Synthesis of 3′-*N*-Methylbiotin

George F. Field[1]

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

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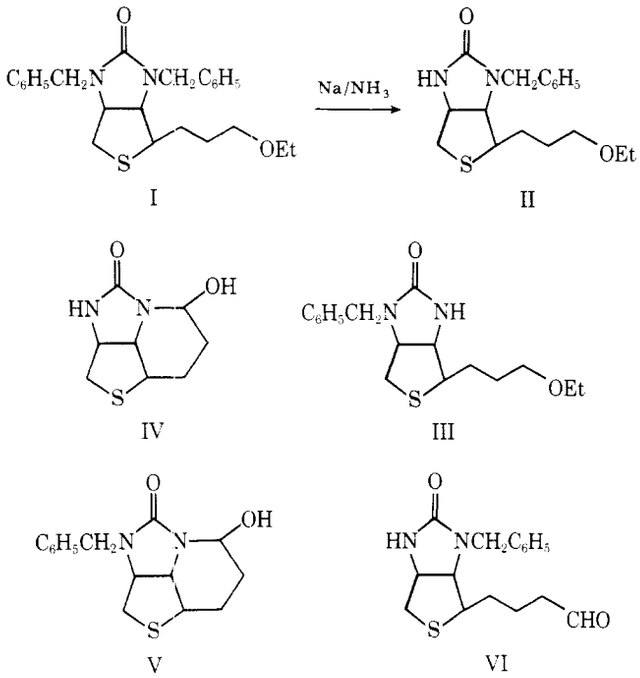
Treatment of *N,N′*-dibenzylurea VII with sodium in liquid ammonia removed the benzyl group in the sterically more crowded environment to give the monobenzyl derivative VIII. The benzyl group which was removed was defined by conversion of VIII to an aldehyde derivative IX, in which the NH group formed had interacted with an aldehyde group generated in the side chain. The monobenzyl derivative VIII methylated on nitrogen and converted to 3′-*N*-methylbiotin by reactions analogous to those used in the synthesis of biotin itself.

A singular observation made by Goldberg and Sternbach during their synthesis of biotin[2] was that treatment of the *N,N′*-dibenzylurea **I** with sodium in liquid ammonia removed only one of the benzyl groups. Furthermore, the reaction was regiospecific in that only one product was obtained. Specifically, this product might be either **II** or **III** depending on which benzyl group is more readily cleaved. Its actual structure was of no consequence to their synthesis, since another cycle of treatment with sodium in liquid ammonia and workup removed the other benzyl group and gave a fully deprotected intermediate. However, the first intermediate **II/III** would be useful for preparing biotin derivatives specifically alkylated on only one of the nitrogens. Of course, in this context, it is now essential to know which benzyl group was removed. The objective was to see if such a compound might be a biotin inhibitor which might have antibiotic activity.

