MHz) δ 8.33 (br d, 1 H, J = 9 Hz), 8.18 (d, 1 H, J = 9 Hz), 8.05 (d, 1 H, J = 9 Hz), 7.80 (m, 2 H), 7.66 (t, 1 H, J = 8 Hz), 7.51 (t, 1 H, J = 8 Hz), 7.30 (t, 1 H, J = 8 Hz), 7.13 (d, 1 H, J = 9 Hz), 7.05 (s, 1 H), 7.03 (d, 1 H, J = 9 Hz), 6.98 (t, 1 H, J = 8 Hz), 1.92 (s, 3 H), 1.24 (s, 2 H); mass spectrum, m/e (relative intensity) 327 (M^+, 72), 312 (100), 149 (22).

Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.83. Found: C, 76.93; H, 5.20; N, 12.54.

Acknowledgment. This investigation was supported by PHS Grant No. CA-27517, awarded by the National Cancer Institute, DHHS. We are grateful to Mr. John Kozlowski for obtaining the proton spectra on the PUBMRL 470-MHz instrument, which is supported by the National Institutes of Health, Research Grant No. RR01077, from the Department of Research Resources.

Synthesis and Stereochemistry of Perhydrobenzo[*b*]thiophene Derivatives

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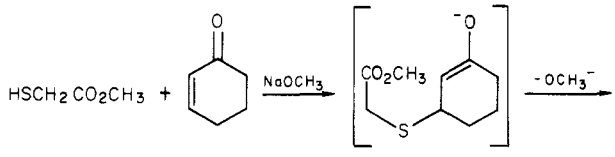
Received June 22, 1981

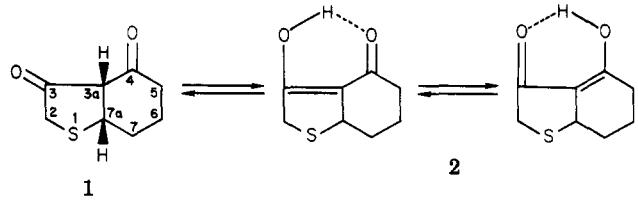
The synthesis of 2,3a,5,6,7,7a-hexahydro-3*H*,4*H*-benzothiophene-3,4-dione (1) and several of its transformation products is discussed. The stereochemistry of various intermediates containing up to four asymmetric centers is assigned on a mechanistic and spectroscopic basis and confirmed unequivocally by a full three-dimensional X-ray determination of 4α-acetamido-3aβ,4,5,6,7,7aβ-hexahydrobenzothiophen-3(2*H*)-one *anti*-oxime (**19**). The thermodynamic stability of the cis ring fusion in this bicyclic system is demonstrated by equilibration studies on the amido ketones **6** and **7**.

In connection with our program directed toward the total synthesis of the growth promotant biotin, we required the preparation of certain derivatives of perhydrobenzo[*b*]thiophene. This effort resulted in several important observations regarding the synthesis and stereochemistry of this class of compounds. We report these results which we believe to be of general interest.

Representatives of this system were found to be easily available from the crystalline diketone **1**, which is the major product of the base-catalyzed reaction between cyclohexenone and methyl mercaptoacetate. The presumed initial product of a Michael addition, the enolate anion **1a**, underwent a spontaneous cyclization with concomitant loss of methoxide to afford the observed product **1**. Spectroscopic data indicated that the diketone **1** is highly enolized and is best represented as the equilibrium mixture of ketone-enol tautomers **2**.

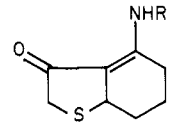


1a

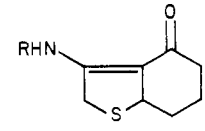


1 2

The diketone **1** reacted with nitrogenous nucleophiles such as ammonia and urethane to afford the keto-enamines **3** and **4**, respectively. Although spectroscopic data indicated that the reaction occurred regiospecifically at the cyclohexanone carbonyl, the evidence at this point did not exclude entirely the alternative structures **3a**. Catalytic hydrogenation of the keto-enamines **3** and **4** could not be cleanly effected. However, acylation of compound **3** with trifluoroacetic anhydride yielded the vinylogous imide **5**.

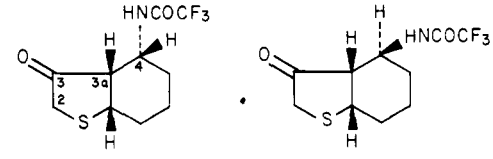


3, R = H
4, R = CO_2Et
5, R = $COCF_3$



3a, R = H, CO_2Et

The presence of the strongly electron withdrawing group on nitrogen deactivated its influence, and hydrogenation of **5** proceeded smoothly to afford the two C(4) epimeric ketones **6** and **7**. These assignments were in part based



6 **7**

upon the following NMR experiment. In CD_3ONa/CD_3OD both ketonic products exchanged exactly three protons. However, the ketones **6** and **7** were shown *not* to interconvert under these conditions. Therefore, the products are clearly epimeric at C(4) and not at the ring fusion, since a facile cis ⇌ trans equilibration would have occurred in the NMR tube if they were C(3a) epimers. The appearance of a two-proton singlet at δ 3.4 corresponding to the C(2) protons in the NMR spectra of **6** and **7** further supports the presence of the ketone at C(3). These conclusions were rigorously confirmed by an X-ray analysis on a later intermediate.

