dosage range.
(6) Piscicidal activity was assayed using a procedure similar to that described by W. A. Gersdorff, *J. Am. Chem. Soc.*, **52**, 3440 (1930). Gnidilatin, gnidilatidin, and gnidiglaucin showed toxicity at concentrations of 50 μg/l.
(7) S. M. Kupchan, J. G. Sweeny, R. L. Baxter, T. Murae, V. A. Zimmerly, and B. R. Sickles, *J. Am. Chem. Soc.*, **97**, 672 (1975).
(8) K. Sakata, K. Kawazu, and T. Mitsui, *Agric. Biol. Chem.*, **35**, 2113 (1971).
(9) A similar proposal has been advanced for the role of the long aliphatic chain in the piscicidal activity of huratoxin; cf. ref 8.

Synthesis of α-Dehydrobiotin[1]

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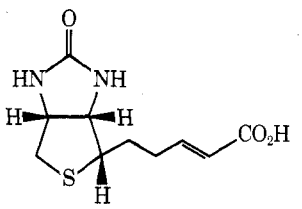
α-Dehydrobiotin has been synthesized from the bicyclic sulfonium salt **7**. The five-carbon acid side chain was elaborated by cleavage of the sulfonium ring with acetate ion, hydrolysis to a hydroxypropyl side chain, oxidation to a propionaldehyde side chain, and coupling with triethyl phosphonoacetate. A new reagent, orthophosphoric acid, was used to effect debenzylation of the urea moiety.

α-Dehydrobiotin (**1**) is an extremely effective antagonist of biotin that has been isolated from a natural source as a



1

consequence of its antibiotic activity against a variety of bacteria and fungi.[2] Subsequently, it was reported that α-dehydrobiotin is accompanied by two other biotin antagonists[3] and that it is a product of the catabolism of biotin.[4]

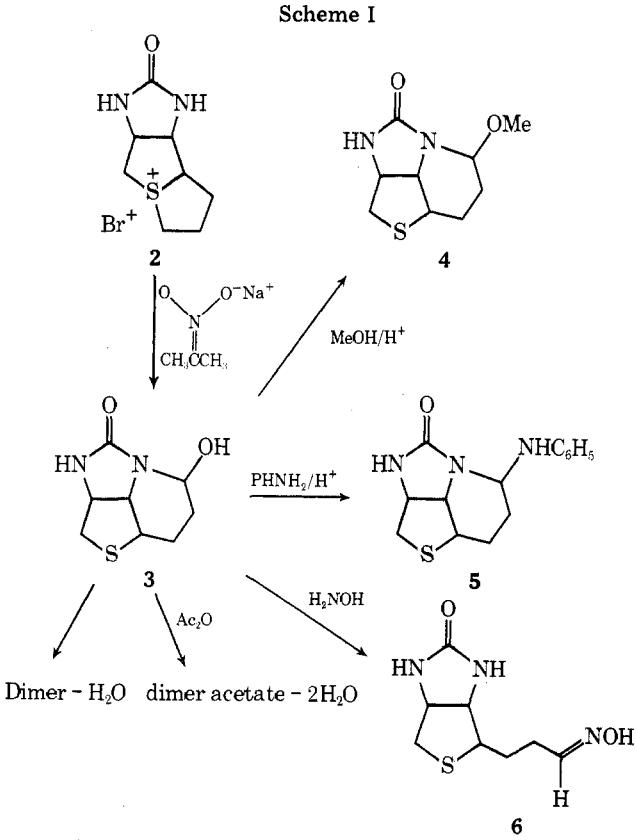
We undertook synthesis of this biologically interesting molecule since we had available experience and intermediates derivingfrom the synthesis of biotin itself.[5] The approach we followed was to divert the biotin synthesis cited above at a stage in which the difficult stereochemical problems have been solved and in which a reactive center is present where the double bond is to be formed.

Debenzylated Series. The intermediate which was expected to be the most useful in this kind of approach is the cyclic sulfonium salt **2**;[5c] however, as will be seen, an unexpected difficulty developed. The first step is oxidation of the terminal carbon atom of the latent side chain in **2** to the oxidation level of an aldehyde. Analogy from the biotin synthesis[5] suggests that sulfonium salt **2** can react as if it were a covalent bromide with the appropriate side chain. Accordingly **2c**[6] was reacted with the sodium salt of 2-nitropropane,[7] to give a compound assigned structure **3c**, a hemiacetal form of desired aldehyde. Since a priori sulfonium salt **2** has two other points where attack of the nitronate anion could have occurred, hemiacetal **3c** was submitted to x-ray crystallographic analysis for confirmation of its structure. Two stereoscopic views of the result are shown in Figure 1. Additional confirmation was obtained by reaction of **3c** with methanol or aniline under acidic conditions to give **4c** or **5c**, respectively. Reaction with hydroxylamine gave oxime **6c**, the only compound of the series with an actual rather than a latent side chain.

