SYNTHESIS OF (±)-BIOTIN FROM A SUBSTITUTED 2,3-DEHYDROTHIOPHANE

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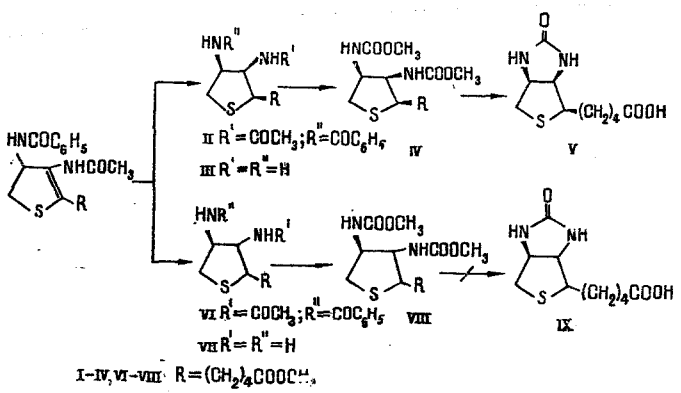
(±)-Biotin has been synthesized from a mixture of cis- and allo-trisubstituted dehydrothiophanes by a scheme providing for the easy elimination of the accompanying allo-substituted thiophane in the form of an intermediate and not as the final isomeric allo-biotin. The imidazoline ring of biotin is formed from a dialkoxycarbonyldiaminothiophane under the conditions of partial hydrolysis of one of the protective groups with the elimination of phosgene from the scheme of synthesis.

We have effected the synthesis of (±)-biotin (V) by the scheme (I-V), starting from a mixture of isomeric cis- and allo-3-acetylamino-4-benzylamino-2-(δ-methoxycarbonylbutyl)-thiophanes (II, VI), obtained from the substituted 2,3-dehydrothiophane (I) by the method of Harris et al. [1], with the exclusion from the scheme of synthesis of the phosgene used in this method [1], and the separation of the corresponding allo- substituted thiophene (VII) in the form of an intermediate and not of the final isomeric allo-biotin (IX) [1]. We synthesized the mixture of substituted thiophanes (II, VI) by the reduction of 3-acetylamino-4-benzylamino-2-(δ-methoxycarbonylbutyl)-2,3-dehydrothiophane (I) by the method of Harris et al. [1], and then subjected this mixture (II, VI) to hydrolysis with 48% hydrobromic acid to a mixture of isomeric dihydrobromides of cis- and allo-3,4-diamino-2-(δ-methoxycarbonylbutyl)thiophane (III and VII). From these isomeric cis- and allo-diamines (III and VII) by the action of chloroformic ester in aqueous methanol in the presence of sodium bicarbonate we obtained a mixture of isomeric cis- and allo-3,4-di(methoxycarbonylamino)-2-(δ-methoxycarbonylbutyl)thiophanes (IV, VIII).

We established the configurations of the substituents in compound (VII) from those of its derivatives (VIII and X) with the aid of the ^{1}H NMR method. Allo-3,4-diureido-2-(δ-methoxycarbonylbutyl)thiophane (X) was obtained by the reaction of the diamine (VII) with potassium isocyanate in aqueous solution at 30-40°C.



In the ^{1}H NMR spectra of compounds (VIII and X), a large difference is observed in the chemical shifts of the protons at 5-C ($\Delta\delta_{5H',5H''}$ 0.51; 0.38 ppm), and similar values of the vicinal spin–spin coupling constant $J_{4H,5H'}$ and $J_{4H,5H''}$, since it has been shown previously [2, 3] that both compounds possess the allo configuration.

After treatment of the mixture of isomeric compounds (IV and VIII) with aqueous solution of barium hydroxide at the boil, the hydrolysis of one protective group of the diamine

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apparently took place and then, as the result of the intramolecular cyclization of the resulting monoalkoxycarbonyldiamide [4, 5], an imidazolidinone ring was formed. After acidification of the reaction mixture with hydrobromic acid to pH 1, (±)-biotin was isolated with mp 230-232°C, and the mother solution yielded the dihydrobromide of the allo-diamine (VII). As we expected, intramolecular cyclization with the formation of the imidazolidinone ring took place only for the cis-di(alkoxycarbonylamine) (IV). Thus, when the individual cis-dimethoxycarbonyl derivatuve (IV) was boiled with barium hydroxide, followed by acidification with hydrobromic acid, (±)-biotin was obtained with a yeild of 95%, while the allo-di(methoxycarbonylamine) (VIII) did not form (±)-allo-biotin (IX) under the same conditions, because of steric hindrance, but the dihydrobromide of the allo-diamine (VII) was isolated.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer 20A spectrometer, the chemical shifts being given in the δ scale relative to TMS, the accuracy of measurement of the chemical shifts of the protons being ±0.01 ppm. The assignment of the signals in the spectra to definite protons of the compounds studied was confirmed by the ratio of the integral intensities of the signals, by homonuclear double resonance, and by comparison of the spectra of closely related compounds [2, 3].

