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105. A Stereospecific Synthesis of Biotin from an Aromatic Precursor

Preliminary Communication

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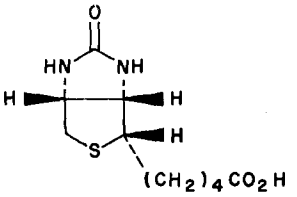
(24. II. 76)

Summary. The total synthesis of the important natural product biotin **1** from the readily available keto diester **3** is described. This approach features the stereospecific hydrogenation of the thiophene intermediate **19** as the key synthetic step.

The required differentiation of the diacid functionality of compound **7** is achieved by selective lactam formation with the terminal acid to yield the 8-membered lactam **8**. A modified *Curtius* reaction then affords the rearranged diurethane **18** through a series of acyl transfers. Finally, a novel conversion of the 3,4-diurethane moiety to the imidazolidone portion of biotin is utilized to complete the synthesis.

One of the crucial aspects in any synthesis of the growth promotant *d*-biotin (**1**) is the construction of the all *cis* configuration about the thiophane nucleus. Recently, we have disclosed a stereospecific synthesis of *d*-biotin which employs a novel oxidative rearrangement of a thiazolidine to solve this problem [1]. Although several earlier workers [2] have used catalytic hydrogenation of a dihydrothiophene in this regard, no synthetically useful approach has been reported which is based on readily available aromatic intermediates [3], presumably a result of the marked resistance



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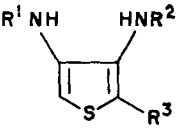

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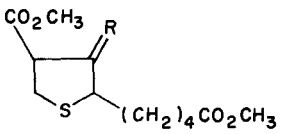
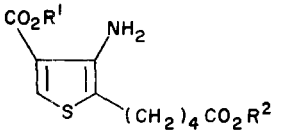
of thiophenes to reduction [4]. We now report a new synthesis of biotin which incorporates an efficient, stereospecific hydrogenation of a thiophene precursor such as **2** to the requisite tetrahydro level.

To this end, the previously described [5] keto diester **3** was quantitatively converted to its oily oxime **4**. Dissolution of **4** in HCl/ether at room temperature allowed the unsaturation concentrated in the oximino function to migrate into the thiophane ring [6]. This rearrangement afforded in 96% yield an easily separable mixture of the amino diester **5**, m.p. 51–52°, and the amino acid **6**, m.p. 131–132°, in a ratio of 6:1, respectively [7]. In practice, this mixture was hydrolysed directly to the desired amino diacid **7**, m.p. 186–187° (dec.), which was best isolated as its chlorhydrate.

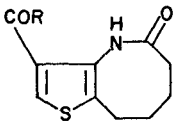


3 R = O
4 R = NOH

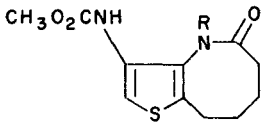


5 $R^1 = R^2 = CH_3$
6 $R^1 = CH_3$, $R^2 = H$
7 $R^1 = R^2 = H$

A smooth differentiation of the diacid functionality of **7** was achieved by heating a suspension of its hydrochloride salt in xylene under reflux (*Dean-Stark* trap). These conditions afforded the eight-membered lactam **8**, m.p. 216–217°, which crystallized upon cooling in 87% yield. Although the amino acid **6** also underwent cyclization to the ester lactam **9**, m.p. 167–168°, in 84% yield, the amino diester **5** failed to react under these conditions. The compound **9** afforded the hydrazide **10**, m.p. 191–192°, upon exposure to anhydrous hydrazine for 2 min at 25°. Diazotation yielded the expected oily acyl azide **11**, which underwent the *Curtius* rearrangement [8] by heating in methanol under reflux to produce the desired urethane **12**, m.p. 209–210°, in 95% overall yield from the ester lactam **9**.



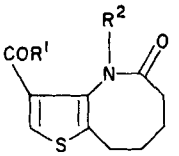
8 R = OH
9 R = OCH_3
10 R = $NHNH_2$
11 R = N_3



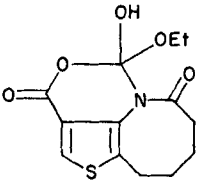
12 R = H
20 R = CO_2Et

An investigation of the modified *Curtius* reaction [9] on the acid **8** revealed a useful rearrangement which allowed reopening of the lactam and lead to the key intermediate for hydrogenation. Treatment of **8** with two equivalents of ethyl chloroformate produced initially the mixed anhydride **13** which immediately underwent acyl transfer to the C(3) nitrogen (presumably *via* the intermediate **14**) to yield the carboxy imide **15**. The second equivalent of ethyl chloroformate then reacted with **15** to furnish the imido anhydride **16**. Addition of aqueous sodium azide lead to the desired acyl azide **17**, isolated in an overall yield of 98% from the acid **8**. Heating of