An interesting reaction of the diketone **1** and hydroxylamine was observed. The product was found to be the pseudo oxime **8**. This compound could be easily converted to either the pseudo oxime ether **9** by methanol/HCl or the pseudo oxime acetate **10** by acetic anhydride, respectively.

LAH reduction of the pseudo oxime **8** produced two crystalline amino alcohols **11** and **12** in a ratio of 6:1, respectively. These compounds were characterized as their

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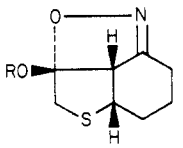
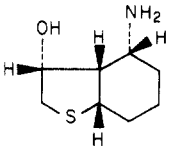


8, R = H
9, R = CH_3
10, R = Ac



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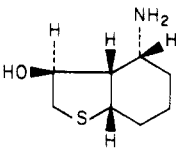

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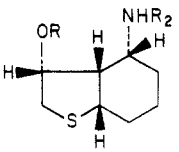
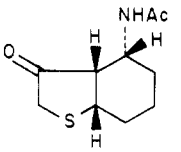
hydrochlorides. To the major product **11** was assigned the α-hydroxy orientation, since delivery of hydride from the less encumbered β side of the molecule is expected. The α configuration of the amino group at C(4) and the cis stereochemistry of the ring junction was shown by the X-ray analysis presented later. The amino alcohol **11** was smoothly converted to the crystalline diacetate **13** by acetic anhydride. Saponification selectively cleaved the *O*-acetate group to afford the crystalline alcohol **14**. Oxidation to the ketone **15** was achieved by the use of Moffatt's conditions.[2] The identical ketone **15** was also obtained by a similar sequence from the other amino alcohol **12**, thus confirming that **11** and **12** are epimeric at C(3).

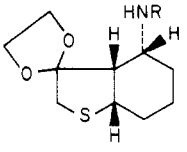


13, $R_1 = R_2$ = Ac
14, R_1 = H; R_2 = Ac

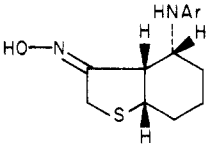


15

At this point, a correlation of the products derived from the hydrogenation of the vinylogous imide **5** with the newly obtained ketone **15** was carried out. To this end, the ketal **16** was prepared from the trifluoroacetamido ketone **6** in the usual fashion. This product was treated without isolation with methanolic potassium hydroxide at 25 °C to cleave the trifluoroamide linkage. The intermediate amino ketal **17** was acetylated to yield the acetamide **18** and deketalized to afford an acetamido ketone which was identical in all respects with the ketone **15** derived ultimately from the pseudo oxime **8**.



16 R = $COCF_3$
17, R = H
18, R = Ac



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For confirmation of the stereochemical assignments given to all these intermediates, a complete three-dimensional X-ray analysis of the highly crystalline oxime **19**, prepared from the ketone **15**, was undertaken.

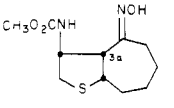
The oxime **19** was crystallized from ethyl acetate as well-formed needles. The crystals are monoclinic, space group $P2_1/a$, with unit cell dimensions a = 7.53 (1) Å, b = 15.13 (1) Å, c = 10.18 (1) Å, β = 91.74 (6)°. The intensity data were measured on a Hilger Watts diffractometer, employing Zr-filtered Mo Kα radiation. The size of the crystal was approximately 0.08 × 0.08 × 0.5 mm; the data were not corrected for absorption (μ = 2.6 cm^{-1}). The structure was solved by a multiple-solution procedure,[3] and the refinement was carried out by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.059 and R_w = 0.038 for 540 observed data. The final difference map has no peaks greater than ±0.2 A^{-3}.

As the stereodrawing indicates, the three hydrogens at C(3a), C(4), and C(7a) are all cis as predicted by our theoretical considerations. The X-ray also unequivocably confirms the location of the oxime function at C(3), also validating the earlier structural arguments regarding the regiochemistry of the adducts **3**, **4**, and **8**. Finally, the hydroxyl group was found to be oriented anti to the acetamide substituent. This is expected since there would be a high degree of steric compression in the corresponding syn isomer (the measure nitrogen–nitrogen distance is only 2.91 Å).[4]

These results prove that the cis ring fusion is thermodynamically favored in the perhydrobenzothiophene system. No trans derivatives were obtained when our cis intermediates (cf. **6**, **7**, and **15**) were subjected to equilibrating conditions. This result parallels the observations pertaining to the carbocyclic five- and six-membered ring fusions.[5] Interestingly, this preference for cis ring fusion is *not* altered by the substitution of a sulfur atom for a CH_2 in the system, in spite of the greater length of the additional two C–S bonds.

Finally, the decreased reactivity of the C(3) carbonyl group with respect to its C(4) competitor in the diketone **1** is possibly a result of the mesomeric contributor **20**, which is expected to deactivate the C(3) carbonyl. In fact, evidence of just such a transannular interaction is found in the IR spectra of the monoketones **6**, **7**, and **15**, which show the stretching vibration for the C(3) ketone at 1725 cm^{-1}, instead of the expected 1745 cm^{-1}.

