A Total Synthesis of Biotin Based on Derivatives of 2,5-Dihydrothiophene[1a]

Pat N. Confalone,* Giacomo Pizzolato, and Milan R. Uskoković

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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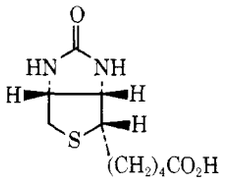
A stereospecific total synthesis of biotin (1) from the ketone **10** has been achieved. The approach features the use of stable derivatives of 2,5-dihydrothiophene (**6**), which allows functional group manipulations at C(3) and C(4) and generation of the all-cis stereochemistry of biotin. The terminal carbomethoxy group of the enamine **11** is selectively hydrolyzed, setting up a modified Curtius reaction of the key acid **16**. The reduction of the mixed diurethane **23** proceeds stereospecifically to afford the all-cis tetrahydrothiophene **24**. Finally, aqueous base simultaneously removes the piperidide protecting group and cyclizes the diurethane substituents directly to the imidazolidone moiety of biotin, which is obtained directly, uncontaminated by any stereoisomers.

A resurgence of interest in the development of new syntheses of the growth promotant *d*-biotin (1) has been sparked by recent disclosures[1b] in the areas of animal health and nutrition. Recently, we reported[2a,b] two total syntheses of this natural product originating from L(+)-cysteine and pimelic acid, respectively. The former approach featured a novel oxidative cyclization of the olefinic thiazolidine **2** to the tetrahydrothiophene **3** and proceeded stereospecifically. The



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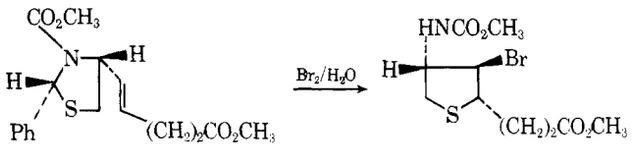

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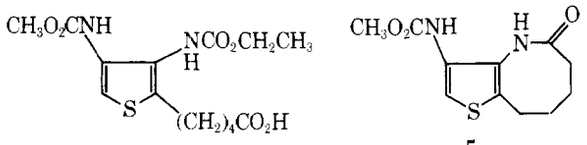
latter effort relied upon catalytic hydrogenation of thiophene substrates such as **4** and **5** in order to generate the required all-cis configuration of the three asymmetric centers of biotin.



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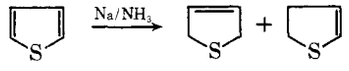
One practical difficulty of this last approach rested in the well-precedented[3] resistance of thiophenes toward reduction, a fact which necessitated the use of rather harsh conditions in this step. We speculated that a synthesis based upon derivatives of a dihydrothiophene might obviate this problem.

Birch first reported[4] the dissolving metal reduction of thiophene to 2,5-dihydrothiophene (**6**), which was isolated but tended to disproportionate, and 2,3-dihydrothiophene (**7**), which readily polymerized.



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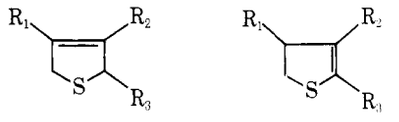
Such ominous precedent augured poorly for the stability of our potential intermediates. However, we planned to elaborate trisubstituted dihydrothiophenes such as **8** or **9**. The substituents must, of course, be capable of transformation into



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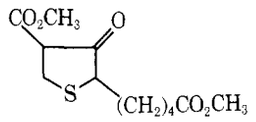
the biotin framework. The additional constraint of requiring that R_1–R_3 stabilize the intervening double bond would greatly increase our ability to carry out the necessary chemistry in this series.[5] We elected to work with derivatives of 2,5-dihydrophene (compounds related to **8**) in light of the greater stability of the parent **6**.