The next operation to be carried out is addition of the remaining two carbon atoms of the side chain. Reaction of **3c** with triethyl phosphonoacetate[8] should have been feasible, but we could obtain no product. Perhaps the hemiacetal ring is so stable that there is no appreciable concentration of the aldehyde form. Reaction of **3c** with malonic acid and piperidine gave a product whose elemental analysis and mass spectrum are consistent with a dimer of a dehydration product of **3c**. This propensity of **3c** to self-condense was also evident when treatment of **3c** with acetic anhydride gave a similar "dimer" acetate. Since these products did not appear to have any synthetic utility, their structures were not investigated further. The NMR spectrum of the "dimer" is not readily interpretable, but is clearly not consistent with any symmetrical dimer.

Racemic Series (a). These unproductive results forced a retreat to the precursor of **3**, the dibenzyl derivative **7** (X = Br). Here we chose a lengthier reaction sequence. The ring was cleaved with acetate ion to give **8a** whose basic hydrolysis gave alcohol **9a**. The next operation was to specifically oxidize the alcohol function to an aldehyde without affecting the thioether function. This was achieved with dimethyl sulfoxide/dicy-

Scheme I



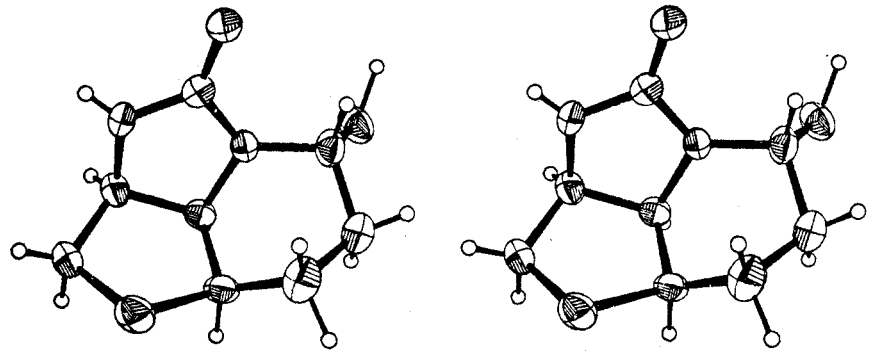
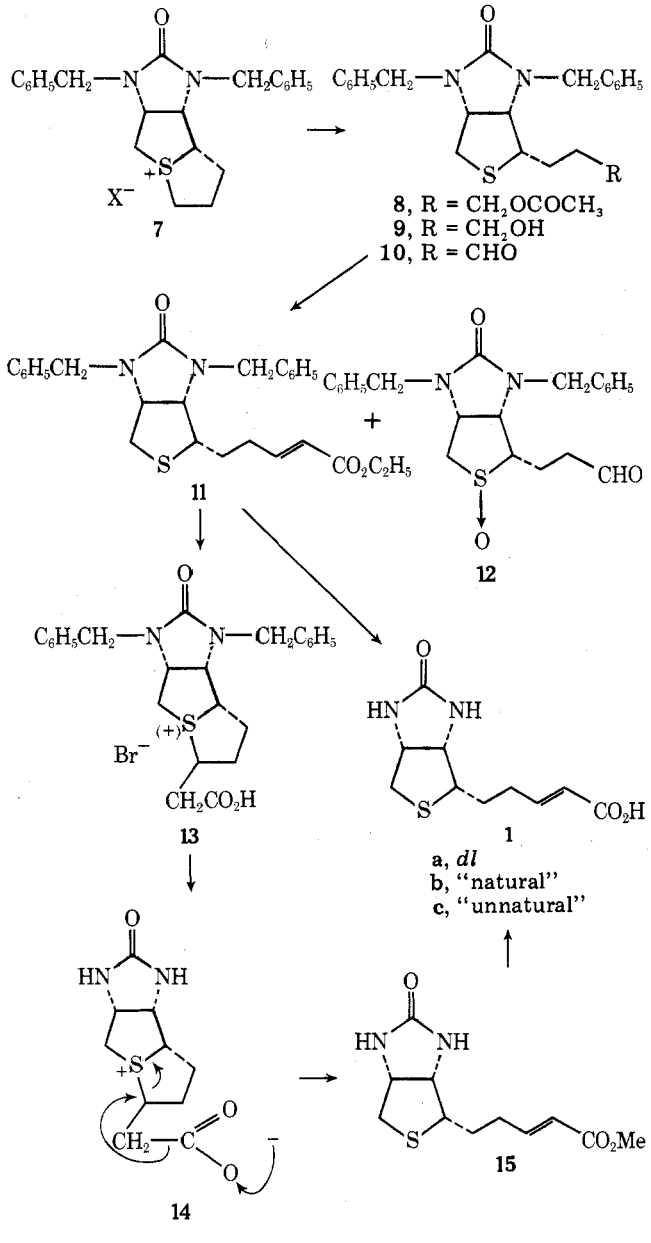


Figure 1.

clohexylcarbodiimide combination[9] in 60% yield. The two-carbon fragment was added with the sodium salt of triethyl phosphonoacetate[8] to give **11a** in 50% crude yield. There remained only removal of the benzyl protecting groups to complete the synthesis.

