Simplified Analogues of Lysergic Acid. 7. Derivatives of 4-Amino-5-oxo-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene

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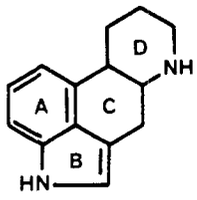
Progress toward the synthesis of the sulfur analogue (**3**) of lysergic acid (**2a**), which involves the isosteric substitution of sulfur for the indole NH, is reported. An improved synthesis of 5-hydroxy-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-dioxide (**14**) is presented. Subsequent transformations yielded 4-bromo-5-oxo-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-dioxide (**22**), which reacted with (methylamino)acetone ethylene ketal to give the ketal-ketone **27**. Conditions for the hydrolysis of the ketal-ketone **27** to the diketone **33** are described.

The pharmacologically important ergot alkaloids have the ergoline ring system (**1**) as the basis of their structure.[1] A number of them are amides of lysergic acid (**2a**),[2] and a



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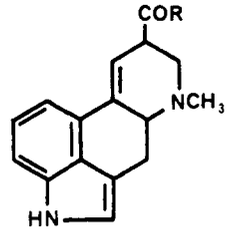
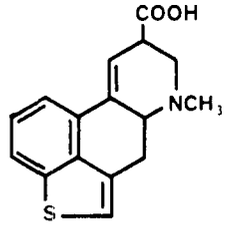


2a: R = OH
2b: R = NEt_2



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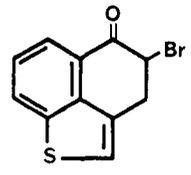

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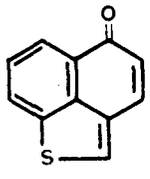

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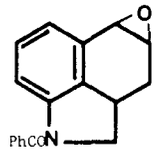

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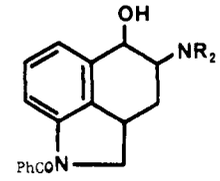
semisynthetic derivative, lysergic acid diethylamide (LSD, **2b**), is the most potent of the known hallucinogens.[3]

Much effort has been devoted to synthesizing structural analogues of the ergot alkaloids in order to determine the effect of structural changes on biological activity.[4] Such information is useful in identifying those features associated with a particular pharmacological action. Furthermore, a number of benzo[*b*]thiophene isosteres of biologically active indole derivatives have been prepared.[5] The present work is directed toward the synthesis of the sulfur isostere **3** of lysergic acid in which the indole nucleus (rings A and B) has been replaced by benzo[*b*]thiophene. This analogue may be useful in determining the importance of the indole NH for various pharmacological effects.

The synthesis of compound **3** has been previously studied by Campaigne and Knapp.[6] A key step in their proposed pathway, the displacement of bromine in the bromo ketone **4** by an amine, could not be carried out due to predominant elimination of HBr to give compound **5**.

In the synthesis of lysergic acid Kornfeld et al.[7] reported that epoxide **6** reacted with amines to give alcohols of type **7**.



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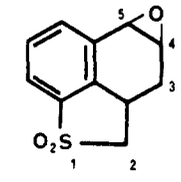

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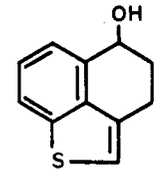

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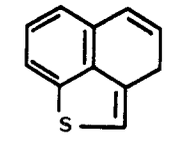

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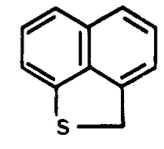

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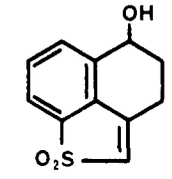

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We therefore first examined the possibility of introducing a C-4 amino function via ring opening of the epoxide **8**. The synthesis of a 4,5-epoxy derivative via a 4,5 olefin necessitated the prior reduction of the 2,2a double bond to prevent isomerization of **10** to **11**.[8] As a prerequisite to reduction of the double bond, the alcohol **9** (obtained in five steps from benzo[*b*]thiophene[6]) was oxidized to the hydroxy sulfone **12** with 2 equiv of *m*-chloroperbenzoic acid. Treating compound **12** with lithium aluminum hydride in refluxing THF for 24 h is reported to give the dihydro sulfide **13** in low yield.[6] Upon repeating the published procedure, we obtained a product which appeared to be homogeneous by TLC and GLC; however, chemical ionization mass spectrometry (CIMS) showed two major ions at *m/e* 175 and 173 in a ratio of 1:4. This suggested a mixture of alcohols **9** and **13**, which were losing H_2O in the mass spectrometer. Indeed, a pure sample of **9** showed only one peak at *m/e* 173. The NMR spectrum of the mixture also displayed peaks characteristic of compound **9**. Apparently

