SYNTHESIS OF DEHYDRODESTHIOBIOTIN

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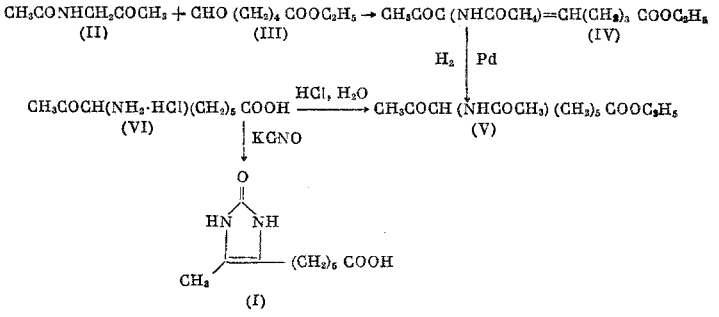
Dehydrodesthiobiotin (I) possesses noticeable growth stimulating activity relative to baker's yeast Saccharomyces cerevisiae [1] and is regarded as being a possible bioprecursor of vitamin H (biotin) [2].

For a further study of the biological properties of (I) we accomplished in the present apper the direct synthesis of (I) from acetamidoacetone (II) and the ethyl ester of adipic semialdehyde (III) [3]. The crotonic condensation of (II) with (III) in the presence of piperidine acetate gave the unsaturated ketoester (IV), the hydrogenation of which over Pd led to the formation of the ethyl ester of 7-acetamido-8-ketopelargonic acid (V). After the hydrolysis of (V) with hydrochloric acid and carbamidation of the intermediate hydrochloride of 7-amino-8-ketopelargonic acid (VI) with potassium cyanate we isolated the desired (I) in an overall yield of approximately 6% when based on the starting (II)



The structures of (I) and (VI) were confirmed by comparison with authentic specimens. (VI) showed 4% of the activity of d-biotin when tested on the yeast Saccharomyces cerevisiae. It is interesting to mention that in its growth stimulating activity the isomeric 7-keto-8-aminopelargonic acid hydrochloride is equal to natural biotin [4].

EXPERIMENTAL

The unsaturated ketoester (IV) [5] (bp 192-194° (3 mm); n_D^{20} 1.4760) was obtained by the condensation of acetamidoacetone (II) with (III) in the presence of a mixture of piperidine and acetic acid in methanol; yield 46%.

7-Amino-8-ketopelargonic Acid Hydrochloride (VI). A solution of 1.28 g of (IV) in 10 ml of alcohol was hydrogenated over 0.3 g of 10% Pd/$CaCO_3$ (room temperature and pressure). After the absorption of 105 ml of H_2 (about 30 min) the catalyst was filtered, while the filtrate was evaporated in vacuo to dryness. The obtained acetamido ketone (V), without purification, was mixed with 22 ml of dilute (1 : 1) HCl solution, refluxed for 2 h, and evaporated in vacuo to dryness. The residue was dissolved in 10 ml of water, active carbon was added, and the mixture was stirred vigorously for 10-15 min. The filtrate was again evaporated in vacuo to dryness, while the residue was treated with 5 ml of isopropanol and the obtained crystals were washed with isopropanol. We obtained 0.35 g (31%) of (VI), mp 124-125°; R_f 0.63 (here and subsequently, TLC on SiO_2 G, acetone – water, 3 : 2). Hydrochloride (VI) specimen (mp 124-125°).

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Dehydrodesthiobiotin (I). A mixture of 0.23 g of (VI) and 0.08 g of KCNO in 5 ml of water was heated at 100° for 20 min, cooled to 20°, and the obtained precipitate was recrystallized from water. We obtained 0.09 g (42%) of (I) with mp 162-164° (R_f 0.30, acetone – water, 9:1). The mixed melting point with an authentic specimen (mp 162-164°) [1] was not depressed.

We wish to express out deep gratitude to Dr. P. Tsuagawa (of the Adzinomoto Company, Japan) for supplying the sample of (VI).

CONCLUSIONS

A four-step synthesis of dehydrodesthiobiotin from acetamidoacetone and the ethyl ester of adipic semialdehyde was accomplished.

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