Two reagents for debenzylation of the cyclic urea moiety are known. Neither one proved very satisfactory owing to the reactivity of the α,β-unsaturated ester functionality. Using one, sodium in liquid ammonia,[5a] on **11a** we obtained a reaction mixture whose NMR spectrum contained peaks for the vinyl hydrogens at only about half the expected intensity. Presumably the conjugated double bond was partially reduced and consequently this method was not investigated further. Using the other, concentrated hydrobromic acid, we obtained, after brief heating, a product in 67% yield to which structure **13a** was assigned on the basis of its NMR spectrum (no vinyl protons). Prolonged heating under reflux gave a poor yield of material presumed to be the hydrobromide of the debenzylated zwitterion **14.** Since we feared a fragmentation reaction[10] as indicated by the arrows on **14,** this crude reaction product was treated directly with methanolic hydrogen chloride to esterify the carboxyl group. Treatment of this reaction mixture with sodium bicarbonate then gave a low yield of methyl ester **15** which on alkaline hydrolysis gave *dl*-α-dehydrobiotin (**1a**).

Scheme II



Optically Active Series. Synthesis of *d*-dehydrobiotin (**1b**) followed along the same lines; that is, the sulfonium salt **7b** (X = *d*-camphorsulfonate) was converted to aldehyde **10b,** the side chain was lengthened with triethyl phosphonoacetate, and then the benzyl groups were removed. However, some experimental modifications could be incorporated with profit. Since we had available large quantities of the optical antipode **7c** (X^- = *d*-camphorsulfonate) a good many model experiments were made with material derived from this substance.

Optically active aldehyde **10b** could not be obtained crystalline. On the suspicion that impurities associated with the dimethyl sulfoxide/carbodiimide method were preventing crystallization and easy purification, other methods of oxidation were examined. Both the Collins reagent[11] and pyridinium chlorochromate[12] gave **10b** in approximately 40% yield accompanied by some sulfoxide **7b.** Thus both of these methods possess a good degree of specificity for oxidation of an alcohol group in the presence of a sulfide. Even though the aldehyde still remained an oil, at least it was demonstrated that these three methods are about equivalent in this case.

The problem of removing the benzyl groups of **11b** was solved in a much more efficient manner than previously by using orthophosphoric acid containing phenol as a benzyl acceptor. The yield of **1b** from **11b** was 53% without any indication of cyclized products such as **13** and **14** which had been obtained using hydrobromic acid. A possible explanation for these differing results might be that the sulfonium salts are formed only by displacement of bromide ion from an intermediary β-bromo acid derived by addition of hydrogen bromide to the double bond.

It does not appear that orthophsphoric acid has been recognized previously as a useful reagent for removing benzyl groups. However, polyphosphoric acid has been used for the removal of α-methylbenzyl groups from amides.[13] Here it was

ineffective. Thus the use of orthophosphoric acid allowed completion of a short synthesis of the antibiotic *d*-α-dehydrobiotin (1) from the sulfonium salt **7b** with all steps going in reasonable yield.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Elemental analyses were conducted under the supervision of Dr. F. Scheidl of our microanalytical laboratory.

3-Hydroxy-1,2,3,6,6aα,7,8aα,8bα-octahydro-5*H*-pyrido[1,-2,3-*cd*]thieno[3,4-*d*]imidazol-5-one (3). A mixture of 18 ml of 2-nitropropane and 65 ml of 3 N sodium hydroxide was heated on the steam bath until the pH was about 7–8. Then 13.2 g of **2c** was added and the mixture was heated under reflux for 3.5 h. It was then cooled in an ice bath and the solid collected to give 7.7 g (75%) of product, mp 184–185 °C dec. Recrystallization from water gave colorless bars, 50% recovery: mp 168–178 °C dec; NMR (Me_2SO) δ 6.65 (s, 1, NH), 5.52 (d, 1, J = 4 Hz, OH), and 5.20 ppm (m, 1, NCHO); ir (KBr) 1590 and 1640 cm^{-1}.

Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.97; H, 6.04; N, 13.99. Found: C, 47.63; H, 6.04; N, 14.14.

Crystallography. Crystals of **3** are monoclinic, space group $P2_1$, with a = 6.44 (1), b = 8.39 (1), c = 8.38 (1) Å, β = 103.67 (5)°, and Z = 2. The intensity data were measured on an automated diffractometer by a peak-top scan technique (narrow θ–2θ scans). Nickel-filtered Cu Kα radiation and pulse height discrimination were used. An empirical correction was applied to convert the peak top data to integrated scan data; no absorption correction was made (μ = 29.3 cm^{-1}). The crystal used for data collection was approximately 0.05 × 0.15 × 0.20 mm in size. A total of 643 independent reflections were recorded for θ <57°, of which 582 were considered observed. The structure was solved by standard Patterson and Fourier methods and was refined by full matrix least squares. The hydrogen atoms were located on a difference map calculated after anisotropic refinement of the heavier atoms. In the final cycles of refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atom parameters were refined. The final unweighted and weighted discrepancy indices are R = 0.036 and wR = 0.049 for the 582 observed reflections. There are no features greater than ±0.3 eA^{-3} on the final difference map.