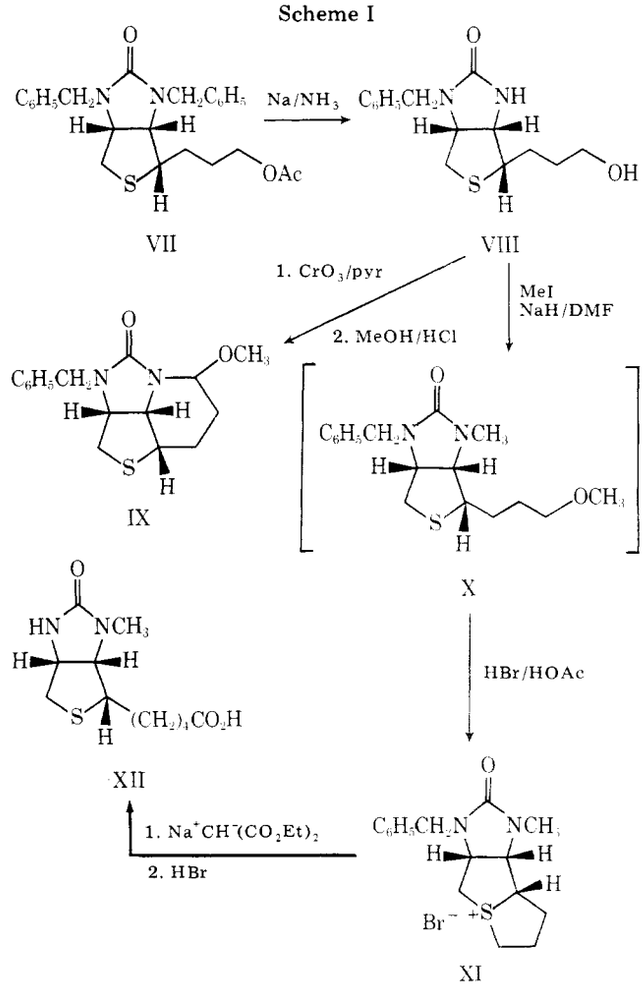


Another observation made during the synthesis of α-dehydrobiotin[3] suggested how a decision between structures **II** and **III** might be made. In that work a fully deprotected intermediate with a propionaldehyde side chain was shown to exist entirely in the hemiaminal form **IV.** By analogy, the monobenzyl aldehyde related to **III** should exist in the cyclic hemiaminal form **V;** inspection of models gave no reason to suppose that the aldehyde related to **II** would have a particularly favored hemiaminal form and therefore should exist in the open aldehyde form **VI.** Consequently, the properties of the monobenzyl aldehyde should permit a decision as to which benzyl group is removed first by sodium in liquid ammonia.

The decisive aldehyde was obtained as shown in Scheme I. We chose to debenzylate the acetate **VII**[3] rather than the ethyl ether **I,** since the acetate was available in optically active form. Treatment of the dibenzyl acetate **VII** with sodium in liquid ammonia gave a monobenzyl alcohol to which structure **VIII** was assigned based on the following evidence. Oxidation with chromium trioxide in pyridine[4] gave a noncrystalline product which when treated with methanolic hydrogen chloride gave the crystalline methyl ether **IX** clearly derived from a cyclic form of the aldehyde. Therefore, sodium in liquid ammonia first removes the benzyl group in the more congested environment in this urea derivative.

Compound **VIII** was then converted to 3′-methylbiotin. Methylation of **VIII** with sodium hydride and methyl iodide gave an oil whose NMR spectrum indicated that the alcohol group had also been etherified to give **X.** Without further characterization, **X** was converted to the thiophanium salt **XI** by treatment with hydrogen bromide in acetic acid. Treatment

Scheme I



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of XI with sodiomalonic ester and then hydrobromic acid as in the synthesis of biotin[2] gave the *N*-methylbiotin **XII**.[5]

Experimental Section[6]

3-Benzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-6-propanol (VIII). To a suspension of 10 g of **VII**[3] in 200 mL of liquid ammonia was added sodium in small pieces until the blue color persisted for 5 min. Ammonium chloride was added to decolorize the suspension, and the ammonia was allowed to evaporate. Water and hydrochloric acid were added to the residue until it was neutral. The solid was collected and recrystallized from ethanol to give 3.5 g of **VIII**, mp 142–145 °C. Further recrystallization from aqueous ethanol gave colorless plates, mp 143–145 °C.

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.62; H, 6.89; N, 9.58. Found: C, 61.43; H, 6.90; N, 9.58.