Dihydrobromide of a Mixture of the Isomeric cis- and allo-3,4-Diamino-2-(δ-methoxycarbonylbutyl)thiophanes (III, VII). A suspension of 5.6 g of a mixture of isomeric cis- and allo-3-acetylamino-4-benzoylamino-2-(δ-methoxycarbonylbutyl)thiophanes (II, VI) [1] in 80 ml of 48% hydrobromic acid was boiled for 5 h, cooled, and extracted with benzene, the aqueous solution was evaporated to dryness, and then 20 ml of methanol was added and the mixture was boiled for 1 h, concentrated to a volume of 7-8 ml, and kept at 0-3°C for 16-18 h. The precipitate that had deposited was filtered off and was washed with ether–methanol (9:1). Yield 4.7 g (95%), mp 180-190°C (decomp, from methanol).

The dihydrobromide of cis-3,4-diamino-2-(δ-methoxycarbonylbutyl)thiophane (III) was obtained by the hydrolytic cleavage of biotin. (±)-Biotin (V) (0.7 g) was added to 7 ml of 48% hydrobromic acid, and the mixture was boiled for 7 h and evaporated, and then the residue was treated with 5 ml of methanol and this mixture was boiled for 1 h, concentrated to 2-3 ml, and kept at 0-3°C for 18 h. A precipitate of the cis-diamine (III) with the composition $C_{10}H_{20}N_2O_2S \cdot 2HBr$ precipitated in the form of colorless plates with mp 215°C (decomp., from methanol). Yield 1.0 g (88.5%). Here and below, the results of analysis of all the compounds corresponded to the calculated figures.

The dihydrobromide of allo-3,4-diamino-2-(δ-methoxycarbonylbutyl)thiophane (VII) was obtained in the individual form from the acidic aqueous mother solution after the isolation of the (±)-biotin (see below). The aqueous mother solution was evaporated to dryness, the residue was treated with 100 ml of methanol, and the methanol was evaporated off in vacuum. This gave 3.8 g of the allo-diamine (VII), $C_{10}H_{20}N_2O_2S \cdot 2HBr$ in the form of colorless plates with mp 205-206°C (decomp.). R_f 0.10 (in the butanol–amyl alcohol–water–acetic acid (20:20:12:1) system; revealing agent – a 0.2% solution of $KMnO_4$).

cis- and allo-3,4-Di(methoxycarbonylamino)-2-(δ-methoxycarbonylbutyl)thiophanes (IV, VII). To 5 mg of a mixture of the dihydrobromides of the isomeric cis- and allo-diamines (III, VII) with mp 180-190°C was added 12 ml of 1 N NaOH, and the mixture was kept at 50°C for 1 h for the formation of the free diamine (pH 7-8). Then 16 ml of methanol was added, the mixture was cooled to 0°C, and 2.7 ml of methyl chloroformate and 20 ml of 9% sodium carbonate solution were added simultaneously at such rates that the pH remained between 7 and 8. The mixture was kept at 0°C for 15 min, heated to 45-50°C, and stirred at this temperature for 2 h. Then it was cooled to 0°C, acidified with 2.5 N HCl to pH 1, and extracted with chloroform; the extract was washed with water and the chloroform was evaporated off in vacuum. This gave the isomeric compounds (IV) and (VIII) in the form of an oily residue.

cis-3,4-Di(methoxycarbonylamino)-2-(δ-methoxycarbonylbutyl)thiophane, $C_{14}H_{24}N_2O_6S$ (IV), was obtained from 0.9 g of the pure compound (III) under conditions analogous to those for obtaining compound (VIII); yield 0.7 g (88%), colorless needles, mp 98-99°C (from methanol).