3-Methoxy-1,2,3,6,6aα,7,8aα,8bα-octahydro-5*H*-pyrido[1,2,-3-*cd*]thieno[3,4-*d*]imidazol-5-one (4). A mixture of 2 g of **3**, 0.2 g of *p*-toluenesulfonic acid, and 100 ml of methanol was heated under reflux for 50 min and then cooled to room temperature. Solid sodium bicarbonate was added until the mixture was neutral. The mixture was then filtered, and the filtrate was concentrated in vacuo to dryness. The residue was crystallized from methanol to give 2.2 g of **4**, mp 155–160 °C. Recrystallization from methanol gave colorless prisms: mp 160–163 °C; ir (KBr) 1720 and 1670 cm^{-1}; NMR (Me_2SO-d_6) δ 1.4–2.4 (m, 4, $-CH_2CH_2-$), 2.63 (d, 1, J_{AB} gem = 12 Hz, CH_AH_BS), 2.94 (dd, 1, J_{AB} gem = 12 Hz, J_{BX} vic = 4 Hz, CH_AH_BS), 3.12 (s, 3, $-OCH_3$), 3.47 (m, 1, -CHS), 4.19 (m, 2, NCHCHN), 4.79 (m, 1, NCHO), 6.75 ppm (s, 1, NH).

Anal. Calcd for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.58; N, 13.07. Found: C, 50.43; H, 6.86; N, 12.83.

Preparation of 5. A mixture of 3 g of **3**, 1.5 ml of aniline, 5 ml of benzene, and a trace of *p*-toluenesulfonic acid was heated on the steam bath for 10 min. The solid was collected from the cooled mixture and washed with benzene to give 3.5 g of crude product. This was dissolved in 50 ml of methylene chloride and washed with 50 ml of saturated sodium bicarbonate solution. The methylene chloride phase was dried over sodium sulfate and evaporated in vacuo to give 3.3 g of foam which was crystallized from ethyl acetate to give 2.5 g of **5**, mp 167–170 °C. Recrystallization from ethyl acetate/ethanol gave colorless needles: mp 181–184 °C (sinter 177 °C); uv max 290 nm (ε 1800) and 243 (13 550); ir ($CHCl_3$) 3450, 3440 (NH), and 1700 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35–2.50 (m, 4, $-CH_2CH_2-$), 2.78 (m, 2, J gem = 13 Hz, CH_2S), 3.41 (m, 1, CHS), 4.14 (m, 2, NCHCHN), 5.17 (m, 1, NCHN), 5.90 (d, 1, J = 6 Hz, NHPh), 6.54 (s, 1, NHCO), and 6.40–7.2 ppm (m, 5, Ph).

Anal. Calcd for $C_{14}H_{17}N_3OS$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.08; H, 6.15; N, 15.23.

4-(3-Hydroxyiminopropyl)perhydro-2*H*-thieno[3,4-*d*]imidazol-2-one (6). A mixture of 1 g of **3**, 0.5 g of hydroxylamine hydrochloride, 0.6 g of sodium acetate, 5 ml of ethanol, and 5 ml of water was heated under reflux for 1 h. The reaction mixture was cooled and concentrated in vacuo. The residue was triturated with water and recrystallized from ethanol/hexane to give 0.5 g of **6**, mp 202–205 °C dec. Recrystallization from ethanol/hexane gave colorless prisms: mp 202–204 °C dec; NMR (Me_2SO) δ 6.65 (m, 1, $-CH{=}N$).

Anal. Calcd for $C_8H_{13}N_3O_2S$: C, 44.64; H, 6.09; N, 19.52. Found: C, 44.42; H, 6.02; N, 19.25.

Dehydration of 3. A mixture of 1 g of **3**, 1 ml of piperidine, 10 ml of methanol, 10 ml of water, and 1 g ofmalonic acid was allowed to stand at room temperature for 24 h and then warmed on the steam bath for 0.5 h. It was then concentrated in vacuo. The residue was crystallized from water to give an amorphous white solid. Recrystallization from ca. 40 ml of water gave 0.7 g. Recrystallization from methanol/ether gave white needles: mp 200–210 °C dec; MS m/e 364.

Anal. Calcd for $C_{16}H_{20}N_4O_2S_2$: C, 52.72; H, 5.53; N, 15.37. Found: C, 52.96; H, 5.41; N, 14.55.

Treatment of 3 with Acetic Anhydride. A mixture of 1 g of 3 and 10 ml of acetic anhydride was heated under reflux for 4 h. The reaction mixture was filtered to remove a small amount of white insoluble material and the filtrate was concentrated in vacuo. The residue was crystallized from ether to give 0.8 g of product, mp 220–230 °C. Recrystallization from 2-propanol gave fine white needles: mp 258–263 °C dec; MS m/e 448.

Anal. Calcd for $C_{20}H_{24}N_4O_4S_2$: C, 53.55; H, 5.40; N, 12.50. Found: C, 53.34; H, 5.59; N, 12.34.

***l*-1,3-Dibenzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-4-propanol Acetate (8b).** A solution of 47.6 g (80 mmol) of *l*-3,4-(1′,3′-dibenzyl-2′-ketoimidazolido)-1,2-trimethylenethiophanium *d*-camphorsulfonate (**7b**) and 16 g (0.2 mol) of anhydrous sodium acetate in 1 l. of ethanol was stirred and heated under reflux for 2.5 h, and then cooled and concentrated in vacuo. The residue was diluted with 1 l. of water to give 30.8 g (90%) of **8b**, mp 95–98 °C. A pure sample was obtained as colorless prisms on two recrystallizations from 2-propanol: mp 98–100 °C; ir ($CHCl_3$) 1730 and 1692 cm^{-1}; $[\alpha]^{25}D$ −50.3° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.89; H, 6.65; N, 6.60; S, 7.55. Found: C, 68.24; H, 6.51; N, 6.68; S, 7.62.