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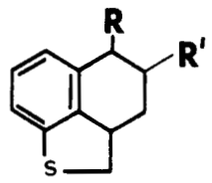
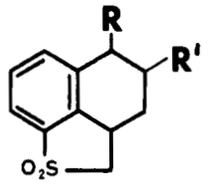
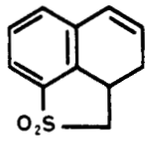


13 R=OH, R'=H
20 R=H, R'=OH



14 R=OH, R'=H
15 R=Cl, R'=H
17 R=OH, R'=$NHCH_3$
18 R=$NHCH_3$, R'=OH
19 R=H, R'=OH



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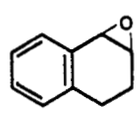
a considerable amount of the sulfone is reduced to reform **9** before the double bond is attacked. The reaction was repeated varying the temperature, time, and amount of reducing reagent; in all cases CIMS showed the two products in about the same ratio of 1:4. These results are consistent with the findings of Rao[9] that the sulfone is completely reduced, and the 2,3 double bond is reduced to varying extents when 2- or 3-alkylbenzo[*b*]thiophene 1,1-dioxides are treated with lithium aluminum hydride. Groups in the 3 position hindered reduction of the double bond much more than did groups in the 2 position.

The clean reduction of the double bond was accomplished by hydroborating compound **12** with diborane in THF, followed by protonolysis with propionic acid in refluxing diglyme. This gave the dihydro sulfone **14** (90% yield), which could then be reduced to the dihydro sulfide **13** with lithium aluminum hydride. Although the literature states[10] that reduction of 2,3-dihydrobenzo[*b*]thiophene 1,1-dioxides is fast (30 min at room temperature), the reduction of **14** to **13** in fact required 48 h at room temperature.

Attempted dehydration of **14** with either thionyl chloride or phosphorus oxychloride in pyridine[11,12] yielded only the chloride **15.** However, treatment of **14** with polyphosphoric acid for 1 h at room temperature produced the desired olefin **16** in 93% yield, and reaction of this olefin with *m*-chloroperbenzoic acid in methylene chloride readily afforded the epoxide **8** (quantitative yield). A mixture of epoxide **8**, methylamine, and benzene was heated at 115 °C for 16 h in a sealed vessel in hope of obtaining the amino alcohol **17.** However, the NMR spectrum of the product suggested that attack had occurred at the 5 position to give the isomeric amino alcohol **18** since the signal for the C-5 proton is displayed at 4.2 ppm, whereas in all derivatives with a C-5 hydroxyl group the C-5 proton appears near 5.0 ppm. Since it is known that hydroboration of styrene places boron predominantly at the β position,[13] the olefin **16** was treated with diborane in THF in an effort to obtain the alcohol **19** containing a C-4 hydroxyl function to check the position of the C-4 proton in the NMR spectrum. However, following treatment with alkaline hydrogen peroxide, the product was identified as the alcohol **14.**

Reduction of epoxide **8** with lithium aluminum hydride simultaneously reduced the sulfone to yield the hydroxy sulfide **20,** with physical properties different from those of the hydroxy sulfide **13.** The C-4 proton appears at 4.15 ppm in the NMR spectrum, which agrees well with the analogous assignment for the amino alcohol **18.**

These results are in accord with a study by Audier et al.[14] on the opening of epoxide **21** with ^{18}O-labeled hydroxide ion,



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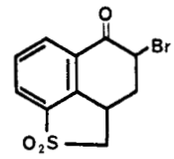

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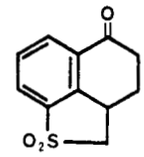

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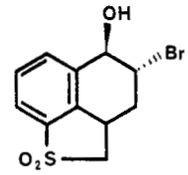

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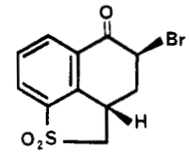