A simple entry into this class of compounds was achieved by the reaction of the ketone **10**[6] with ammonium formate to



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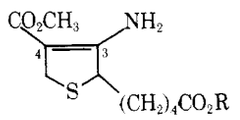
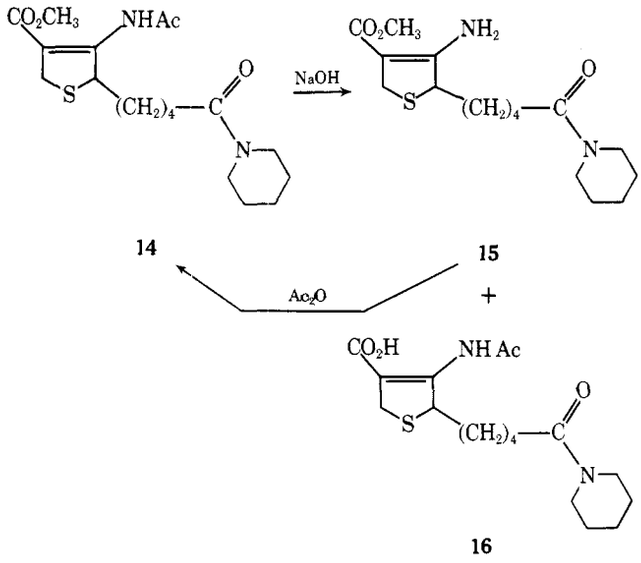


11, R = CH_3
12, R = H
13, R = CO_2Et

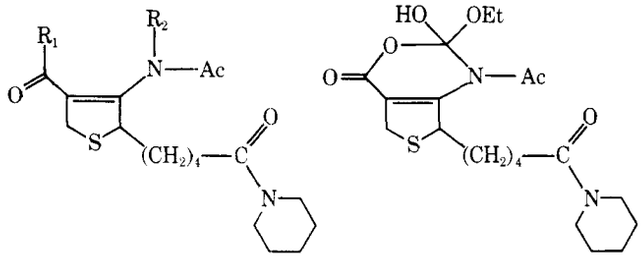
yield the enamine diester **11**. This particular substitution pattern afforded a nicely stable dihydrothiophene. Since our plans called for a Curtius reaction[7] at C(4), a differentiation of the redundant ester functionality present in the diester **11** had to be accomplished. Although hydrazine did not distinguish between these esters, methanolic potassium hydroxide selectively hydrolyzed the terminal carbomethoxy group to afford the crystalline monoacid **12**. The ester at C(4) is presumably less susceptible to hydrolysis by virtue of its stabilizing electronic interaction with the C(3) amine.

The acid group of **12** was protected as its piperidide **15** by reaction of piperidine with the corresponding mixed anhydride **13**. Acylation of the relatively unreactive amino group of **15** was carried out by acetic anhydride/perchloric acid to yield the acetamide **14** in 92% overall yield based on the ketone **10**. Hydrolysis of the acetamide **14**, which contains four reactive sites, afforded a mixture of the desired acid **16** and the amino ester **15**. These compounds were readily separated during workup by a bicarbonate extraction and the compound **15** was then recycled. In this manner, yields of the acid **16** approached 90%.

The stage was now set for the introduction of the C–N bond at C(4) via a modified Curtius reaction[8] on the acid **16**. This would afford the first dihydrothiophene in our series lacking the electronic stabilization through the C(3)–C(4) double bond that had been relied upon to this point. Treatment of the acid

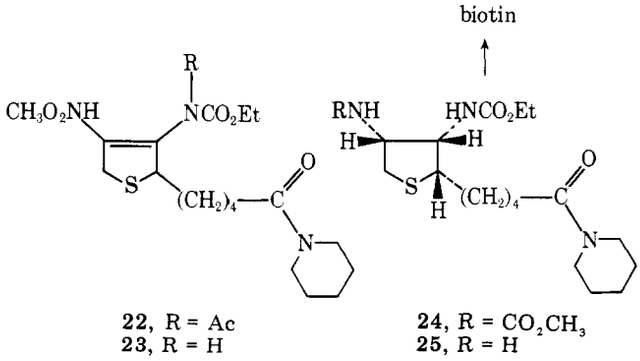


16 with 2 equiv of ethyl chloroformate yielded ultimately the imido mixed anhydride **20,** a result of the initial formation[9]