Preparation of 8a. An analogous reaction of **7a** bromide gave **8a** as colorless prisms from 2-propanol, mp 100–103 °C.

Anal. Found: C, 67.89; H, 6.56; N, 6.63.

***l*-1,3-Dibenzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-4-propanol (9b).** A solution of 25.4 g (60 mmol) of **8b** in 500 ml of ethanol and 60 ml of 1 N sodium hydroxide was heated under reflux for 3 h and allowed to stand overnight at room temperature. After the solution had been diluted with water and brine, it was extracted with methylene chloride in three portions. The residue obtained after the methylene chloride extracts had been dried over sodium sulfate and concentrated in vacuo was crystallized from methylene chloride/petroleum ether to give 18.8 g (82%) of **9b**, mp 75–77 °C. Recrystallization from methylene chloride/petroleum ether gave colorless needles: mp 85–87 °C; ir ($CHCl_3$) 3650 and 1690 cm^{-1}; $[\alpha]^{25}D$ −54° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{22}H_{26}N_2O_2S$: C, 69.09; H, 6.85. Found: C, 69.09; H, 6.89.

Preparation of 9a. This compound was obtained similarly from **8a** as colorless prisms from methylene chloride/petroleum ether, mp 105–107 °C. Anal. Found: C, 69.33; H, 6.66.

***dl*-1,3-Dibenzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-4-propionaldehyde (10a).** To 10 ml of dry dimethyl sulfoxide were added in this order 3.5 g of **9a**, 5.6 g of *N,N′*-dicyclohexylcarbodiimide, 0.7 ml of pyridine, and 0.5 ml of trifluroacetic acid. This mixture was stirred for 4 h, and excess carbodiimide was decomposed by addition of 5 g of oxalic acid in 25 ml of methanol and some ether. After having been stirred for 1 h, the mixture was filtered and the precipitate washed with ether. The filtrate was diluted with water and extracted with four portions of ether. The ethereal extracts after drying and concentrating gave 3.8 g of an oil. This oil was dissolved in benzene and adsorbed on 90 g of silica gel which was then eluted with 250 ml of benzene, 300 ml of methylene chloride, and 250 ml of methylene chloride/ethyl acetate (4:1). Crystallization of the residue left on concentrating of the last eluate from hexane gave 2.5 g (62%) of crude **10a**, mp 95–106 °C. Recrystallization from methylene chloride/hexane gave off-white prisms: mp 110–113 °C; ir ($CHCl_3$) 1720 and 1690 cm^{-1}; NMR ($CDCl_3$) 9.74 ppm (–CHO).

Anal. Calcd for $C_{22}H_{24}N_2O_2S$: C, 69.45; H, 6.36; N, 7.36; S, 8.41. Found: C, 69.39; H, 6.48; N, 7.10; S, 8.32.

Oxidation of 9b with Pyridinium Chlorochromate. A mixture of 50 g (0.13 mol) of **9b**, 298 g of pyridinium chlorochromate, and 3 l.

of methylene chloride was stirred at room temperature for 1.5 h. The methylene chloride solution was then decanted from the black tars, washed with 2 × 1 l. of 3 N hydrochloric acid, and dried over sodium sulfate. It was then filtered through 500 g of Florisil in a sintered glass funnel. The Florisil was washed with 4 l. of methylene chloride. The eluates were combined and concentrated in vacuo to give 19.9 g of crude **10b** as an oil. Next, the Florisil was eluted with 3 l. of tetrahydrofuran. The eluate was concentrated in vacuo and the residue was crystallized from ether to give 4.7 g of crude **12b**, mp 80–84 °C. Recrystallization from benzene/ether gave colorless prisms, mp 85–90 °C.

Anal. Calcd for $C_{22}H_{24}N_2O_3S$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.94; H, 6.02; N, 7.31.

Oxidation of 9c with Dipyridinechromium Oxide. To a mixture of 200 g of dipyridinechromium oxide, 5 g of phosphorus pentoxide, and 2 l. of methylene chloride was added a solution of 50 g of **4c** in 200 ml of methylene chloride with good stirring. A dark tar began to separate immediately and stirring was stopped. After 20 min the methylene chloride solution was filtered through Celite and the residual tar washed with methylene chloride. The combined methylene chloride filtrates were concentrated in vacuo to 500 ml, washed with 2 × 250 ml of N hydrochloric acid, 250 ml of water, and 250 ml of brine, and dried over sodium sulfate. This solution was filtered through 200 ml of Florisil. The Florisil was washed with methylene chloride. Concentration of the first 500 ml of eluate in vacuo left 27.2 g of brownish oil. A further 14.9 g of less pure product was obtained on concentration of the second 500 ml of eluate (TLC 1:1 ether/benzene; silica gel G plates).