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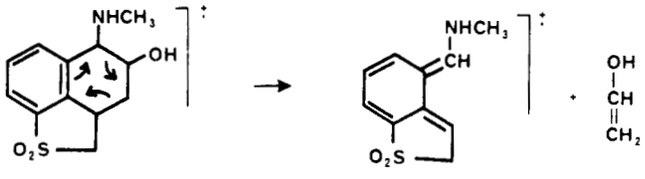
which showed that 90% of attack occurred at the benzylic position. The position of attack occurred at the benzylic position. The position of attack was determined by locating the labeled oxygen by electron impact mass spectral fragmentation. It was shown that 1,2-disubstituted tetralins undergo fragmentation via a retro-Diels–Alder pathway. The electron impact mass spectrum of the product from the methylamine opening of epoxide **8** displays a molecular ion at *m/e* 253 of 2% relative abundance and a peak at *m/e* 209 of 40% relative abundance due to retro-Diels–Alder fragmentation, in agreement with the structure **18** (Scheme I).

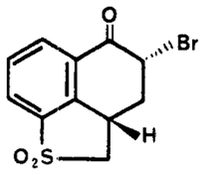
In order to introduce an amino function of C-4, the bromo ketone **22** was next investigated. Campaigne and Knapp[6] suggested that this compound might be less susceptible to elimination than compound **4** and synthesized the ketone **23,** but reported failure in attempts to brominate **23.** We therefore prepared the bromohydrin **24** by treating the olefin **16** with *N*-bromosuccinimide in wet Me_2SO.[15] By analogy with the reactions of epoxide **8**, the opening of the intermediate bromonium ion by H_2O should occur at the benzylic position to give the trans-diaxial bromohydrin **24.** The NMR spectrum supports this structure. The C-5 proton is displayed as a doublet of doublets at 4.5 ppm due to coupling to the OH proton (J = 3 Hz). The C-4 proton appears as a quartet at 4.2 ppm (J = 3 Hz), implying that $J_{4,5} = J_{3,4} = J_{3',4}$. Inspection of a Dreiding model of **24** shows that the dihedral angle H_{4-5} is 120° and angle $H_{3-4} = H_{3'-4} = 60°$. Application of the Karplus relationship[16] gives equal values for $J_{4,5}$, $J_{3,4}$, and $J_{3',4}$. Also, the electron impact mass spectrum shows a peak at *m/e* 196 of 40% relative abundance due to retro-Diels–Alder fragmentation, consonant with the structure **24.**

Oxidation of the bromohydrin **24** with Jones reagent gave a diastereomeric mixture of the *cis*- and *trans*-bromo ketones **25** and **26.** Since the bromohydrin appeared to have been a single isomer, the acidic reaction conditions must have caused equilibration α to the carbonyl. The NMR spectrum indicates a mixture of diastereomers, as two sets of signals are observed for the C-4 proton at 5.7 and 5.1 ppm, integrating to 0.33 and 0.67 protons, respectively. In the minor isomer the C-4 proton is displayed as a doublet of doublets (J = 5, 13 Hz), while in the major isomer it appears as a triplet (J = 3 Hz). In the cis

Scheme I



18 m/e 209



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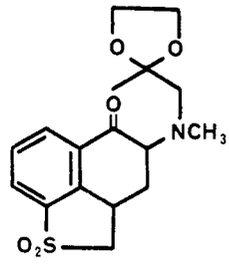

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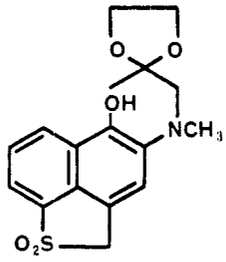

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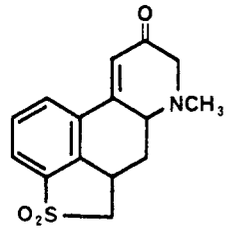

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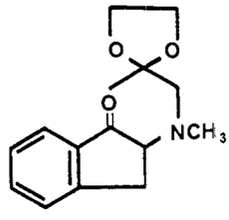

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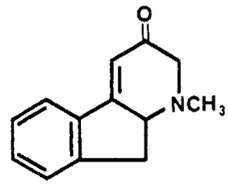

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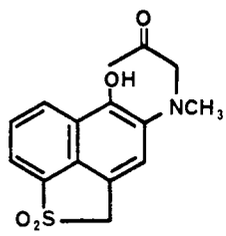
isomer **25** the dihedral angle $H_{3-4} = H_{3'-4} = 60°$ (from Dreiding models), whereas in the trans isomer **26** the angle $H_{3-4} = 60°$ and $H_{3'-4} = 180°$. Application of the Karplus relationship[16] assigns the cis compound **25** (equatorial C-4 H) as the major product and the trans compound **26** (axial C-4 H) as the minor product. It is known[17] that in α-halocyclohexanones the methine proton is less shielded when it occupies the axial position than when it is equatorial. Furthermore, in a study of 2-bromocyclohexanones, Corey[18] found that, in the absence of steric effects, the most stable conformation had the bromine in the axial position. When bromine is equatorial, the C=O and C–Br dipoles are parallel and repel each other, which causes a destabilization estimated to be about 2.7 kcal/mol.[18]