17, R_1 = OCO_2Et; R_2 = H
19, R_1 = OH; R_2 = CO_2Et
20, R_1 = OCO_2Et; R_2 = CO_2Et
21, R_1 = N_3; R_2 = CO_2Et

of the amido mixed anhydride **17,** intramolecular acyl transfer presumably via **18** to yield the imido acid **19,** and further reaction to the observed product **20.**[10] Addition of sodium azide, which readily selected the most reactive of the five carbonyl groups present in **20,** yielded the desired acyl azide **21** as a colorless oil. The acyl azide **21** underwent a smooth Curtius reaction upon heating in methanol under reflux and yielded the desired imido urethane **22,** containing the required ni-



22, R = Ac
23, R = H
24, R = CO_2CH_3
25, R = H

trogen atom attached to C(4). Mild hydrolysis of **22** with 1 N sodium hydroxide in tetrahydrofuran selectively deacetylated the compound and afforded the crystalline diurethane **23** in an overall yield of 75% from the acid **16.** The product **23** is a stable substance showing no tendency to disproportionate, which was in marked contrast to the properties of 2,5-dihydrothiophene itself.[4]

As had been hoped, catalytic hydrogenation of **23** occurred smoothly under conditions which had no effect upon similarly substituted thiophenes.[11] This reflects the absence of the resonance energy barrier to reduction characteristic of the aromatics.[12] The reduction proceeds stereospecifically, and only the desired all-cis tetrahydrothiophene **24** is produced in 91% yield. Basic hydrolysis of the product **24** led directly to *dl*-biotin (**1**) in 60% yield. Presumably, the less hindered urethane at C(4) is hydrolyzed to the corresponding amine **25,** which then cyclizes onto the C(3) urethane before the latter suffers hydrolysis.[13] This use of a C(3)–C(4) diurethane as a precursor to the imidazolidone moiety of biotin is a convenient and expeditious use of these amine protecting groups which are then partially incorporated into the target molecule.

Thus, the use of suitably chosen derivatives of 2,5-dihydrothiophene as intermediates for a stereospecific total synthesis of biotin has been demonstrated. These compounds are stable representatives of the class and allow the required manipulations to be carried out on the system before they perform the final task of generating the all-cis stereochemistry of biotin.

The resolution of *dl*-biotin to the biologically active *d* enantiomer has been accomplished in excellent yield by Harris and co-workers.[14] Therefore, this work constitutes a total synthesis of *d*-biotin itself.

Experimental Section

Melting points were determined on a Rinco Model M-50 melting point apparatus and are uncorrected. IR spectra were obtained using a Beckman IR-9 spectrophotometer. A Cary 14 recording spectrophotometer was used for UV absorption spectra. NMR spectra were determined with Varian T-60 and HA-100 spectrometers using tetramethylsilane as the internal reference. Mass spectra were recorded on a CEC 21-110B mass spectrometer at 70 eV using a direct insertion probe. Thin layer chromatography was carried out using Merck F-254 silica gel plates.

3-Amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric Acid Methyl Ester (11). A solution of 50.0 g (0.182 mol) of 4-carbomethoxy-2-[4,5-dihydrothiophen-3(2*H*)-one]valeric acid methyl ester (**10**) in 550 mL of absolute ethanol was treated with 91.6 g (1.45 mol) of ammonium formate. The reaction mixture was heated under reflux for 5.0 h, cooled, and concentrated. The residue was partitioned between methylene chloride and water. The aqueous phase was further extracted with three 50-mL portions of methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated, leaving 50 g of enamino diester **11** as a colorless oil, suitable for use in the next step: IR ($CHCl_3$) 3500, 3350 (NH_2), 1735 (ester), 1680 (Ar ester), 1620 (enamine), 1290 cm^{-1}; UV max (CH_3OH) 282 nm (ϵ 10 100); NMR ($CDCl_3$) δ 5.93 (b, 2 H, NH_2), 4.11 (b, 1 H, CH), 4.00–3.60 (m, 2 H, CH_2S), 3.69 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 2,32 (t, 2 H, CH_2), 2.0–1.3 (m, 6 H); mass spectrum *m/e* 273 (M^+), 241 (base), 210, 208, 158, 99. For analysis, a sample of **11** was chromatographed on silica, eluting with ethyl acetate/hexane (1:1).