***dl*-1,3-Dibenzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-4-α-penta-Δ$^{\alpha}$-enoic Acid Ethyl Ester (11a).** To a suspension of 0.25 g (50% oil dispersion, 5 mmol) of sodium hydride in 30 ml of dry tetrahydrofuran was added dropwise a solution of 1.2 g (5 mmol) of triethyl phosphonoacetate in 20 ml of dry tetrahydrofuran at 10 °C. The solution was stirred for 1 h at room temperature, and then cooled to 10 °C. A solution of 1.9 g (5 mmol) of **10a** in 25 ml of tetrahydrofuran was added dropwise at 5–8 °C. The reaction mixture was then stirred for 1 h in the ice bath, diluted with water, and extracted with three portions of ether. The residue from the dried ether extracts (sodium sulfate) was crystallized from ethyl acetate/hexane to give 1.4 g (60%) of crude **11a**, mp 79–85 °C. Recrystallization from ethyl acetate/petroleum ether and from aqueous ethanol gave colorless prisms: mp 96–100 °C; NMR ($CDCl_3$) δ 5.80 (d, 1, J = 15.5 Hz) and 6.8 ppm (m, 1, -CH=CH-).

Anal. Calcd for $C_{26}H_{30}N_2O_3S$: C, 69.30; H, 6.71; N, 6.22; S, 7.12. Found: C, 69.27; H, 6.78; N, 6.57; S, 6.97.

Preparation of 11b. Treatment of **10b** in an analogous fashion gave a 50% yield of crude **11b** from hexane/petroleum ether, mp 70–75 °C. Recrystallization from petroleum ether/hexane gave colorless plates, mp 90–92 °C. Anal. Found: C, 69.40; H, 6.90; N, 6.10; S, 7.21.

***dl*-1,3-Dibenzyl-2-oxo-6-carboxymethyldecahydroimidazo-[4,5-*c*]thieno[1,2-*a*]thiolium Bromide (13a).** A mixture of 2.2 g (5 mmol) of **11a** and 22 ml of 48% hydrobromic acid was heated under reflux for 0.5 h, cooled, washed with benzene, and concentrated in vacuo. The residue crystallized from water to give 1.7 g (67%) of **13a**, mp 203–208 °C. Recrystallization from methanol gave colorless prisms, mp 214–216 °C.

Anal. Calcd for $C_{24}H_{27}BrN_2O_3S$: C, 57.25; H, 5.41; N, 5.56; S, 6.37. Found: C, 57.39; H, 5.44; N, 5.47; S, 6.50.

Preparation of 13c. Treatment of 5 g of **11c** in a similar manner gave 2 g of **13c** from 2-propanol, mp 182–188 °C. For characterization this material was dissolved in 20 ml of warm water to give a cloudy solution which was filtered and then neutralized with solid sodium bicarbonate. The inner salt which precipitated was collected and recrystallized from chloroform to give colorless needles: mp 113–115 °C dec; ir ($CHCl_3$) 1700 and 1600 cm^{-1}.

Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.22; H,6.20; N, 6.63. Found: C, 67.90; H, 6.32; N, 6.45.

6-Carboxymethyl-2-oxodecahydroimidazo[4,5-*c*]thieno-[1,2-*a*]thiolium Inner Salt (14c). A mixture of 5 g of **11c**, 10 ml of xylene, and 100 ml of 48% hydrobromic acid was heated under reflux for 5.5 h with an apparatus such that the heavier of the two phases was returned to the flask. The reaction mixture was cooled, treated with charcoal, and concentrated in vacuo. The residue was dissolved in water, and the solution passed through a column of 125 ml of Amberlite IRA-400 ion exchange resin in the hydroxide form using water to elute. Concentration of the first 100 ml of eluate in vacuo left 1.25 g of crude **14c**, mp 140–150 °C (with foaming). Recrystallization from ethanol/water gave colorless needles: mp 217–221 °C; ir (KBr) 1680, 1650, and 1560 cm^{-1}; uv max none above 200 nm; NMR (D_2O) no band in the vinyl region.

Anal. Calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56. Found: C, 49.81; H, 5.91; N, 11.60.

***d*-α-Dehydrobiotin (1b). A. Via Hydrobromic Acid Debenzylation.** A mixture of 2 g of **11b** and 50 ml of 48% hydrobromic acid was stirred for 1 h at room temperature. During this time most of the ester dissolves. The solution was then slowly heated to reflux and slow distillation maintained for 1 h. During this time 10 ml of hydrobromic acid and 0.8 ml of immiscible material distilled out. The solution was heated under reflux without distillation for 1 h, and then the distillate was collected for 0.5 h to give a further 15 ml of hydrobromic acid and 1 ml of immiscible material. The solution was washed with benzene and concentrated in vacuo to 1 g of residue. This residue was diluted with 1 ml of 48% hydrobromic acid and 100 ml of anhydrous methanol and the solution stored at room temperature for 2 days. The solution was stirred with excess sodium bicarbonate for 5 h at 25 °C, filtered, and concentrated in vacuo. The residue was dissolved in methylene chloride. The solution was filtered, washed with saturated sodium bicarbonate, dried, and concentrated in vacuo. The residue was crystallized from acetone/ether to give 0.3 g (25%) of crude methyl ester **15b**, mp 133–140 °C. This ester was warmed on the steam bath for 5 min with 1.2 ml of 1 N sodium hydroxide; the solution was filtered and kept for 0.5 h at room temperature. The acid **1b** was precipitated by addition of 1.7 ml of 1 N hydrochloric acid to give 0.2 g, mp 235–242 °C. This material was combined with that from three similar reactions and recrystallized from water with addition of chloroform to dissolve any monobenzyl derivative which might be present. Two more recrystallizations from water with charcoal and one from methanol gave white prisms: mp 256–257.5 °C; ir (KBr) 3420, 1710, 1675 cm^{-1}; $[\alpha]^{25}D$ + 105.7° (*c* 1.2, 0.1 N NaOH) [reported[2] mp 238–240 °C; $[\alpha]^{25}D$ +92° (0.1 N NaOH)].