In summary, we have synthesized some representatives of the perhydrobenzo[*b*]thiophene system and determined the stereochemical consequences of a number of reactions carried out on the key substrate diketone **1** and several of its derivatives. An important result of this study is the



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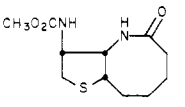

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See P. N. Confalone, G. Pizzolato, D. L. Confalone, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **102**, 1954–60 (1980).

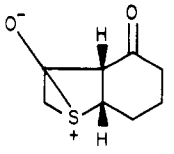
(1) Present address: E. I. du Pont de Nemours Inc., Central Research and Development Department, Experimental Station, Wilmington, DE 19898.

(2) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661 (1965).

(3) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr. Sect. B*, **26**, 274 (1970).

(4) It was precisely this observation that led to a successful synthesis of biotin from cycloheptene by targeting the oxime **20** for synthesis. In this compound, the now-expected anti orientation of the oximino-OH with respect to the urethane substituent should and does direct migration of the required C(3a) carbon in a Beckmann rearrangement to yield the biotin precursor **21**.

(5) P. W. Concannon and J. Ciabattoni, *J. Am. Chem. Soc.*, **95**, 3285 (1973).



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rigorous demonstration of the thermodynamic stability of the cis ring fusion in this system, a result not entirely predictable.

Experimental Section

Melting points were determined on a Rinco Model M-50 melting point apparatus and are uncorrected. IR spectra were obtained with a Beckmann 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 with Merck F-254 silica gel plates.

2,3a,5,6,7,7a-Hexahydro-3*H*,4*H*-benzothiophene-3,4-dione (1). To 100 mL of methanol was added 2.50 g (109 mmol) of sodium at room temperature. The methanolate solution was then cooled to 0 °C and treated dropwise with 11.05 g (104 mmol) of methyl thioglycolate dissolved in 20 mL of methanol. Next, a solution of 10.00 g (104 mmol) of cyclohexenone in 20 mL of methanol was added dropwise at 0 °C to the reaction mixture. The reaction mixture was then allowed to warm up at room temperature and was refluxed overnight. After removal of the solvent, the brown residue was dissolved in ether and extracted with 2 N sodium hydroxide. Acidification of the alkaline extracts, extraction with ether, and evaporation of the solvent gave 11.30 g of crude diketone (64% yield). Two crystallizations from cold pentane gave 4.35 g of white, waxy crystals, mp 27–28 °C (yield 24.6%). Spectra indicate the product exists as its enol tautomer **2**: IR ($CHCl_3$) 1660 (HC=O), 1600 cm^{-1} (C=C); NMR ($CDCl_3$) δ 11.20 (br s, 1, 3-OH), 4.07 (br s, 1H, 7a-CH), 3.74 and 3.27 (AB q, 2 H, J_{AB} = 17.0 Hz, 2-CH_2); mass spectrum, *m/e* 170 (M^+), 155, 143; UV (EtOH) λ_{max} 282 nm (ϵ 6810).

Anal. Calcd for $C_8H_{10}O_2S$ (170.23): C, 56.44; H, 5.69; S, 18.93. Found: C, 56.65; H, 5.82; S, 18.87.

4-Amino-5,6,7,7a-tetrahydrobenzo[*b*]thiophen-3(2*H*)-one (3). A mixture of 5.00 g (29.3 mmol) of **2** and 10.0 g (158.5 mmol) of ammonium formate was heated at 80 °C for 2 h in 80 mL of ethanol. Workup gave 6.25 g of yellow semisolid liquid. Two crystallizations from a benzene–hexane mixture afforded 3.80 g of **3** (76%): yellow crystals, mp 131–132 °C; IR (KBr) 3400, 3330, 3290, 3200 (NH_2), 1620 (C=O), 1500 cm^{-1} (C=C); NMR ($CDCl_3$) δ 9.00–5.00 (very br s, 2 H, 4-NH_2), 4.06 (d, d, 1 H, J = 11.5 and 3.5 Hz, 7a-CH), 3.57 and 3.17 (AB q, 2 H, J_{AB} = 16.0 Hz, 2-CH_2); mass spectrum, *m/e* 169 (M^+), 141 (M^+ – CO); UV (EtOH) λ_{max} 323 nm (ϵ 11 500).

Anal. Calcd for $C_8H_{11}NOS$ (169.25): C, 56.78; H, 6.55; N, 8.28; S, 18.95. Found: C, 56.67; H, 6.70; N, 8.32; S, 18.88.

