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Abstract

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A NEW SYNTHESIS OF 2,3,4,5-TETRADEHYDROBIOTIN

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One of the principally possible routes for the synthesis of biotin is the hydrogenation [1] of so-called aromatic biotin (2,3,4,5-tetradehydrobiotin). A number of methods are known for the synthesis of the latter (see, for example, [2]), but all of them are complicated and multistage. A comparatively simple route for the synthesis of 2,3,4,5-tetradehydronorbiotin, including the Beckmann rearrangement of the oxime of 2′,3′-thiopheno-1,2-cyclohexanone-3 (I) to lactam (II), was proposed by Nishimura et al. [3]; however, their attempt to carry out this rearrangement proved unsuccessful. Nor did they succeed in attaining the intended goal by the Schmidt reaction [3], since in this case a lactam isomeric with compound II was formed. For this reason the proposed route for the synthesis of tetradehydronorbiotin was abandoned by them.

$$\text{I} \longrightarrow \text{II} \qquad \text{III}$$

Meanwhile, lactam II and its nearest homolog III can be obtained, as we showed earlier [4], by the Beckmann rearrangement of I and, correspondingly, of the oxime of 2′,3′-thiopheno-1,2-cycloheptanone-3 with the aid of benzenesulfochloride. Having lactams II and III at our disposal, we decided to test the possibility of realizing the method proposed by the Japanese investigators for the synthesis of tetradehydronorbiotin and tetradehydrobiotin. The scheme of this method appeared to us in the following form:

$$\text{IV} \xrightarrow{\text{Br}_2} \text{V} \xrightarrow{\text{HNO}_3} \text{VI} \xrightarrow{\text{HCl}} \text{VII} \xrightarrow{\text{Sn, HCl}} [\text{VIII}] \xrightarrow{\text{COCl}_2} \text{IX}$$

$n = 3$: 2,3,4,5-tetradehydronorbiotin, $n = 4$: 2,3,4,5-tetradehydrobiotin.

The bromination of lactams IV was carried out by treating them with a solution of bromine in acetic acid. The brominated lactams V ($n = 3$ and 4) upon

were obtained in good yields. We were unable to nitrate these lactams with nitric acid in acetic acid or acetic anhydride, i.e., by a method often used in the thiophene series. However, by the action of potassium nitrate on a solution

of the brominated lactams V in concentrated sulfuric acid, it was possible to obtain the bromonitrolactams VI ($n = 3$ and 4). It should be noted, however, that lactam VI ($n = 3$), needed for the synthesis of tetradehydronorbiotin, was formed under these conditions in only a very low yield, and therefore it did not appear possible to carry the work on obtaining tetradehydronorbiotin to completion. From lactam V ($n = 4$), the corresponding bromonitrolactam VI was obtained in a yield of about 50%, which made it possible to complete the work on the synthesis of tetradehydrobiotin.

As can be seen from the scheme, the next stage on the route to tetradehydrobiotin was the saponification of lactam VI ($n = 4$) to the amino acid VII ($n = 4$). However, as a result of boiling this lactam with concentrated hydrochloric acid, a product with m.p. 213–214°, containing no bromine and, according to analysis, corresponding to hydroxy compound X, was formed (the structure of this substance was not studied by us). This result forced us to introduce an additional stage, namely debromination of bromonitrolactams VI to nitrolactams XI. The latter

$$\text{X} \xrightarrow{\text{VI}} \text{XI} \qquad \text{XII}$$

operation was accomplished by brief boiling of solutions of lactams VI ($n = 3$ and 4) in propionic acid with powdered copper, i.e., by the method proposed earlier (5), but somewhat modified by us.