Anal. Calcd for $C_{12}H_{19}NO_4S$ (273.35): C, 52.73; H, 7.01; N, 5.12; S, 11.73; Found: C, 52.53; H, 7.07; N, 4.81; S, 11.43.

3-Amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric Acid (12) To a solution of 27.3 g (0.1 mol) of the enamino diester **11** in 250 mL of absolute methanol was added 4.0 g (0.1 mol) of sodium hydroxide. The reaction was heated under reflux for 4.0 h, cooled, and concentrated. The residue was partitioned between methylene chloride and 10% sodium bicarbonate. The aqueous layer was further extracted with methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated to yield 6.4 g (23%) of unreacted starting material. The aqueous phase was acidified and extracted thrice with methylene chloride. These extracts were dried and evaporated to yield 18.3 g (0.071 mol, 71%) of the monoacid **12** as a tan solid. The recovered enamino diester was recycled using the above procedure to yield an additional 5.3 g of product, bringing the total yield of the monoacid **12** to 23.6 g (0.092 mol, 92%). For analysis, the product was recrystallized from ethyl acetate/petroleum ether to give white cubes: mp 102–103 °C, IR (KBr) 3425, 3300 (NH_2), 2800–2600 (OH), 1740 (ester), 1690 (acid), 1640 (enamine), 1560 cm^{-1}; UV max (CH_3OH) 283 nm (ϵ 13 300); NMR (ME_2SO) δ 11.78 (b, 1 H, acid), 7.00 (b, 2 H, NH_2), 4.01 (b, 1 H, CH), 3.56 (s, 3 H, OCH_3), 3.55 (s, 2 H, CH_2S), 2.30 (t, 2 H, CH_2), 2.0–1.2 (m, 6 H); mass spectrum *m/e* 259 (M^+), 227 (base), 158, 126.

Anal. Calcd for $C_{11}H_{17}NO_4S$ (259.32): C, 50.95; H, 6.61; N, 5.40; S,

12.36. Found: C, 50.96; H, 6.68; N, 5.31; S, 12.29.

3-Amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric Acid Piperidide (15). To a solution of 5.18 g (0.02 mol) of the monoacid **12** in 60 mL of tetrahydrofuran at 25 °C was added 2.8 mL (0.02 mol) of triethylamine, followed by 1.98 mL (0.02 mol) of ethyl chloroformate. The reaction was allowed to proceed for 1.5 h and the mixture treated dropwise at 25 °C with 2.0 mL (0.20 mol) of piperidine. After an additional 2.0 h the mixture was concentrated and taken up in 100 mL of methylene chloride. The solution was washed with 10% sodium bicarbonate and 1 N hydrochloric acid and the organic phase was dried and evaporated to afford 6.50 g of the amino ester **15** as a pale yellow oil. This product is used directly in the next step: IR ($CHCl_3$) 3500, 3350 (NH_2), 1680, 1660 (amide, vinylogous urethane), 1440, 1290 cm^{-1}; UV max (CH_3OH) 283 nm (ϵ 10 620); NMR ($CHCl_3$) δ 6.25 (b, 2 H, NH_2), 4.15 (b, 1 H, CH), 3.68 (s, 3 H, OCH_3), 3.8–3.3 (bm, 6 H), 2.3 (t, 2 H, CH_2), 2.0–1.3 (b, 12 H); mass spectrum *m/e* 326 (M^+), 295, 267, 241, 140, 127, 112, 86 (base), 84.