4-(Carbethoxyamino)-5,6,7,7a-tetrahydrobenzo[*b*]thiophen-3(2*H*)-one (4). A mixture of 10.20 g (60 mmol) of **2**, 5.35 g (60 mmol) of ethyl urethane, and 200 mg of *p*-toluenesulfonic acid in 200 mL of benzene was refluxed for 64 h with a Dean–Stark moisture receiver. Workup gave 9.50 g (66%) of a yellow, solid material. Recrystallization from a ether–hexane mixture gave 4.75 g (33%) of **4** as pale yellow crystals: mp 75–76 °C; IR ($CHCl_3$) 3550, 3425 (NH), 1740 (C=O of carbethoxy), 1660 (C=O of ketone), 1600 (C=C), 1490 cm^{-1} (amide II band); NMR ($CDCl_3$) δ 11.05 (br s, 1 H, N-H), 4.16 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 3.57 and 3.18 (AB q, 2 H, J_{AB} = 16.0 Hz, 2-CH_2), 1.30 (t, 3 H, J = 7.0 Hz, OCH_2CH_3); mass spectrum, *m/e* 240 (M^+), 213 (M^+ – CO), 184 (M^+ – C_3H_5O), 195 (M^+ – C_2H_6O); UV (EtOH) λ_{max} 304 nm (ϵ 10 700).

Anal. Calcd for $C_{11}H_{15}NO_3S$ (241.31): C, 54.75; H, 6.27; N, 5.80; S, 13.29. Found: C, 54.74; H, 6.42; N, 6.01; S, 13.24.

4-(Trifluoroacetamido)-5,6,7,7a-tetrahydrobenzo[*b*]thiophen-3(2*H*)-one (5). 4-Amino-5,6,7,7a-tetrahydrobenzo[*b*]-thiophen-3(2*H*)-one (**3**; 4.34 g, 25.6 mmol) was stirred 5 min at room temperature with 20 mL of trifluoroacetic anhydride. The excess trifluoro anhydride was then removed in vacuum and the product was purified by chromatography on silica gel with benzene as eluant. Six grams of a brown waxy product was obtained (88%). Due to the instability of the product, it was used without further purification: IR ($CHCl_3$) 3180 (NH), 1750 (C=O of trifluoroacetyl), 1670 (C=O of ketone), 1630 (C=C), 1520 cm^{-1} (amide II band); NMR ($CDCl_3$) δ 12.35 (br s, 1 H, NH), 4.02 (m, 2 H, 7a-CH), 3.09 and 2.80 ppm (AB q, 2 H, J_{AB} = 16.0 Hz, 2-CH_2); mass spectrum, *m/e* 265 (M^+), 237 (M^+ – CO), 219 (M^+ – CH_2S); UV (EtOH) λ_{max} 302 nm (ϵ 12 830).

Hydrogenation of the Vinylogous Imide 5. 4-(Trifluoroacetamido)-5,6,7,7a-tetrahydrobenzo[*b*]thiophen-3(2*H*)-one (**5**; 1.93 g, 7.27 mmol) in 200 mL of acetic acid was hydrogenated at 1800-psi pressure and 50 °C, using 5 g of 10% palladium on carbon as catalyst. The hydrogen uptake ceased after 6 h. The catalyst was filtered and the resulting solution was evaporated in vacuo to give 1.7 g of a dark brown solid. Chromatography on silica gel, using a benzene–ethyl acetate 5:1 mixture as eluant, gave two main hydrogenation products **6** and **7**, which were recrystallized from methylene chloride–hexane mixtures to give 185 mg (10%) of **6**, mp 140–141 °C and 110 mg (6%) of **7**, mp 111–112 °C. The spectral and analytical data showed them to be the indicated isomers of 4-(trifluoroacetamido)hexahydrobenzo[*b*]thiophen-3-(2H)-one.

4α-(Trifluoroacetamido)-3aβ,4,5,6,7,7aβ-hexahydrobenzothiophen-3(2*H*)-one (6): IR ($CHCl_3$) 3400 (NH), 1730 (C=O of trifluoroacetyl and ketone), 1540 (amide II band); NMR ($CDCl_3$) δ 8.18 (br s, 1 H, NH), 4.26 (br s, 1 H, 4-CH), 3.39 (s, 2 H, 2-CH_2), 2.75 (m, 1 H, 7a-CH), 2.57 (t, 1 H, J = 6 Hz, 3a-CH); mass spectrum, *m/e* 267 (M^+), 154 (bp, M^+ – $C_2H_2F_3NO$).

Anal. Calcd for $C_{10}H_{12}F_3NO_2S$ (267.27): C, 44.94; H, 4.53; N, 5.24; S, 12.00. Found: C, 44.73; H, 4.74; N, 5.15; S, 12.27.

4β-(Trifluoroacetamido)-3aβ,4,5,6,7,7aβ-Hexahydrobenzothiophen-3(2*H*)-one (7): IR ($CHCl_3$) 3440 (NH), 1725 (C=O of trifluoroacetyl and of ketone), 1540 (amide II band); NMR ($CDCl_3$) δ 6.52 (br s, 1 H, NH), 4.53 (br s, 1 H, 4-CH), 3.60 (br s, 1 H, 7a-CH), 3.40 (s, 2 H, 2-CH_2), 2.69 (t, 1 H, J = 6 Hz, 3a-CH); mass spectrum, *m/e* 267 (M^+), 154 (bp, M^+ – $C_2H_2F_3NO$).

Anal. Calcd for $C_{10}H_{12}F_3NO_2S$ (265.27): C, 44.94; H, 4.53; N, 5.24; S, 12.00. Found: C, 44.74; H, 4.74; N, 5.16; S, 12.21.