3-Benzylhexahydro-5-methoxy-1-thia-3,4a-diaza-2*H*-cyclopent[*cd*]inden-4(3*H*)-one (IX). To 1.25 L of pyridine was added 60 g of chromium trioxide with stirring during 2 h so that the temperature did not go above 30 °C. Then 29.25 g of *l*-3-benzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-6-propanol (**VIII**; unnatural antipode) was added and the mixture stirred for 1.2 h at room temperature. A solution of 100 g of sodium pyrosulfite in 500 mL of water was added dropwise over ca. 20 min so that the temperature of the reaction mixture did not rise above 30 °C. The reaction mixture was concentrated in vacuo to ca. 0.5 L and diluted with 500 mL of methylene chloride. Then 900 mL of 3 N sulfuric acid was added followed by 150 mL of concentrated hydrochloric acid until the mixture was acidic. A further 500 mL of methylene chloride was added and the organic phase separated. The aqueous phase was washed with a further 500 mL of methylene chloride. The organic phases were combined, washed with 500 mL of 2 N hydrochloride acid and then 500 mL of water, dried over sodium sulfate, and concentrated in vacuo to give 32 g of dark-green oil. This was dissolved in 70 mL of methanol with 3 drops of 3 N hydrochloric acid and allowed to stand overnight. This solution was neutralized at room temperture with sodium bicarbonate solution and diluted to 200 mL with water to precipitate 25.9 g of crude green solid. This was combined with 2.7 g from a similar experiment and dried by azeotropic distillation of benzene. A methylene chloride solution was placed on a column of 100 g of alumina. The column was eluted with methylene chloride. The first 200 mL contained 0.3 g of green material. The next 1.5 L of eluate was concentrated in vacuo. The residues were combined and dissolved in 100 mL of methanol. Water was added to the solution until cloudy to give 17 g of **IX**: mp 113–117 °C; IR ($CHCl_3$) 1700 cm^{-1}; NMR ($CDCl_3$) δ 3.33 (s, 3, $-OCH_3$) and 5.1 ppm (m, 1, CH_3OCHN).

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.22; N, 9.20. Found: C, 62.86; H, 6.59; N, 9.13.

(3a*R*,8a*S*,8b*S*)-3-Benzyldecahydro-1-methyl-2-oxoimidazo[4,5-*c*]thieno[1,2-*a*]thiolium Bromide (XI). To a stirred solution of 18 g (61.6 mmole) of *d*-**VIII** in 200 mL of tetrahydrofuran at 60 °C was added, in portions, 6 g (0.12 mol) of 50% sodium hydride in mineral oil. The reaction mixture was stirred at this temperature for 1 h and then 10 mL (0.16 mol) of methyl iodide was added dropwise so that the temperature did not go above 65 °C. The reaction mixture was then stirred at 65 °C for 2 h, cooled to room temperature, carefully diluted with 100 mL of water, and extracted with 3 × 250 mL of ether. The combined organic extracts were washed with 100 mL of water, dried over sodium sulfate, and concentrated in vacuo to leave 20 g of oil. A mixture of this oil with 200 mL of 30% hydrogen bromide in acetic acid was stirred and heated to 60 °C for 3 h, cooled to room temperature, and concentrated to dryness in vacuo. The residue was partitioned between 200 mL of water and 150 mL of benzene. The benzene phase was washed with water; the combined aqueous phases were washed with benzene and concentrated to dryness in vacuo. The residue was stirred with 100 mL of acetone and the solid was collected to give 12.5–17 g (55–77%) of **XI**: mp 230–231 °C; IR (KBr) 1680 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}BrN_2OS$: C, 52.03; H, 5.73; N, 7.58. Found: C, 51.71; H, 5.69; N, 7.41.

(3a*S*,8a*R*,8b*R*)-3-Benzyldecahydro-1-methyl-2-oxoimidazo[4,5-*c*]thieno[1,2-*a*]thiolium Bromide (XI; Unnatural). This compound was prepared in the same manner as its antipode, except that dimethyl sulfoxide was used as solvent for the methylation. An NMR spectrum of the oil before hydrogen bromide treatment showed singlets at δ 2.9 and 3.3 ppm in $CDCl_3$. This was taken to indicate that the hydroxyl group had been etherified. The final product had mp 230–231 °C.

Anal. Calcd for $C_{16}H_{21}BrN_2OS$: C, 52.03; H, 5.73; N, 7.58. Found: C, 51.62; H, 5.71; N, 7.39.