3-Acetamido-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric Acid Piperidide (14). To a solution of 7.4 g (0.0226 mol) of the amino ester **15** in 50 mL of acetic anhydride was added dropwise 1 mL of perchloric acid. The reaction was allowed to proceed for 1.5 h at 25 °C and the mixture concentrated in vacuo. The residue was partitioned between 10% sodium bicarbonate and methylene chloride. The aqueous phase was further extracted with three 30-mL portions of methylene chloride. The organic phases were pooled, dried over sodium sulfate, and evaporated to yield 8.2 g of the acetamide **14** as a colorless oil. Owing to its instability, the product was immediately hydrolyzed to the acid: NMR ($CDCl_3$) δ 6.80 (bs, 1 H, NH), 4.20 (m, 1 H, CH), 3.70 (s, 3 H, OCH_3), 3.8–3.1 (m, 7 H), 2.2 (t, 2 H, CH_2CO), 2.1 (s, 3 H, Ac), 1.8–1.2 (b, 12 H).

3-Acetamido-4-carboxy-2,5-dihydro-2-thiophenevaleric Acid Piperidide (16). A solution of 8.2 g (0.022 mol) of the acetamide **14** in 80 mL of methanol was treated with 40 mL of 1 N sodium hydroxide. The reaction mixture was stirred at 25 °C for 3.0 h and concentrated. The residue was partitioned between methylene chloride and water. The aqueous phase was further extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, and evaporated to yield 2.45 g (34%) of the amino ester **15** which was saved for recycling. This aqueous layer was acidified with 50 mL of 1 N hydrochloric acid and extracted with three 75-mL portions of methylene chloride. These organic extracts were pooled, dried, and evaporated to afford 4.8 g [0.0136 mol, 61% (94% corrected)] of the acid **16** as a colorless oil which was used directly in the next step: IR ($CHCl_3$) 3500 (NH), 2800–2500 (acid), 1700, 1620, 1260 cm^{-1}; UV max 268 nm (ϵ 9825); NMR ($CDCl_3$) δ 9.0 (b, 1 H, CO_2H), 5.1 (b, 1 H, NH), 4.0–3.2 (m, 7 H), 2.30 (t, 2 H, CH_2), 2.10 (s, 3 H, NAc), 1.9–1.3 (b, 12 H); mass spectrum *m/e* 354 (M^+), 336, 310 (base), 277, 140.

4-Azidocarbonyl-3-(*N*-carbethoxyacetamido)-2,5-dihydro-2-thiophenevaleric Acid Piperidide (21). A solution of 2.12 g (0.006 mol) of the acid **16** in 25 mL of acetone to which 1.3 mL of water had been added was cooled in an ice bath for 15 min and treated with 1.8 mL (0.0129 mol) of triethylamine in 25 mL of acetone. To this mixture was added dropwise 1.23 mL (0.0129 mol) of ethyl chloroformate in 2.7 mL of acetone. The reaction was allowed to proceed at 0 °C for 1 h. At this point a solution of 0.8 g (0.0063 mol) of sodium azide in 5 mL of water was added dropwise over 5 min. The mixture was stirred at 0 °C for an additional 2 h and then partitioned between ice water and methylene chloride. The aqueous phase was further extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, and evaporated to afford 2.8 g of the acyl azide **21** as a colorless oil: IR (CH_2Cl_2) 2100 (N_3), 1740 (acyl azide), 1690 (piperidide), 1680 (CO_2Et), 1620, 1200 cm^{-1}.

3-(*N*-Carbethoxyacetamido)-4-carbomethoxyamino-2,5-dihydro-2-thiophenevaleric Acid Piperidide (22). A solution of 2.8 g (0.066 mol) of the acyl azide **21** in 50 mL of methanol was slowly brought up to reflux temperature over a 15-min period. The reaction mixture was maintained at that temperature for 5.0 h, cooled, and evaporated to yield 2.33 g (0.0056 mol, 85%) of the imido urethane **22** as a colorless oil. The product can be used in the next step without further purification: IR ($CHCl_3$) 3410 (NH), 1740 (urethanes), 1710, 1690 (amides), 1620, 1500, 1260 cm^{-1}; UV max (CH_3OH) 230 (infl) (ϵ 12 040), 275 nm (sh) (ϵ 720); NMR ($CDCl_3$) δ 6.4 (b, 1 H, NH), 4.20 (q, 2 H, OCH_2), 4.10 (bs, 1 H, CH), 4.0–3.2 (m, 7 H), 3.8 (s, 3 H, OCH_3), 2.53 (s, 3 H, NAc), 2.30 (t, 2 H, CH_2), 1.8–1.3 (b, 12 H), 1.3 (t, 3 H, CH_3); mass spectrum *m/e* 455 (M^+), 423, 380, 292 (base), 276.