17 in methanol under reflux afforded the diurethane **18**, m.p. 60–61°, as well as the urethane **12** in a ratio of 5:1, respectively. These products, which are easily separable by chromatography, arise from the two possible modes of methanolysis of the imide function of the azide **17**. This result illustrates the marked preference for ring-opening, leading to **18**, *vs.* attack at the carbethoxy group to give **12**. Since the acid **19** was actually desired, the above product mixture was carefully saponified to afford **19**, m.p. 159–160°, which was isolated by simple extraction in an overall yield of 80% based on the acyl azide **17**.



13 $R^1 = OCO_2Et$, $R^2 = H$
15 $R^1 = OH$, $R^2 = CO_2Et$
16 $R^1 = OCO_2Et$, $R^2 = CO_2Et$
17 $R^0 = N_3$, $R^2 = CO_2Et$



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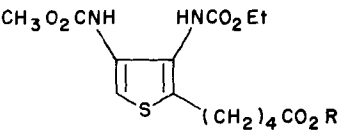
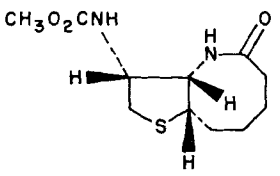


18 $R = CH_3$
19 $R = H$

A useful conversion of the by-product **12** to the desired diurethane **19** was also achieved. Treatment of the urethane **12** in neat ethyl chloroformate under reflux quantitatively acylated the C(3) nitrogen to afford the imido urethane **20**. Exposure to mild aqueous base opened the lactam and smoothly afforded the diurethane **19**.

Catalytic hydrogenation of the urethane **12** produced a low yield of the all-*cis*-tetrahydrothiophene **21**. Subsequent hydrolysis with barium hydroxide to the diamino acid **22**, followed by exposure to phosgene afforded *d,l*-biotin **26** in an overall yield of 10% based on the urethane **12**. However, when the hydrogenation (Pd/C, HOAc, 124 bars, 50°, 10 h) was carried out on the diurethane carboxylic acid **19**, an excellent yield (> 95%) of the all-*cis*-acid **23** was obtained. The degree to which this hydrogenation is substrate specific is evidenced by the fact that the ester **18** would not hydrogenate at all under identical conditions. Presumably, this reflects the greater ability of the carboxyl function to enter the coordination sphere of the palladium catalyst. Once this occurs, the closer proximity of the aromatic substract to the catalyst surface favors the subsequent reduction. Studies designed to elucidate the effects of both chain length and the nature of the terminal functional group upon



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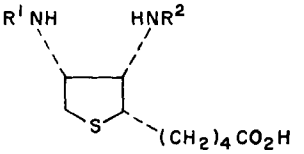
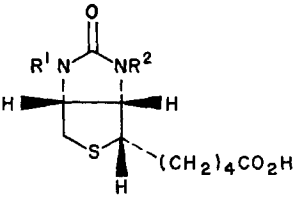


22 $R^1 = R^2 = H$
23 $R^1 = CO_2CH_3$, $R^2 = CO_2Et$
24 $R^1 = H$, $R^2 = CO_2Et$
25 $R^1 = CO_2CH_3$, $R^2 = H$



26 $R^1 = R^2 = H$
27 $R^1 = CO_2CH_3$, $R^2 = H$
28 $R^1 = H$, $R^2 = CO_2Et$

the reduction are currently in progress. Hydrolysis of the all-*cis*-acid **23** with barium hydroxide at 100° for one hour led directly to *d,l*-biotin **26** in excellent yield, obviating the need for a subsequent phosgene step. Interestingly, no previous approaches to biotin have explored the use of a 3,4-diurethane to fulfill the dual role of a protecting group for nitrogen as well as a synthon for the imidazolidone moiety. This result implicates the intermediacy of the amino urethanes **24** and **25**, or perhaps the biotin derivatives **27** and **28**. The overall yield of pure *d,l*-biotin in the main line synthesis is 37% based on the readily available keto-diester **3**.

Since the resolution of *d,l*-biotin to the naturally occurring *d*-enantiomer has been reported [10], these results constitute a total synthesis of *d*-biotin.

The authors wish to thank the staff of the *Physical Chemistry Department of Hoffmann-La Roche* for the determination of spectral and analytical data.

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