The bromination of ketone **23** with phenyltrimethylammonium perbromide (PTAB)[19] was next investigated. Ketone **23** was obtained in 96% yield by Jones oxidation of alcohol **14.** Treatment of **23** with 1 equiv of PTAB in THF–acetonitrile gave an oil which crystallized from benzene to yield the same mixture of bromo ketones **25** and **26.** The two samples were identical by melting range, NMR, and mass spectra. However, the yield and purity by this route were inferior to those via the bromohydrin **24.**

Treatment of the bromo ketone mixture (**25**–**26**) with 2 equiv of (methylamino)acetone ethylene ketal in benzene gave the ketal–ketone **27.** The free base **27** was extremely labile and readily underwent base-catalyzed oxidation to the naphthalene derivative **28.** The presence of **28** as a contaminant could be detected by the appearance of a singlet in the NMR spectrum at 5.0 ppm for the C-2 protons. Following the successful cyclization of the ketal–ketone **30** to **31** in PPA,[20] cyclization of the ketal–ketone **27** to the tetracyclic ketone **29** was attempted. Treatment of the hydrochloride of **27** in nitromethane with PPA for various lengths of time (12–48 h) gave complex mixtures, the chemical ionization mass spectra of which displayed a prominent peak at *m/e* 306, probably due to the oxidation product **32.** No olefinic signals were seen in the NMR spectra of any of the mixtures.



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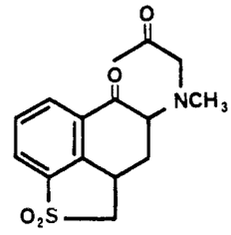

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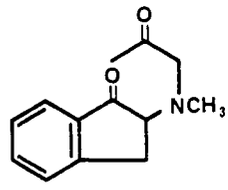

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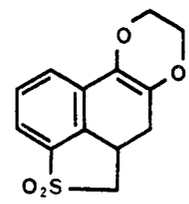

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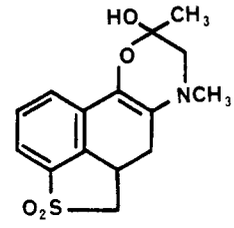

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Preparation of the diketone **33** as a precursor to compound **29** was next examined. Applying the conditions used for the conversion of the ketal–ketone **30** to the diketone **34,**[20] compound **27** was heated in 6 N HCl. After 24 h at 75 °C, the product isolated was not the diketone **33,** but the totally unexpected dioxane derivative **35.** The IR spectrum displayed no carbonyl bands but rather a strong absorbance at 1640 cm^{-1}. The NMR spectrum showed the four dioxane ring protons at 4.3 ppm.[21] However, hydrolysis of **27** under milder conditions (37 °C, 5 days) gave the desired diketone **33** in 70% yield, showing correct IR and NMR spectra. In pyridine solution, compound **33** slowly underwent isomerization to the lactol **36** (see Experimental Section for details of the NMR spectra). The cyclization of **33** to **29** is being further investigated.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The 60-MHz NMR spectra were recorded on a Perkin-Elmer R12B instrument, and the 100-MHz NMR spectra were recorded on a Varian XL-100-15 instrument. Me_4Si was used as an internal standard in organic solvents, and sodium (trimethylsilyl)propanesulfonate (TMSP) was used in D_2O. IR spectra were recorded on a Perkin-Elmer 337 instrument. The electron impact mass spectra were obtained on an AEI MS-12 instrument at 70 eV, and the chemical ionization mass spectra were obtained on an AEI MS-902 instrument modified for chemical ionization using isobutane as the reagent gas. GLC analyses were performed on a Varian Aerograph Model 2100 gas chromatograph with a 6-ft U-shaped Pyrex column packed with 3% SE-30 on Chromosorb W. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley. Solutions were dried over $MgSO_4$.