Exchange Experiments with $^-$OD. To the hydrogenation products **6** and **7** separately dissolved in tetradeuteriomethanol was added a drop of a 1 N solution of sodium trideuteriomethanolate in tetradeuteriomethanol. After the solution was shaken for a few seconds, the NMR spectrum was taken. In both cases, complete disappearance of the signals for the 2-CH_2 and 3a-CH protons was observed.

3,4aβ,5,6,7,7bβ-Hexahydro-2a*H*-benzo[*l*]thieno[4,3-*cd*]-isoxazol-2aβ-ol (8). To a solution of 12.31 g (0.0724 mol) of the enol ketone **2** in 150 mL of 95% ethanol were added 5.90 g (0.085 mmol) of hydroxylamine hydrochloride and 9.30 mL of pyridine. The reaction was refluxed for 1 h, the mixture was cooled, and the product was collected by filtration, washed with cold ethanol, and dried to afford 9.30 g of pseudo oxime. An additional 1.02 g of product could be obtained by concentrating the filtrate and partitioning the residue between methylene chloride–1 N HCl. The organic phases from three extractions were dried over sodium sulfate, combined, and evaporated. Total yield is 10.32 g (76%). The analytical sample was prepared by recrystallization from methanol as colorless needles: mp 215–217 °C; IR (KBr) 3250 (OH), 2900 (CH), 1635 (C=N), 1300 cm^{-1}; NMR (Me_2SO) δ 7.6 (1 H, s, OH), 4.0 (1 H, ddd, SCH), 3.4 (1 H, d, J = 8 Hz, CH), 3.0 (2 H, s, CH_2S), 2.6–1.6 (6 H, m); mass spectrum, *m/e* 185 (M^+), 169 (M^+ – O), 138 (M^+ – CH_3S), 122 (base).

Anal. Calcd for $C_8H_{11}NO_2S$ (185.23): C, 51.87; H, 5.99; N, 7.56; S, 17.31. Found: C, 51.98; H, 6.15; N, 7.68; S, 17.14.

3,4aβ,5,6,7,7bβ-Hexahydro-2aβ-methoxy-2a*H*-benzo[*l*]-thieno[4,3-*cd*]isoxazole (9). Gaseous hydrogen chloride was bubbled into a solution of 185 mg (1 mmol) pseudo oxime **8** in 30 mL of ether/methanol (1:1) for 15 min at 0 °C. After the solution was stirred for 4.0 h at room temperature, the solvents were evaporated to afford 195 mg (98%) of the pseudo oxime ether **9** as a white solid: mp 97–98 °C; IR (CH_2Cl_2) 2850 (CH), 1630 (C=N), 1440, 1290, 1110 cm^{-1}; NMR (Me_2SO) δ 4.0 (m, 1 H, SCH), 3.8 (d, 1 H, CH), 3.2 (s, 3 H, OCH_3), 3.1 (s, 2 H, SCH), 2.4–1.6 (m, 6 H); mass spectrum, *m/e* 199 (M^+), 154, 122 (base).

3,4aβ,5,6,7,7bβ-Hexahydro-2aβ-acetoxy-2a*H*-benzo[*l*]thieno[4,3-*cd*]isoxazol-2aβ-ol (10). The solution of 200 mg (1.08 mmol) of 3,4aβ,5,6,7,7bβ-hexahydro-2a*H*-benzo[*l*]thieno[4,3-*cd*]isoxazol-2aβ-ol (8) in a mixture of 1 mL of dry pyridine and 1 mL of acetic anhydride was kept under argon overnight. The solvents were removed in vacuo, and the residue was dissolved in ethyl acetate and washed with 1 N hydrochloric acid and then with 2 N bicarbonate. Evaporation of the solvent after drying with magnesium sulfate gave 235 mg of a yellow oil (96%): IR ($CHCl_3$) 1740 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.15 (s, 3 H, CH_3CO), 3.40 (s, 2 H, 2-CH_2).

4α-Amino-3α-hydroxy-2,3,3aβ,4,5,6,7,7aβ-octahydrobenzothiophene Hydrochloride (11). To a suspension of 5.32 g (0.14 mol) of lithium aluminum hydride in 400 mL of dry THF under argon was added 12.65 g (0.068 mol) of pseudo oxime 8, in small portions. The reaction was allowed to reflux for 20 h, and the mixture was cooled and quenched by the dropwise addition of a saturated aqueous solution of sodium sulfate. The solid which separated was filtered and washed with THF. The filtrate was concentrated and acidified with 1 N HCl. The reaction mixture was extracted with methylene chloride, and the organic phase was discarded. The aqueous phase was made basic by the addition of 2 N sodium hydroxide and extracted 5 times with 100-mL portions of methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated to afford 9.0 g (77%) of amino alcohols 11 and 12, obtained in a ratio of 6:1, respectively. The mixture was generally used as such for the next step. The major isomer 11 was best isolated by dissolving the mixture in ether and introducing gaseous HCl. The highly crystalline hydrochloride salt of 11 was then easily separable by recrystallization from methanol ether to afford colorless needles: mp 217–218 °C; IR (KBr) 3300 (OH), 3060 ($^+NH_3$), 2950 (CH), 2600 cm^{-1}; NMR (D_2O) δ 4.3 (1 H, m, CHOH), 4.0 (1 H, dd, J = 12.8 Hz), 3.9 (1 H, m, $CHNH_2$), 3.4 (1 H, dd, J = 12.7 Hz), 3.3 (1 H, m, CHS), 2.5 (5 H, m), 2.1 (2 H, m); mass spectrum, m/e 173 (M^+), 155 ($M^+ - H_2O$), 139 ($M^+ - H_2S$), 138 ($M^+ - H_2O - NH_3$), 56 (base).