Anal. Calcd for $C_1H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.50. Found: C, 49.29; H, 5.62; N, 11.38.

B. Via Phosphoric Acid Debenzylation. A mixture of 12 g of **11b**, 2.8 g of phenol, and 120 g of orthophosphoric acid[14] was heated in an oil bath at 150 °C for 3 h. The reaction mixture was cooled, diluted with ice to 1 l., and extracted with 2 × 500 ml of ether. The ether was washed with 200 ml of water. The aqueous layers were combined, neutralized with solid potassium carbonate, and made strongly basic with solid sodium hydroxide. The alkaline solution was heated on a steam bath for 1 h, cooled, and extracted with 800 ml of ethyl acetate. It was then acidified with concentrated sulfuric acid. The precipitate was collected, dissolved in 1 N sodium hydroxide, and reprecipitated with sulfuric acid to give 3.4 g of α-dehydrobiotin (**1b**), mp 255–258 °C.

***dl*-α-Dehydrobiotin Methyl Ester (15a).** Treatment of **11a** according to procedure A above and treatment of the residue of the neutralized esterification solution with saturated aqueous sodium bicarbonate solution which had been adjusted to pH 8 with 3 N sodium hydroxide gave crude **15a**, mp 160–170 °C. Recrystallization from methanol/ether gave colorless plates, mp 169.5–172 °C.

Anal. Calcd for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93. Found: C, 51.84; H, 6.63; N, 11.01.

***dl*-α-Dehydrobiotin (1a).** Alkaline hydrolysis of **15a** and recrystallization from ethanol gave **1a** as colorless needles, mp 238–240 °C.

Anal. Calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56. Found: C, 49.36; H, 5.78; N, 11.38.

Registry No.—**1a**, 27368-91-8; **1b**, 10118-85-1; **2c**, 60209-09-8; **3c**, 60184-13-6; **4c**, 60184-14-7; **5c**, 60184-15-8; **6c**, 60184-16-9; **7a** (X = Br), 60209-10-1; **7b** (X = *d*-camphorsulfonate), 68-91-7; **8a**, 27368-86-1; **8b**, 27368-82-7; **9a**, 27368-87-2; **9b**, 27368-83-8; **10a**, 27512-85-2; **10b**, 29455-31-0; **11a**, 27368-88-3; **11b**, 27368-84-9; **11c**, 60209-11-2; **12b**, 60184-17-0; **13**, 27368-89-4; **14**, 60184-18-1; **15a**, 27368-90-7; **15b**, 60209-12-3; 2-nitropropane, 79-46-9; methanol, 67-56-1; aniline, 62-53-3; hydroxylamine hydrochloride, 5470-11-1.

Supplementary Material Available. Tables of positional and thermal parameters for the structure of **3** (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) A portion of this work was reported in preliminary form: *J. Am. Chem. Soc.*, **92**, 3520 (1970).
(2) L. J. Hanka, M. B. Bergy, and R. B. Kelly, *Science*, **154**, 1667 (1967).
(3) D. G. Martin, L. J. Hanka, and L. M. Reineke, *Tetrahedron Lett.*, 3791 (1971).
(4) L. J. Hanka, L. M. Reineke, and D. G. Martin, *J. Bacteriol.*, **100**, 42 (1969).
(5) M. W. Goldberg and L. H. Sternbach, U.S. Patents (a) 2 489 23; (b) 2 489 235; (c) 2 489 238 (1949). This work is outlined by L. H. Sternbach in "Comprehensive Biochemistry", Vol. 11, M. Florkin and E. H. Stotz, Ed.,

Elsevier, Amsterdam, 1963, Chapter 6.
(6) Since the absolute configuration has little effect on the chemistry, a convention will be used in which a behind the numeral refers to racemic compounds, b refers to compounds with absolute configuration of *d*-biotin, and c refers to compounds with absolute configuration opposite to that of *d*-biotin.
(7) H. B. Hass and M. L. Bender, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 932.
(8) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
(9) K. E. Pfitzner and S. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661 (1965).
(10) See C. A. Grob and P. W. Schiess, *Angew. Chem.*, **79**, 1, (1967).
(11) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968); H. H. Sisler, J. D. Buch, and O. E. Accountius, *J. Am. Chem. Soc.*, **70**, 3827 (1948); R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(12) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975). We used this reagent independently under the mistaken assumption that it was pyridine dichromate, whose use as an oxidizing agent was described by W. M. Coats and J. R. Corrigan, *Chem. Ind. (London)*, 1594 (1969). Consequently, we did not use the excellent conditions of Corey and Suggs.
(13) A. G. Mohan and R. T. Conley, *J. Org. Chem.*, **34**, 3259 (1969).
(14) We first heated **11** with polyphosphoric acid from an old bottle with a cracked cap and did obtain debenzylation. However, when a fresh bottle was used, no product was obtained. This result suggested that the material in the old bottle had become hydrated and that effective reagent had been orthophosphoric acid.