3-Carbethoxyamino-4-carbomethoxyamino-2,5-dihydro-2-thiophenevaleric Acid Piperidide (23). A solution of 100 mg (0.219 mol) of the imido urethane **22** in 10 mL of tetrahydrofuran was treated with 2 mL of 1 N sodium hydroxide, stirred at 25 °C for 2.0 h, and concentrated in vacuo. The residue was partitioned between water and methylene chloride. The aqueous phase was further extracted with methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated to give 80 mg (90%) of the diurethane **23** as a white solid. For analysis, the product was recrystallized from ethyl acetate to give white needles: mp 121–122 °C; IR (KBr) 3550, 3400 (NH), 1730 (urethanes), 1690 (amide), 1520, 1300, 1240 cm^{-1}; UV max (CH_3OH) 205 nm (ϵ 15 200), 232 (sh) (9700); NMR ($CDCl_3$) δ 7.35 (bd, 1 H, NH), 7.12 (bd, 1 H, NH), 4.20 (q, 2 H, OCH_2), 4.0 (b, 1 H, CH), 3.80 (s, 3 H, OCH_3), 4.0–3.2 (m, 6 H), 2.4 (t, 2 H, CH_2), 2.0–1.4 (m, 12 H), 1.3 (t, 3 H, CH_3); mass spectrum *m/e* 413 (M^+), 381, 367, 338, 324, 292 (base).

Anal. Calcd for $C_{19}H_{31}N_3O_5S$ (413.54): C, 55.19; H, 7.56; N, 10.16; S, 7.75. Found: C, 54.97; H, 7.63; N, 10.24; S, 7.95.

***all-cis*-3-Carbethoxyamino-4-carbomethoxyamino-2-tetrahydrothiophenevaleric Acid Piperidide (24).** A solution of 347 mg (0.840 mmol) of the diurethane **23** in 200 mL of acetic acid was hydrogenated at 50 °C for 10.0 h at a pressure of 1800 psi in the presence of 2.0 g of 10% Pd/C catalyst. The autoclave was cooled and vented, and the catalyst was filtered and washed with acetic acid. The filtrate was evaporated to dryness and the residue dried under high vacuum to give 320 mg (91%) of the all-cis tetrahydrothiophene **24**, which traveled as one spot in several TLC systems. The product was obtained as a colorless oil and was suitable as such for direct conversion to *dl*-biotin: IR (CH_2Cl_2) 3320 (NH), 1730 (urethanes), 1640 (amide), 1540, 1240 cm^{-1}; NMR ($CDCl_3$) δ 6.3 (b, 1 H, NH), 5.8 (b, 1 H, NH), 4.8–4.0 (bm, 5 H), 3.8 (s, 3 H, OCH_3), 3.8–3.0 (m, 6 H), 2.2 (t, 2 H, CH_2CO), 2.0–1.3 (b, 12 H), 1.2 (t, 3 H, CH_3).