Anal. Calcd for $C_8H_{15}NOS$·HCl (209.74): C, 45.82; H, 7.69; N, 6.68; S, 15.29; Cl, 16.90. Found: C, 45.85; H, 7.76; N, 6.70; S, 15.26; Cl, 16.83.

4α-Amino-3β-hydroxy-2,3,3aβ,4,5,6,7,7aβ-octahydrobenzothiophene Hydrochloride (12). The minor isomer 12 was best obtained by chromatography of the amino alcohol mixture on thick-layer silica plates, using the system of $CHCl_3/CH_3OH/NH_4OH$ (89:10:1). The slower moving amine was collected and converted to its hydrochloride as carried out for the major isomer. The same was easily recrystallized from methanol/ether to yield colorless needles, mp 185–187 °C.

Anal. Calcd for $C_8H_{15}NOS$·HCl (209.74): C, 45.82; H, 7.69; N, 6.68; S, 15.29; Cl, 16.90. Found: C, 45.75; H, 7.60; N, 6.42; S, 15.29; Cl, 16.86.

4α-Acetamido-3α-acetoxy-2,3,3aβ,4,5,6,7,7aβ-octahydrobenzothiophene (13). To a solution of 10.0 g (0.0578 mol) of amino alcohol 11 in 160 mL of pyridine was added 30 mL of acetic anhydride. The reaction was stored at 25 °C for 20 h and the mixture was evaporated to dryness on the rotary evaporator, employing a vacuum pump. After extended drying, the residue consisted of 14.85 g (100%) of essentially pure diacetate 13. An analytical sample was prepared by recrystallization from ethyl acetate to yield colorless needles: mp 194–195 °C; IR (KBr) 3270 (free NH), 3100 (bonded NH), 2950, 2870 (CH), 1740 (ester CO), 1650 (amide CO), 1560 (amide II), 1380, 1245, 1020 cm^{-1}; NMR ($CDCl_3$) δ 6.3 (1 H, br d, N-H), 5.4 (1 H, m, CHOAc), 4.2 (1 H, b, CHNHAc), 3.4 (2 H, m), 2.8 (2 H, m), 2.1 (3 H, s, acetate), 1.9 (3 H, s, acetamide), 1.7 (6 H, m); mass spectrum, m/e 214 ($M^+ - CH_3CO$), 197 (M^+ – HOAc), 138 (base, M^+ – HOAc – acetamide).

Anal. Calcd for $C_{12}H_{19}NO_3S$ (257.35): C, 56.01; H, 7.44; N, 5.44; S, 12.46. Found: C, 56.17; H, 7.74; N, 5.47; S, 12.54.

4α-Acetamido-3α-hydroxy-2,3,3aβ,4,5,6,7,7aβ-octahydrobenzothiophene (14). To a solution of 15.38 g (0.060 mol) of diacetate 13 in 200 mL of methanol was added 85 mL of 1 N sodium hydroxide. The reaction mixture was refluxed for 1 h, cooled, and concentrated. The residue was partitioned between water/methylene chloride. The aqueous phase was further extracted twice with 100-mL portions of methylene chloride. The organic phases were combined, dried over sodium sulfate, and evaporated to afford 11.0 g (85%) of the desired alcohol 14 as a crystalline solid. For analysis, a sample was recrystallized from ethyl acetate and afforded colorless needles: mp 131–132 °C; IR (KBr) 3350 (OH), 3175 (NH), 2950 (CH), 1650 (amide CO), 1560 (amide II), 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (1 H, br d), 4.6 (2 H, br d, CHOH), 4.1 (1 H, br s, CHNHAc), 3.2 (2 H, m), 2.8 (1 H, m), 2.4 (1 H, m), 1.9 (3 H, s, acetamide), 2.0–1.2 (6 H, m); mass spectrum, m/e 197 ($M^+ - H_2O$), 138 (base, $M^+ - H_2O$ – acetamide), 110, 81, 60, 44.

Anal. Calcd for $C_{10}H_{17}NO_2S$ (215.32): C, 55.78; H, 7.96; N, 6.51; S, 14.89. Found: C, 55.93; H, 7.98; N, 6.45; S, 15.03.