5-Hydroxy-3,4-dihydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide (12). A solution of 6.0 g (0.0315 mol) of the alcohol **9** and 13.4 g (0.066 mol) of 85% *m*-chloroperbenzoic acid in 150 mL of methylene chloride was allowed to stand at room temperature overnight. The mixture was thoroughly washed with saturated Na_2SO_3 and saturated

$NaHCO_3$, dried, and evaporated. The resultant oil was crystallized from benzene to give the sulfone **12** (6.2 g, 90%): mp 125–126 °C (lit.[6] mp 125–126 °C); IR (KBr) 3500 (OH), 1300, 1130 (SO_2) cm^{-1}; NMR (100 MHz, Me_2SO-d_6) δ 8.0–7.6 (m, 3, aromatic H), 7.1 (t, 1, J = 1.5 Hz, C-2 H), 5.7 (broad s, 1, OH), 5.0 (d of d, 1, J = 4, 8 Hz, C-5 H), 3.0–2.7 (m, 2, C-3 H), 2.4–1.8 (m, 2, C-4 H).

Anal. Calcd for $C_{11}H_{10}O_3S$: C, 59.43; H, 4.53; S, 14.42. Found: C, 59.29; H, 4.36; S, 14.24.

Lithium Aluminum Hydride Reduction of 5-Hydroxy-3,4-dihydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide (12). A solution of the sulfone **12** (2.2 g, 10 mmol) in 50 mL of dry THF was added dropwise to a stirred suspension of 1.2 g (30 mmol) of lithium aluminum hydride in 50 mL of dry THF under N_2, and the mixture was refluxed for 24 h. The excess $LiAlH_4$ was destroyed by the sequential addition of 1.2 mL of H_2O, 1.2 mL of 30% NaOH, and 3.6 mL of H_2O. The precipitate was collected and washed with THF. The combined THF washings were dried and evaporated to give an oil which was analyzed as a 4:1 mixture of the alcohols **9** and **13.**

5-Hydroxy-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide (14). (a) From Sulfone 12. A solution of 6.2 g (0.028 mol) of the sulfone **12** in 75 mL of dry THF was added dropwise with stirring to 50 mL of 1 N BH_3–THF solution (0.05 mol) under N_2. The mixture was stirred at room temperature for 20 h. The excess BH_3 was destroyed with 5 mL of H_2O, and the solvent was evaporated at reduced pressure. The residue was dissolved in 150 mL of diglyme and 15 mL of propionic acid, and the solution was heated at 145 °C for 3.5 h. The solvent was evaporated in vacuo and the resultant oil taken up in $CHCl_3$. The $CHCl_3$ was washed with 5% $NaHCO_3$, dried, and evaporated to yield the dihydro sulfone **14** (5.5 g, 90%). A sample was recrystallized from benzene: mp 137–138 °C (lit.[6] mp 138–139 °C); IR (KBr) 3500 (OH), 1280, 1120 (SO_2) cm^{-1}; NMR (100 MHz, Me_2SO-d_6) δ 7.8–7.4 (m, 3, aromatic H), 5.6 (d, 1, J = 6 Hz, OH), 4.8–4.6 (m, 1, C-5 H), 3.9–3.1 (m, 3, C-2 and C-2a H), 2.4–1.5 (m, 4, C-3 and C-4 H).

Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.35; S, 14.30. Found: C, 58.68; H, 5.15; S, 14.28.

(b) From Olefin 16. To a solution of 1.0 g (4.8 mmol) of the olefin **16** in 50 mL of dry THF was added 5 mL (5 mmol) of 1 N BH_3–THF solution. The reaction mixture was stirred at room temperature under N_2 for 2 h, and then the excess BH_3 was decomposed with 1 mL of H_2O. The organoborane intermediate was oxidized by adding 1.5 mL of 3 N NaOH, followed by the slow dropwise addition of 1.5 mL of 30% H_2O_2 at a rate such that the temperature did not rise above 50 °C. After being stirred for an additional 30 min at 40 °C, the mixture was dried and evaporated. The resultant oil was recrystallized from benzene to yield 0.9 g (83%) of the sulfone **14,** mp 137–138 °C. A mixture melting point of the samples from methods a and b was not depressed.