***dl*-Biotin (1).** A sample of 320 mg (0.77 mmol) of the all-cis tetrahydrothiophene **24** in 5 mL of 1 N sodium hydroxide was heated under reflux for 4.0 h, cooled, and acidified to pH 1 with 1 N hydrochloric acid. Pure *dl*-biotin separated from the solution as a white solid which was collected by filtration. The yield after drying was 113 mg (60%). The product was recrystallized from water to yield an analytical sample, mp 232–233 °C, identical in all respects with an authentic sample of *dl*-biotin: IR (KBr) 3300, 3250 (NH), 2700–2500 (acid), 1705 (urea), 1690 cm^{-1} (acid); NMR (Me_2SO) δ 6.7 (bs, 1 H, NH), 6.5 (bs, 1 H, NH), 4.30 (m, 2 H, NCHCHN), 3.15 (b, 1 H, CHS), 2.75 (m, 2 H, CH_2S), 2.22 (t, 2 H, CH_2), 1.5 (bm, 6 H); mass spectrum *m/e* 244 (M^+), 184, 112, 97 (base), 85. No biotin stereoisomers were detected in this reaction.

Anal. Calcd for $C_{10}H_{16}N_2O_3S$ (244.29): C, 49.16; H, 6.60; N, 11.47; S, 13.12. Found: C, 49.12; H, 6.52; N, 11.50; S, 13.40.

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

Registry No.—**1**, 22377-59-9; **10**, 59851-05-7; **11**, 61617-88-7; **12**, 61617-89-8; **14**, 61617-90-1; **15**, 61617-91-2; **16**, 61617-92-3; **21**, 61617-93-4; **22**, 61617-94-5; **23**, 61617-95-6; **24**, 61617-96-7; ammonium formate, 540-69-2; piperidine, 110-89-4.

References and Notes

(1) (a) We wish to dedicate this paper to Professor Robert Burns Woodward on the occasion of his 60th birthday. (b) D. B. McCormick, *Nutr. Rev.*, **33**, 97 (1975); R. Blair and C. Whitehead, *Feedstuffs*, **48**, 30 (1976).
(2) (a) P. N. Confalone, G. Pizzolato, E. G. Baggiolini, E. D. Lollar, and M. R. Uskoković, *J. Am. Chem. Soc.*, **97**, 5936 (1975); (b) P. N. Confalone, G. Pizzolato, and M. R. Uskoković, *Helv. Chim. Acta*, **59**, 1005 (1976); P. N. Confalone, G. Pizzolato, and M. R. Uskoković, *J. Org. Chem.*, in press.
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(5) This concept has proven useful in numerous cases. For applications pertinent to our work see A. Grussner, J. P. Bourquin, and O. Schnider, *Helv. Chim. Acta*, **28**, 510, 517 (1945); B. R. Baker et al., *J. Org. Chem.*, **12**, 167, 186, 322 (1949); S. A. Harris et al., *J. Am. Chem. Soc.*, **66**, 1756 (1944).
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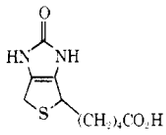
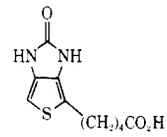
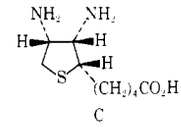
(8) A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **28**, 4131 (1972); J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).
(9) The amido mixed anhydride **17** can in fact be isolated if only 1 equiv of ethyl chloroformate is used.
(10) A similar rearrangement was observed in the aromatic series as reported in ref 2b.
(11) P. N. Confalone and J. Vasilevskis, unpublished results, 1975.
(12) A nonstereospecific chemical reduction of dehydrobiotin (A) to biotin and *epi*-biotin has recently been reported. The conditions employed have no effect on aromatic biotin (B). G. F. Field, Abstracts, 172nd National Meeting



A



B



C

of the American Chemical Society, San Francisco, Calif., Aug 29–Sept 3, 1976.

(13) Some material is completely hydrolyzed to the diamino acid (C). Treatment of the mother liquors with phosgene will convert C to biotin, thus affording an additional 10% of the final product.

(14) D. E. Wolf, R. Mozingo, S. A. Harris, R. C. Anderson, and K. Folkers, *J. Am. Chem. Soc.*, **67**, 2100 (1945).