4α-Acetamido-3aβ,4,5,6,7,7aβ-hexahydrobenzothiophen-3-(2*H*)-one (15). To a solution of 30 g (0.145 mol) of dicyclohexylcarbodiimide in 125 mL of dry Me_2SO were added 3.75 mL of pyridine, 2.0 mL of trifluoroacetic acid, and 10.0 g (0.047 mol) of the alcohol 14. The reaction was allowed to proceed for 24 h at 25 °C. A solution of 13.5 g (0.150 mol) of oxalic acid in 130 mL of methanol was added dropwise. After the addition was complete, the reaction mixture was stirred at 25 °C for 0.5 h and diluted with 1 L of water. After an additional 0.5 h of stirring, the dicyclohexylurea was filtered off and washed with methylene chloride. The filtrate was extracted 3 times with 100-mL portions of methylene chloride. The organic phases were pooled, dried over sodium sulfate, and evaporated. The residue was taken up in the minimum amount of hot ether (some dicyclohexylurea was again filtered) and 6.0 g (60%) of the desired ketone 15 was deposited upon cooling. An analytical sample was prepared by recrystallization from ether to yield colorless needles: mp 140–141 °C; IR (CH_2Cl_2) 3430 (NH); 3020, 2950 (CH), 1730 (ketone), 1670 (amide), 1520 (amide II) cm^{-1}; NMR ($CDCl_3$) δ 7.1 (1 H, br s, NH), 4.2 (1 H, m, CHNHAc), 3.4 (2 H, s, CH_2S), 3.3 (1 H, m), 3.0 (1 H, m), 2.0 (3 H, s, acetamide), 2.0–1.2 (6 H, m): mass spectrum, m/e 213 (M^+), 195 ($M^+ - H_2O$), 154 (base, M^+ – acetamide), 126.

Anal. Calcd for $C_{10}H_{15}NO_2S$ (213.30): Calcd: C, 56.31; H, 7.09; N, 6.57; S, 15.03. Found: C, 56.50; H, 7.07; N, 6.50; S, 14.94.

Correlation of the Trifluoroacetamido Ketone 6 with the Ketone 15. A solution of 200 mg (0.75 mmol) of 4-(trifluoroacetamido)hexahydrobenzo[*b*]thiophen-3(2*H*)-one (6) in 20 mL of benzene, to which 2 mL of ethylene glycol and 20 mg of p-toluenesulfonic acid were added, was stirred and refluxed overnight, using a Dean–Stark trap. After workup, 215 mg of ketal 16 remained. Without purification, the crude ketal was dissolved in 2 mL of a solution of 1 N potassium hydroxide in 80% of methanol and kept for 2 h at room temperature. The reaction mixture was then acidified with 2 N hydrochloric acid, stirred 30 min at room temperature, and worked up. The crude residue (150 mg) was acetylated at room temperature overnight, using a mixture of 1 mL of acetic anhydride and 1 mL of pyridine. The acetylation product was crystallized twice from methanol–water to give 73 mg of 4-acetamidohexahydrobenzo[*b*]thiophen-3-(2H)-one (15) (46% overall yield), mp 140–141 °C, identical in all respects with the sample prepared in the preceding experiment.

4α-Acetamido-3aβ,4,5,6,7,7aβ-hexahydrobenzothiophen-3-(2*H*)-one *anti*-Oxime (19). To a solution of 600 mg (2.8 mmol) of the ketone 15 in 20 mL of 95% ethanol were added 5.0 mL of pyridine and 280 mg (4.0 mmol) of hydroxylamine hydrochloride. The mixture was allowed to reflux for 1.5 h, cooled, concentrated, and partitioned between 1 N HCl/methylene chloride. After three extractions, the organic phases were combined, dried over sodium sulfate, and evaporated to yield 550 mg (90%) of essentially pure oxime 19. For analysis, a sample was prepared by recrystallization from ethyl acetate to afford colorless needles: mp 175–176 °C; IR (KBr) 3370 (OH), 3250 (NH), 2900 (CH), 1620 (amide + C=N), 1540 (amide II), 950 cm^{-1}; NMR ($CDCl_3$) δ 9.4 (1 H, s, OH), 7.5 (1 H, br d), 4.3 (1 H, br m, CHNHAc), 3.57, 3.88 (2 H, AB, J = 7.5 Hz, CH_2S), 3.3 (2 H, m), 2.0 (3 H, s, acetamide), 2.0–1.2 (6 H, m); mass spectrum, m/e 228 (M^+), 211 ($M^+ - H_2O$), 169 (M^+ – acetamide), 152 (base, M^+ – acetamide–H_2O).

Anal. Calcd for $C_{10}H_{16}N_2O_2S$ (228.31): C, 52.61; H, 7.06; N, 12.27; S, 14.04. Found: C, 52.65; H, 7.07; N, 12.45; S, 14.25.

Acknowledgment. We thank the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for the determination of physical and analytical data, particularly Dr. J. F. Blount who carried out the X-ray structure determination.

Registry No. 1, 79233-94-6; 2, 79233-95-7; 3, 79233-96-8; 4, 79233-97-9; 5, 79233-98-0; 6, 79233-99-1; 7, 79297-70-4; 8, 79234-00-7; 9, 79234-01-8; 10, 79234-02-9; 11, 79234-03-0; 11·HCl, 79297-71-5; 12, 79297-72-6; 12·HCl, 79355-24-1; 13, 79234-04-1; 14, 79234-05-2; 15, 79234-06-3; 16, 79234-07-4; 17, 79234-08-5; 18, 79234-09-6; 19, 79234-10-9; methyl thioglucolate, 2365-48-2; cyclohexenone, 930-68-7; ethyl urethane, 51-79-6.

