The mixture was then refluxed for 45-60 min (ammonium carbonate sublimed in the reflux condenser), and the ethylene glycol was removed by distillation on an oil bath (the bath temperature was no higher than 140° C) at a residual pressure of no more than 5 mm until the residue was almost solid. The residue was dissolved in 30-35 ml of water, and the solution was filtered. The filtrate was cooled and acidified with concentrated hydrochloric acid, which induced the crystallization of VI. The mixture was allowed to stand in a refrigerator for 24 h, and the resulting precipitate was removed by filtration, washed with 5 ml of ice water, and dried to give 2.1-2.2 g of VI with mp 132-136° C. Storage of the mother liquor in a refrigerator precipitated another 0.4-0.5 g of a product with mp 150-154° C. The overall yield of VI based on I was 50-55%. The yield of VI from the condensation of purified dihydrochloride IV with urea was 83%. Compound VI can be recrystallized from an approximately 10-fold amount of boiling water. A sample of VI with mp 132-136° C had mp 135-138° C after recrystallization from water.

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