By saponification of nitrolactam XI ($n = 4$), hydrochloride XII ($n = 4$) was obtained. The latter, on reduction with tin in hydrochloric acid (2), gave the dihydrochloride of diaminocarboxylic acid VIII in the form of a complex compound with stannous chloride, which, however, was not isolated in pure form. On treatment of the reduction product with phosgene, impure tetradehydrobiotin was isolated, but in a yield lower than that reported (2) for the analogous case of condensation. After purification, the product had the melting point given for 2,3,4,5-tetradehydrobiotin (2). The 2,3,4,5-tetradehydrobiotin obtained by us corresponded in its UV spectrum to the data available in the literature.

Experimental part

Lactam of γ-(5-bromo-3-aminothienyl-2)-valeric acid (V, $n = 4$). To a solution of 9.34 g of the lactam of γ-(3-aminothienyl-2)-valeric acid* (IV, $n = 4$) in 40 ml of glacial acetic acid, a solution of 8.32 g of bromine in 20 ml of acetic acid was gradually added. After standing (4 hours at 20°), the mixture was poured into 300 ml of water. The precipitate was filtered off, washed with water, and dried. Yield of crude product 13.3 g (99%), m.p. 188–190° (with decomposition). This product was dissolved in 50 ml of boiling acetic acid, the solution was treated with charcoal, and water was added to the boiling filtrate until crystallization began. The precipitated solid was filtered off, washed with water, and dried. Yield 11.4 g (85%), m.p. 205–206° (with decomposition).

Found, %:	C 41.91; 41.84; H 3.94; 3.86
$C_9H_{10}BrNOS$. Calculated, %:	C 41.55; H 3.87

* For the preparation of this lactam, see (4).

Lactam of γ-(5-bromo-3-aminothienyl-2)-butyric acid (V, $n = 3$) was obtained by bromination of the lactam of γ-(3-aminothienyl-2)-butyric acid* (IV, $n = 3$) by the method described above. M.p. 183.5–185°.

C_8H_8BrNOS.

Found, %: C 38.86; 38.80; H 3.18; 3.27
Calculated, %: C 39.04; H 3.27

Lactam of δ-(5-bromo-4-nitro-3-aminothienyl-2)-valeric acid (VI, $n = 4$). To a solution of 6.95 g of the lactam of δ-(5-bromo-3-aminothienyl-2)-valeric acid in 40 ml of concentrated sulfuric acid, cooled to −5°, at a temperature from −5 to 0° there was gradually added 3.5 g of ground, dried potassium nitrate. After stirring for 20 min at 0°, the solution was poured onto 200 g of ice. The precipitate was filtered off, washed with water, with a 20% solution of sodium acetate, again with water, and then dried. Weight of the crude product 6.57 g (80%), m.p. 171–175°. After recrystallization from alcohol with charcoal treatment, 4.15 g (51%) of substance with m.p. 195–196.5° (with decomposition) was obtained.

$C_9H_9BrN_2O_3S$.

Found, %: C 35.58; 35.44; H 3.03; 2.99; N 9.25; 9.06
Calculated, %: C 35.42; H 2.97; N 9.18

Lactam of γ-(5-bromo-4-nitro-3-aminothienyl-2)-butyric acid (VI, $n = 3$) was obtained by nitration of γ-(5-bromo-3-aminothienyl-2)-butyric acid by the method described above. Yield of crude product 69%, m.p. 112–118°. After a series of recrystallizations from alcohol with a yield of less than 10%, pure bromonitrolactam was obtained, m.p. 162–164° (with decomposition).

$C_8H_7BrN_2O_3S$.

Found, %: C 33.26; 33.23; H 2.43; 2.39
Calculated, %: C 33.00; H 2.43

Lactam of δ-(4-nitro-3-aminothienyl-2)-valeric acid (XI, $n = 4$). 2.66 g of the lactam of δ-(5-bromo-4-nitro-3-aminothienyl-2)-valeric acid with m.p. 188–190° were dissolved in 36 ml of boiling propionic acid. To the solution was added 2 g of powdered copper. After the mixture had boiled for 5 min, the precipitate was filtered off and washed with hot propionic acid. The green filtrate was evaporated to dryness in vacuo. The residue was washed with water,

dried, and dissolved in 35 ml of boiling alcohol. The hot solution was filtered through a glass filter No. 4. To the filtrate was added 70 ml of hot water. On cooling with ice, lustrous yellow plates precipitated. Yield of pure nitrolactam 1.9 g, i.e., 72%, m.p. 168–169°.