Supplementary Material Available: Tables I–IV, listing atomic coordinates, thermal parameters, bond distances, and angles for 19 (3 pages). Ordering information is given on any current masthead page.

3,4,9,9a-Tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one Derivatives and N,3-Disubstituted 3,3a,4,4a,10,10a-Hexahydro-3a-hydroxy-2-oxo-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-5(2*H*)-carboxamides

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Received May 5, 1981

The treatment of 2-[[2-(1*H*-indol-3-yl)ethyl]imino]cyclohexanone (1) with hot concentrated sulfuric acid to give the pentacyclic compound 4 is described. The treatment of 4 with 2 equiv of isocyanate gave N,3-disubstituted 3,3a,4,4a,10,10a-hexahydro-3a-hydroxy-2-oxo-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-5(2*H*)-carboxamides 11. When bulky isocyanates were used, the reaction stopped at the diurea stage 10. The latter were irreversibly converted to 11 by heating at 140 °C.

In another paper[1] we have described the acid-catalyzed cyclization of the Schiff base 1 to the spiro ketone 2 by using Pictet–Spengler[2] reaction conditions. However, when 1 was treated under strong acid conditions (Scheme I), an isomeric compound was obtained which still contained the ketone function as shown by infrared absorption at 1721 cm^{-1}. The ultraviolet absorption spectrum [248 nm (ϵ 8580) and 303 (3450); in acid solution, 248 nm (ϵ 610) and 304 (305)] was characteristic of an indoline chromophore[3] rather than of an indole.

Structure 3 was suggested for this compound on the basis of the strong-acid-catalyzed rearrangement of 1-[(3,4-dihydroxyphenyl)methyl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles to polycyclic fused indolines as described by Harley-Mason and Waterfield.[4] This structure (3) would arise by cyclization to the indole 3-position followed by electrophilic attack of the indolenium ion on the enol.

Alternatively, another oxoindoline, 4, could have arisen by diprotonation of 1a, cyclization to the indole 3-position, and electrophilic attack of the indolenium ion on the enol.

To decide between these two structures, we turned to nuclear magnetic spectral analysis. The proton magnetic resonance spectrum is in agreement with the structure 4. The aromatic protons exhibit two multiplets centered at δ 6.82 and 6.43. The former multiplet is due to H-5 and H-7 (ortho and para to the aniline nitrogen), while the latter results from H-6 and H-8. The aniline proton as a doublet at δ 5.64 (J = 3.0 Hz) is coupled with H-9a and disappears on exchange with deuterium oxide. The H-12 (NH) as a broad multiplet resonates at δ 2.82 (D_2O exchangeable). The decoupling experiments gave the location of the lone aliphatic protons and their mutual relationships. Thus, the doublet at δ 3.75 (J = 4.2 Hz)[5] corresponds to H-9a being coupled to H-1 at δ 2.33. The doublet at δ 2.96 (J = 3.0 Hz) is due to H-3 which is coupled to H-4 at δ 1.97. The latter split signal, which sits on the top of that for the methylene group, collapses to a sharp spike on decoupling. Four complex envelopes centered at δ 2.45 (2 H, NCH_2, partly burried under Me_2SO-d_6 band), 1.95 (2 H), 1.40 (2 H), and 1.25 (2 H) account for the remaining aliphatic protons. Decoupling without deuterium oxide was also carried out. On irradiating the aniline proton (δ 5.64), the 9a-proton (originally appearing as a triplet) collapsed to a sharp doublet at δ 3.75 (J = 4.2 Hz). Thus, the position of H-9a is unambiguously established. The ^{13}C NMR partially decoupled spectrum ($CDCl_3$) of 4 shows only one aliphatic quaternary carbon at 47.03 ppm which corresponds to C-4a. The resonances of aromatic carbons resemble closely those of indoline. The resonances of tertiary carbons show four distinct lines at δ 61.9, 60.9, 49.1, and 47.0, respectively. There are also four methylene carbon resonances at δ 38.8, 37.4, 20.1, and 15.4. These data give support to structure 4 and eliminate the alternative structure 3 since it would contain two quaternary carbon atoms.

Compound 4 forms the diacetyl derivative 5 with cold acetic anhydride. It reacts with carbonyl reagents, forms an oxime 6, and is also reduced to the secondary alcohol 7 by potassium borohydride at room temperature. The treatment of 7 with acetic anhydride at 25 °C gives the

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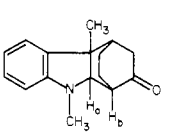
(2) W. M. Whaley and T. R. Govindarchari, *Org. React.*, 6, 151–190 (1951).
(3) (a) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Pergamon Press, Oxford, 1964, p 298; (b) J. R. Williams and L. R. Unger, *Chem. Commun.* 1605–1606 (1970); (c) J. E. D. Barton and J. Harley-Mason, *ibid.*, 298–299 (1965).
(4) J. Harley-Mason and W. R. Waterfield, *Tetrahedron*, 19, 65–76 (1963).
(5) P. A. Cranwell and J. E. Saxton, *Tetrahedron*, 20, 877–881 (1964). In a partly similar structure (but lacking aminoethano bridge), the authors report H_a as a doublet at 3.40 ppm (J = 4.5 Hz); obviously, the neighboring *N*-methyl group causes partial shielding.



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