5-Hydroxy-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene (13). To a suspension of 1.0 g (15 mmol) of lithium aluminum hydride in 20 mL of dry THF was added dropwise 1.0 g (4.5 mmol) of the alcohol **14** in 20 mL of dry THF under N_2. The mixture was stirred at room temperature for 48 h. The excess $LiAlH_4$ was destroyed by the sequential addition of 1 mL of H_2O, 1 mL of 30% NaOH, and 3 mL of H_2O. The precipitate was filtered off, and the filtrate was evaporated to yield a yellow oil which slowly crystallized. Recrystallization from benzene–hexane afforded 0.65 g (75%) of the hydroxy sulfide **13:** mp 126–127 °C (lit.[6] mp 123–126 °C); IR (KBr) 3300 cm^{-1} (OH); NMR (100 MHz, Me_2SO-d_6) δ 7.1 (m, 3, aromatic H), 5.2 and 5.0 (2d, 1/2 each, J = 6 Hz, OH), 4.5 (m, 1, C-5 H), 3.4–2.8 (m, 3, C-2 and C-2a H), 2.2–1.4 (m, 4, C-3 and C-4 H).

Anal. Calcd for $C_{11}H_{12}OS$: C, 68.61; H, 6.29; S, 16.68. Found: C, 68.98; H, 6.24; S, 16.77.

5-Chloro-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide (15). A mixture of the alcohol **14** (0.45 g, 2 mmol), $POCl_3$ (2.5 mL), H_3PO_4 (10 mg), CH_2Cl_2 (25 mL), and anhydrous pyridine (25 mL) was heated at 50 °C for 3 h under N_2. The solution was cooled to room temperature and 100 mL of $CHCl_3$ added. The excess $POCl_3$ was decomposed with ice. The organic layer was separated, washed with 1 M HCl and H_2O, dried, and evaporated. The solid (0.40 g, 83%) was recrystallized from 95% EtOH to yield the chloride **15:** mp 183–185 °C; IR (KBr) 1260, 1070 (SO_2) cm^{-1}; NMR (100 MHz, Me_2SO-d_6) δ 7.8–7.5 (m, 3, aromatic H), 5.8–5.3 (m, 1, C-5 H), 4.0–1.6 (m, 7, C-2, C-2a, C-3, and C-4 H).

Anal. Calcd for $C_{11}H_{11}ClO_2S$: C, 54.42; H, 4.57; S, 13.20. Found: C, 54.82; H, 4.57; S, 13.40.

2a,3-Dihydro-2*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide (16). A solution of 5.0 g (22 mmol) of the alcohol **14** in 11 mL of nitromethane was dissolved in 65 g of 83% polyphosphoric acid, and the solution was allowed to stand at room temperature for 1 h. The reaction mixture was decomposed with ice and extracted with $CHCl_3$. The $CHCl_3$ was washed with H_2O, dried, and evaporated to give the olefin **16** (4.6 g, 93%). Recrystallization from 95% EtOH gave an analytical sample: mp 148–149 °C; IR (KBr) 1290, 1115 (SO_2) cm^{-1}; NMR (100 MHz, Me_2SO-d_6) δ 7.7–7.3 (m, 3, aromatic H), 6.7 (d of d, 1, J = 2, 9 Hz, C-5 H), 6.3–6.0 (m, 1, C-4 H), 4.0–1.8 (m, 5, C-2, C-2a, and C-3 H).

Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.56. Found: C, 63.93; H, 4.79; S, 15.72.

4,5-Epoxy-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide (8). A solution of 0.5 g (2.5 mmol) of the olefin **16** and 0.52 g (2.5 mmol) of 85% *m*-chloroperbenzoic acid in 30 mL of CH_2Cl_2 was allowed to stand at room temperature overnight. The mixture was washed with saturated Na_2SO_3 and saturated Na_2CO_3, dried, and evaporated. The resultant solid (0.55 g, 100%) was recrystallized from benzene to yield the epoxide **8:** mp 196–197 °C; IR (KBr) 1300, 1110 (SO_2) cm^{-1}; NMR (100 MHz, Me_2SO-d_6) δ 8.0–7.6 (m, 3, aromatic H), 4.15 (d, 1, J = 4 Hz, C-5 H), 4.0–3.2 (m, 4, C-2, C-2a, and C-4 H), 2.7 (d of d of d, 1, J = 3, 16, 16 Hz, C-3 H cis to the epoxide ring), 1.7 (m, 1, C-3 H trans to the epoxide ring).

Anal. Calcd for $C_{11}H_{10}O_3S$: C, 59.45; H, 4.53; S, 14.43. Found: C, 59.13; H, 4.48; S, 14.28.