Mesoionic Compounds. 39. Synthesis of Some Functionally Substituted Five-Membered Systems Using 1,2-Bielectrophiles as Cyclization Agents[1a]

Kevin T. Potts,* Samuel J. Chen,[1b] John Kane,[1c] and John L. Marshall[1d]

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

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α-Bromoacyl chlorides, functioning as 1,2-bielectrophiles, undergo ready reaction in the presence of Et_3N with several monoprotonic 1,3-binucleophiles to provide an especially convenient synthesis of some five-membered mesoionic ring systems containing diverse functional substituents. The *anhydro*-4-hydroxythiazolium hydroxide system results from N-monosubstituted thioamide derivatives, the *anhydro*-4-hydroxy-1,3-dithiolium hydroxide system from dithiobenzoic acids, and the *anhydro*-5-hydroxy-1,3-oxathiolium hydroxide system from thiobenzoic *S*-acids. These ring systems all undergo ready cycloaddition with dimethyl acetylenedicarboxylate to provide a convenient synthetic procedure for thiophenes containing a variety of substituents in the 2 position.

The majority of five-membered mesoionic ring systems can generally be synthesized[2] by one of five synthetic routes involving either (1) a cyclodehydration; (2) a cyclization via an intermediate isocyanate or isothiocyanate; (3) cyclizations involving nitriles; (4) interconversion of other mesoionic systems; or (5) dealkylation of suitable quaternary heterocycles. The cyclodehydrative process has been widely applied and, as would be anticipated, an extensive variety of cyclodehydration agents has been utilized. The synthesis of the appropriately substituted carboxylic acid precursor often presents difficulties, and in this report we describe a simple and effective route to several of these ring systems that not only overcomes the above disadvantages but also enables functional groups other than the usual alkyl and aryl groups to be introduced into the ring system. These syntheses are now readily accomplished by using a suitable monoprotonic 1,3-binucleophile with a 1,2-bielectrophile such as an α-haloacyl halide, and the following applications illustrate this synthetic approach.

***anhydro*-4-Hydroxythiazolium Hydroxide System.** The usual method of preparation[3a–c] of this system involves the S-alkylation of N-monosubstituted thioamides with an α-halo acid, followed by cyclodehydration of the resulting acid with Ac_2O/Et_3N. This method was often unsuccessful with thioamides containing a variety of substituents attached to the thioxo carbon atom; e.g., attempted alkylation of the thiourea **1** [R = $N(CH_3)_2$] or the dithiocarbamate **1** (R = SR) with α-bromophenylacetic acid (**2**, R^1 = Ph; X = Br; Y = OH) led to hydrolysis products, while the use of ethyl α-bromomalonate (**2**, R^1 = COOEt; X = Br; Y = OH) as an alkylating agent for thiobenzanilide was complicated by concomitant decarboxylation. However, the use of an α-bromoacyl chloride derivative **2** (R^1 = Ph, COOEt; X = Br; Y = Cl) allows the initial alkylation and subsequent ring closure to be accomplished in one step. The intermediate **3** (Y = Cl) is most likely involved, although the ketene derived from it by loss of HCl cannot be definitely excluded. The various substituted derivatives of **4** prepared by this procedure are described in Table I. In this instance the thioamide behaves as a 1,3-binucleophile, resulting in the formation of a five-membered ring on reaction with the 1,2-bielectrophile. In an earlier publication[3d] the reaction of the thioamide with a 1,3-bielectrophile, chlorocarbonylphenylketene, resulted in the ready formation of the six-membered mesoionic system, *anhydro*-6-hydroxy-4-oxo-2,3,5-trisubstituted-4*H*-1,3-thiazinium hydroxide, in excellent yields.

It is possible for four different intermediates to be involved, depending on the site of the initial condensation, but only two isomeric reaction products are possible. If reaction had occurred initially at the acid chloride function to give the intermediate **5**, then ring closure would result in formation of the isomeric *anhydro*-5-hydroxythiazolium hydroxide system **6**. The formation of **6** was excluded in two ways. The intermediate acid **3** (R = *S*-alkyl; R^1 = Ph; Y = OH) was prepared and cyclized with dicyclohexylcarbodiimide to **4** (R = *S*-alkyl;