$C_9H_{10}N_2O_3S$.

Found, %: C 47.78; 48.05; H 4.49; 4.36; S 14.31; 14.30
Calculated, %: C 47.77; H 4.46; S 14.17

Lactam of γ-(4-nitro-3-aminothienyl-2)-butyric acid (XI, $n = 3$) was obtained by debromination of the lactam of γ-(5-bromo-4-nitro-3-aminothienyl-2)-butyric acid by the method described above. Yield of crude substance 90%, m.p. 158–161°. After recrystallization from dilute alcohol (with charcoal), m.p. 164.5–165.5°.

$C_8H_8N_2O_3S$.

Found, %: C 45.53; 45.46; H 3.84; 3.85; S 14.99; 15.16
Calculated, %: C 45.28; H 3.80; S 15.11

Hydrochloride of δ-(4-nitro-3-aminothienyl-2)-valeric acid (XII). 1.5 g of the lactam of δ-(4-nitro-3-aminothienyl-2)-valeric acid was added to 20 ml of hydrochloric acid. The solution was boiled for 15 min and then treated with activated charcoal. On cooling of the filtrate, pale-yellow crystals precipitated. Yield 1.46 g, i.e., 78.5%, m.p. 178–181° (with decomposition). Recrystallization from con-

* For the preparation of this lactam, see (4).

1.06 g of almost colorless crystals, m.p. 179–181° (with decomposition), was obtained from concentrated hydrochloric acid. On addition of water to this hydrochloride, a brown precipitate is formed, probably the free nitroamino acid.

Found, %: C 38.66; 38.75; H 4.57; 4.57
$C_9H_{13}ClN_2O_4S$. Calculated, %: C 38.50; H 4.67

2,3,4,5-Tetradehydrobiotin (IX, $n = 4$). 1.5 g of the lactam of δ-(4-nitro-3-aminothienyl-2)-valeric acid was boiled for 15 min with 50 ml of hydrochloric acid. The hot solution was treated with charcoal, and 3 g of tin shavings was gradually added to the warm (35–40°) filtrate. The mass was stirred until all the tin had dissolved, and was then treated with charcoal. The solution was evaporated in vacuo, and the residue was dried in vacuo over phosphorus anhydride. The yellow substance (6.6 g) was dissolved in 60 ml of water. To the solution, cooled to 5°, 40% sodium hydroxide solution was gradually added until a clear solution formed. Phosgene was passed into the latter under ice cooling until an acid reaction appeared (to Congo). A little hydrochloric acid was added to the mixture; the brown precipitate was filtered off and washed with dilute hydrochloric acid and then with water. The weight of the dry substance was

1.2 g, m.p. 218-223° (decomposition; in an apparatus heated to 200°). This substance was washed several times with hot acetone, then with ether. The weight of the dry gray-yellow product was 0.55 g (yield 34%), m.p. 233-238°, i.e., close to that reported in the literature ([2]) for unpurified tetradehydrobiotin. After a series of recrystallizations from dilute alcohol and acetic acid, a pure product was obtained, m.p. 253-255° (with decomposition), λ_{max} 2580 Å, ε 21000 (in alcohol). Lit. ([2]): m.p. 254-254.5°, λ_{max} 2600 Å.

Found, %: C 50.00; 50.05; H 4.86; 4.85; S 13.50; 13.56
$C_{10}H_{12}N_2O_3S$. Calculated, %: C 49.98; H 5.03; S 13.34

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Note: Figure translations are in progress. See original paper for figures.