5-(Methylamino)-4-hydroxy-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide (18). A solution of the epoxide **8** (1.0 g, 4 mmol), liquid methylamine (15 mL), and dry benzene (10 mL) was heated at 115 °C in a bomb for 16 h. The mixture was cooled to room temperature, and the excess methylamine was allowed to evaporate. The residue was chromatographed over silica gel (100 g) using 5% EtOH in benzene as eluent to yield 0.95 g (83%) of the amino alcohol **18.** Recrystallization from benzene afforded an analytical sample: mp 117–118 °C; IR (KBr) 3300, 3100 (NH, OH), 1300, 1125 (SO_2) cm^{-1}; NMR (100 MHz, Me_2SO-d_6) δ 7.7–7.3 (m, 3, aromatic H), 5.1 (broad s, 1, exchangeable H), 4.2 (broad s, 1, C-5 H), 3.9–1.6 (m, 7, C-2, C-2a, C-3, and C-4 H and NH), 2.4 (s, 3, NCH_3); mass spectrum, *m/e* (relative intensity) 253 (2), 209 (40).

Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.96; S, 12.65. Found: C, 56.76; H, 5.84; S, 12.80.

4-Hydroxy-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene (20). A solution of the epoxide **8** (1.2 g, 5.5 mmol) and lithium aluminum hydride (1.2 g, 30 mmol) in 75 mL of dry THF was stirred for 48 h at room temperature under N_2. The excess hydride was destroyed by the sequential addition of 1.2 mL of H_2O, 1.2 mL of 30% NaOH, and 3.6 mL of H_2O. The inorganic salts were filtered off and washed with THF. The combined THF washings were dried and evaporated to give the sulfide **20** (0.7 g, 83%). An analytical sample was obtained by recrystallization from benzene–hexane: mp 112–113 °C; IR (KBr) 3300 cm^{-1} (OH); NMR (100 MHz, Me_2SO-d_6) δ 7.1 (d, 2, J = 4 Hz, C-6 and C-8 H), 6.8 (q, 1, J = 4 Hz, C-7 H), 4.8 (d, 1, J = 3 Hz, OH), 4.3 (broad s, 1, C-4 H), 3.6–2.5 (m, 5, C-2, C-2a, and C-5 H), 2.2 (d of t, 1, J = 5, 16 Hz, C-3 H cis to the C-4 OH), 1.5 (t, 1, J = 16 Hz, C-3 H trans to the C-4 OH).

Anal. Calcd for $C_{11}H_{12}OS$: C, 68.61; H, 6.21; S, 16.68. Found: C, 68.89; H, 6.41; S, 16.88.

5-Oxo-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide (23). To a solution of 4.6 g (21 mmol) of the alcohol **14** in 100 mL of acetone was added dropwise 7 mL of Jones reagent while cooling the reaction in an ice bath. The mixture was stirred for 1 h, 5 mL of EtOH was added, and the solution was poured into 200 mL of H_2O. The product was extracted into $CHCl_3$ and the $CHCl_3$ was washed with H_2O, dried, and evaporated. The crude yield was 4.4 g (96%), mp 190–194 °C. An analytical sample was prepared by recrystallization from benzene: mp 205–206 °C (lit.[6] mp 185–187 °C); IR (KBr) 1695 (C=O), 1300, 1120 (SO_2) cm^{-1}; NMR (60 MHz, Me_2SO-d_6) δ 8.1–7.4 (m, 3, aromatic H), 4.0–1.5 (m, 7, aliphatic H).

Anal. Calcd for $C_{11}H_{10}O_3S$: C, 59.45; H, 4.53; S, 14.43. Found: C, 59.21; H, 4.64; S, 14.24.

4-Bromo-5-hydroxy-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide (24). *N*-Bromosuccinimide (11.2 g, 0.063 mol) was added to a cooled solution (10 °C) of 6.5 g (0.0315 mol) of the olefin **16,** 1.14 g (0.063 mol) of H_2O, and 150 mL of Me_2SO. The mixture was stirred for 40 min at 15 °C and then poured into 500 mL of saturated aqueous NaCl. The precipitate was collected and recrystallized from 95% EtOH to yield 8.2 g (86%) of the bromohydrin **24:** mp 188–189 °C; IR (KBr) 3500 (OH), 1290, 1120 (SO_2) cm^{-1}; NMR (100 MHz, Me_2SO-d_6) δ 7.2 (m, 3, aromatic H), 5.7 (d, 1, J = 6 Hz, OH), 4.5 (d of d, 1, J = 3, 5 Hz, C-5 H), 4.2 (q, 1, J = 3 Hz, C-4 H), 3.6–2.8 (m, 3, C-2 and C-2a H), 1.8 (m, 2, C-3 H).