allo-3,4-Di(methoxycarbonylamino)-2-(δ-methoxycarbonylbutyl)thiophane (VIII). A solution of 0.9 g of compound (VII) in 3 ml of water was treated with 0.3 g of sodium carbonate, and the mixture was stirred at 30°C for 15 min, after which 3 ml of methanol was added, the

mixture was cooled to 0°C, and, with stirring, 0.26 ml (0.081 g) of methyl chloroformate and 0.36 g of sodium carbonate in the form of a 9% aqueous solution were added simultaneously. The reaction mixture was kept at 18-20°C for 30 min and was then extracted with chloroform, and the extracts were washed with water and dried with magnesium sulfate. The chloroform was driven off in vacuum, the residue was treated with ether, and the mixture was kept at 0-3°C for 16-18 h. A precipitate of (VIII), $C_{14}H_{24}N_2O_6S$, deposited with a yield of 0.75 g (94.3%) in the form of colorless needles with mp 149-150°C. ^{1}H NMR (C_5D_5N, 70°C, δ, ppm, J, Hz): 3.50-3.85, 2H; 4.22-4.75; 3H, 4.22-4.75, 4H; 3.33, 5H'; 2.95, 5H"; 7.62, 3-NH; 7.39, 4-NH; $J_{4H;5H'}$ 5.9, $J_{4H,5H"}$ 5.2; $J_{5H,5H"}$ 11.5; $J_{4H,4-NH}$ 8.4.

(±)-Biotin (V). The oily mixture of isomeric compounds (IV and VIII) obtained from 5 g of the dihydrobromides of the mixture of cis- and allo-diamines (III and VII) was treated with 31 g of $Ba(OH)_2 \cdot 8H_2O$ and 127 ml of water, and the mixture was boiled for 1.5 h, cooled to 0°C, acidified with 12% hydrobromic acid to pH 1, concentrated in vacuum to 1/3 of its initial volume, and kept at 0°C for 18 h. The (±)-biotin that separated out was filtered off and dried. Yield 0.67 g; colorless needles with 230-232°C (according to the literature [1], mp 230-232°C). R_f 0.61 (butanol—amyl alcohol—water—acetic acid (20:20:12:1) system; revealing agent — 0.2% solution of $KMnO_4$). ^{1}H NMR (CF_3COOH, 34°C, δ, ppm, J, Hz) 4.34, 3aH; 4.17, 6aH; 2.84, 4H'; 2.61, 4H"; 3.12, 5H; $J_{4H',4H"}$ 12.3; $J_{4H",3aH}$ 1.7; $J_{4H',3aH}$ 4.1; $J_{3aH,6aH}$ 7.8; $J_{6aH,5H}$ 4.4. The (±)-biotin obtained showed 50% of the growth activity of natural (+)-biotin on *Lactobacillus plantarum* and *Candida tropicalis* SK-4. The yield of (±)-biotin on the amount of the dihydrobromide of the cis-diamine (III) contained in the initial mixture was 90%.

The acidic aqueous mother solution after the separation of the (±)-biotin contained the allo-diamine (VII) in the form of the dihydrobromide: R_f 0.10.

From 0.7 g of the pure compound (IV), 0.46 g (95%) of (±)-biotin was obtained with mp 230-232°C.

allo-3,4-Diureido-2-(δ-methoxycarbonylbutyl)thiophane (X). At 18-20°C with vigorous stirring, 2 g of KCNO was added to a solution of 2 g of compound (VII) in 7 ml of water, the mixture was stirred at 30-40°C for 2 h, and the precipitate that deposited was filtered off and washed with water. Yield 1.4 g (87%), colorless needles with the composition $C_{12}H_{22}N_4O_4S$, mp 211°C (decomp.). ^{1}H NMR (CD_3COOD, 100°C, δ, ppm, J, Hz): 3.15-3.68, 2H; 4.00-4.37, 3H; 4.00-4.37; 4H; 3.15, 5H'; 2.64, 5H"; $J_{4H,5H'}$ 6.0; $J_{4H,5H"}$, 4.4; $J_{5H',5H"}$ 12.

SUMMARY

1. (±)-Biotin has been synthesized from a mixture of cis- and allo-trisubstituted 2,3-dehydrothiophanes by a method providing for the easy separation of the accompanying allo-substituted thiophane in the form of an intermediate and not of the final isomeric allo-biotin.

2. The formation of the imidazolidinone ring of biotin was performed from a di(alkoxycarbonylamino)thiophane under the conditions of the partial hydrolysis of one protective group, with the exclusion of phosgene from the scheme of synthesis.

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