(3a*R*,4*R*,6a*S*)-(−)-Hexahydro-3-methyl-2-oxo-1*H*-thieno-[3,4-*d*]imidazole-4-valeric Acid (XII; Unnatural). To a solution of 1.38 g (60 mmol) of sodium in 300 mL of freshly distilled diethyl malonate was added 13.2 g (47.3 mmol) of **XI**. The reaction mixture was heated to 140–150 °C for 2 h, cooled, and partitioned between 250 mL of water and 250 mL of ethyl acetate. The organic phase was separated, washed with water, dried over sodium sulfate, and concentrated in vacuo (water pump) to 290 g; the excess malonic ester was distilled off at 100 °C under oil pump vacuum to leave 16.1 g of dark oil. This oil was stirred with 136 mL of 36% hydrobromic acid. The mixture was heated slowly to 90–100 °C for 0.5 h while the distillate was collected. Then the temperature was raised to 125 °C (inside temperature) for 1 h while 25–30 mL of distillate was collected. The reaction was then heated under reflux for 3 h, cooled, and concentrated in vacuo to leave 19.1 g of dark oil, which was heated under reflux with 40 mL of water for 10 min. The aqueous solution was decanted and allowed to stand in the refrigerator to give 6.6 g of crude product. Recrystallization from alcohol gave 5.2 g (43%) of **XII**: mp 211–212 °C; $[\alpha]^{25}_D$ −10.95 (*c* 2, 0.1 N NaOH); IR (KBr) 1740, 1676, and 1642 cm^{-1}; NMR (Me_2SO) δ 11.84 (m, 1, $-CO_2H$), 6.54 (s, 1, –NH), 4.28 (m, 1, CHN), 4.00 (m, 1, CHN), 3.20 (m, 1, $-CH_3$), 2.84–2.60 (m, 2, $-SCH_2$), 2.70 (s, 3, $-NCH_3$), 2.20 (t, 2, $-CH_2CO$), and 1.80–1.30 ppm (m, 6, $-(CH_2)_3-$); mass spectrum *m/e* (rel intensity) 258 (1.5, M^+), 241 (0.6), 225 (0.2), 211/212 (0.5), 199 (0.3), 193 (0.2), 184 (4), 166 (0.8), 160 (0.7), 125 (0.7), 111 (100), 99 (25), 87 (6), 85 (6), 75 (45), 45 (5), and 42 (10).

Anal. Calcd for $C_{11}H_{18}N_2O_3S$: C, 51.14; H, 7.02; N, 10.84. Found: C, 50.95; H, 7.06; N, 10.62.

(3a*S*,4*S*,6a*R*)-(+)-Hexahydro-3-methyl-2-oxo-1*H*-thieno-[3,4-*d*]imidazole-4-valeric Acid (XII; Natural). This compound was obtained in the same way as its optical antipode in 40% yield: mp 211–212 °C; $[\alpha]^{25}_D$ +12.55 (*c* 2, 0.1 N NaOH).

Anal. Calcd for $C_{11}H_{18}N_2O_3S$: C, 51.14; H, 7.02; N, 10.84. Found: C, 50.92; H, 7.11; N, 10.66.

Registry No.—VII, 27368-82-7; VIII natural, 64871-79-0; VIII unnatural, 64912-41-0; IX, 64871-80-3; XI natural, 64871-81-4; XI unnatural, 64912-42-1; XII natural, 64871-82-5; XII unnatural, 64912-43-2; diethyl malonate, 105-53-3.

References and Notes

(1) Work done at F. Hoffmann-La Roche and Co., A. G. Basel, Switzerland.
(2) M. W. Goldberg and L. H. Sternbach, U.S. Patents 2 489 232; 2 489 235, and 2 489 238, Nov. 22, 1949. This work is outlined by L. H. Sternbach, *Compr. Biochem.*, **11**, 66 (1963).
(3) G. F. Field, W. J. Zally, L. H. Sternbach, and J. Blount, *J. Org. Chem.*, **41**, 3853 (1976).
(4) G. I. Poos, G. E. Arthur, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).
(5) S. E. Polakis, R. B. Guchhait, E. E. Zwergel, M. D. Lane, and T. G. Cooper, *J. Biol. Chem.*, **249**, 6657 (1974), have described the methylation of *d*-biotin methyl ester with diazomethane, but they did not fully characterize their product.
(6) All compounds are optically active. Those designated "natural" are the antipodes shown in the formula scheme. This distinction is, of course, immaterial for synthetic purposes. Melting points are corrected. Alumina used was Woelm grade I. Elemental analyses were performed under the direction of Dr. A. Dirscherl. Spectra were determined in the Physical Chemistry Department. I thank Dr. P. Zeller for the hospitality of his laboratory and Mr. A. Senn for his skillful technical assistance.