An Improved Synthesis of Octaethylporphyrin

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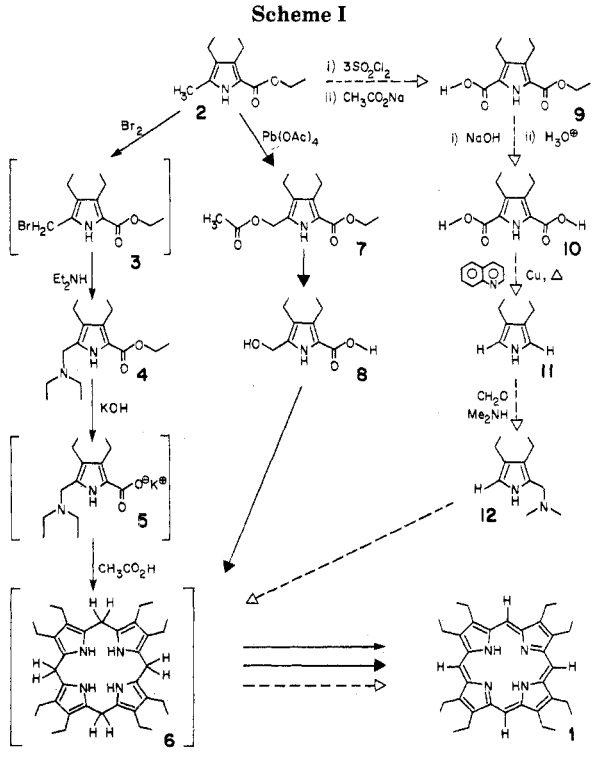
A convenient and economical synthesis of octaethylporphyrin, which proceeds via 2-*N*,*N*-diethylaminomethyl-5-ethoxycarbonyl-3,4-diethylpyrrole, is reported.

Octaethylporphyrin (OEP, **1**) is, by reason of its symmetry, high solubility, and stability, one of the more important and widely used models for the study of porphyrin chemistry. In the past, its synthesis has been tedious and erratic, particularly whenever more than a few grams were required. The usual syntheses, those of Inoffen et al.[1] and of Whitlock and Hanauer[2] (based on earlier work of Eisner, Lichtarowicz, and Linstead),[3] are summarized by Scheme I.

Scheme I



We report here an improved means of converting the common intermediate, 2-ethoxycarbonyl-3,4-diethyl-5-methylpyrrole (**2**), to OEP by procedures that are both facile and expeditious, which avoid the need to isolate overly sensitive intermediates such as **8**, **10**, **11**, or **12**, and which give improved overall yields. We also report procedures of improved convenience and reliability for the synthesis of the pyrrole **2** in especially high purity, using unpurified ethyl propionylacetate.

The Grignard synthesis of ethyl propionylacetate from ethyl cyanoacetate[4] requires a large excess of expensive ethyl iodide, some of which is wasted in formation of the cyanoacetate ester anion. The ethyl propionylacetate formed, however, is of high purity. An alternative synthesis has been devised by Kenner[5] and MacDonald:[6] Ethoxymagnesium diethyl malonate and propionyl chloride give diethyl propionylmalonate, which, after isolation in pure form by vacuum distillation, was hydrolyzed in boiling water. The hydrolysis gave ethyl propionylacetate, in moderately good yield, contaminated, however, by regenerated diethyl malonate, which was difficult to separate by distillation without an especillly efficient column. MacDonald,[6] unlike Kenner,[5] took note of this impurity and purified his ethyl propionylacetate via the bisulfite complex, not, however, without loss of yield.

We prefer to carry this impurity into the Knorr reaction with 2,4-pentanedione, and thereby maximize use of the ethyl propionylacetate. Nitrosation converts part of the diethyl malonate impurity to diethyl oximinomalonate which under the Knorr conditions with 2,4-pentanedione gives the otherwise useful 2-ethoxycarbonyl-3,5-dimethylpyrrole[7] (**22**).

Even when pure ethyl propionylacetate was used, pyrrole **22** was still generated via the Fischer–Fink[8] side reaction. As this impurity requires removal at a later stage in any case, purification of ethyl propionylacetate made from diethyl malonate was clearly superfluous for our purposes.

Although 2-ethoxycarbonyl-3,5-dimethylpyrrole (**22**) can be removed from the β-acetyl pyrrole (**21**) by several recrystallizations, considerable loss of product ensues, and so we have found it desirable to carry this impurity through the subsequent diborane reduction, which it survived intact. Treatment of the crude reduction product at reflux with ex-