Anal. Calcd for $C_{11}H_{11}BrO_3S$: C, 43.58; H, 3.65; Br, 26.35. Found: C, 43.50; H, 3.63; Br, 26.32.

4-Bromo-5-oxo-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thio-

phene 1,1-Dioxide (25–26 Mixture). (a) Oxidation of Bromohydrin 24. To a solution of 7.4 g (25 mmol) of the bromohydrin **24** in 250 mL of acetone was added dropwise 8 mL of Jones reagent while cooling the mixture in an ice bath. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The excess Jones reagent was destroyed with EtOH and the mixture poured into 500 mL of H_2O. The product was extracted into $CHCl_3$, and the $CHCl_3$ was washed with H_2O, dried, and evaporated to give a mixture of the bromo ketones **25** and **26** (7.0 g, 95%). An analytical sample was prepared by three recrystallizations from benzene: mp 168–175 °C; IR (KBr) 1695 (C=O), 1310, 1125 (SO_2) cm^{-1}; NMR (100 MHz, Me_2SO-d_6) δ 8.2–7.8 (m, 3, aromatic H), 5.7 (d of d, 1/3, J = 5, 13 Hz, C-4 H in **26**), 5.1 (t, 2/3, J = 3 Hz, C-4 H in **25**), 4.2–3.8 (m, 2, C-2 H), 3.8–3.6 (m, 1, C-2a H), 3.0–2.4 (m, 2, C-3 H); mass spectrum, *m/e* (relative intensity) 302 and 300 (5), 222 (20), 220 (30), 194 (18), 141 (18), 130 (100), 128 (50), 115 (28), 102 (60), 76 (22).

Anal. Calcd for $C_{11}H_9BrO_3S$: C, 43.87; H, 3.01; S, 10.65. Found: C, 43.76; H, 2.97; S, 10.54.

(b) Bromination of Ketone 23. A solution of 5.65 g (15 mmol) of phenyltrimethylammonium perbromide in 70 mL of THF was added dropwise to a stirred solution of 3.0 g (13.5 mmol) of the ketone **23** in 200 mL of acetonitrile. After the reaction mixture was stirred for 3 h at room temperature, the solvent was evaporated at reduced pressure. The residue was poured into 100 mL of H_2O, and the H_2O was extracted with $CHCl_3$. The $CHCl_3$ was dried and evaporated. Recrystallization of the resultant oil from benzene gave a mixture of the bromo ketones **25** and **26** (2.5 g, 65%) in the same ratio as above, mp 168–174 °C. The spectral properties of the two samples were identical.

Anal. Calcd for $C_{11}H_9BrO_3S$: C, 43.87; H, 3.01; S, 10.65. Found: C, 43.60; H, 3.14; S, 10.61.

5-Oxo-4-[methyl[(2-methyl-1,3-dioxolan-2-yl)methyl]amino]-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide Hydrochloride (27 HCl). A solution of (methylamino)acetone ethylene ketal (2.15 g, 16 mmol) and the bromo ketone mixture **25–26** (2.0 g, 6.5 mmol) in 50 mL of dry benzene was heated at reflux for 14 h with a slow stream of N_2 bubbling through the stirred solution. The mixture was cooled to 5 °C and filtered. The filtrate was washed with ice water, dried, and acidified with Et_2O–HCl. After the solvents were removed in vacuo, the resultant foam was crystallized from EtOH–Et_2O to give the hydrochloride salt of the ketal **27** containing 1.5 mol of H_2O of crystallization (1.8 g, 72%): mp darkens 135 °C, melts 145–150 °C dec; IR (KBr) 3500–3400 (OH), 1720 (C=O), 1300, 1130 (SO_2) cm^{-1}; NMR (100 MHz, pyridine-d_5) δ 8.9 (s, 3, H_2O of crystallization), 8.2–7.4 (m, 3, aromatic H), 4.3–3.2 (m, 8, C-2, C-2a, and C-4 H and OCH_2CH_2O), 3.1 (d, 2, J = 5 Hz, NCH_2COO), 2.7 (s, 3, NCH_3), 2.6–2.0 (m, 2, C-3 H), 1.5 (s, 3, CH_3COO).

Anal. Calcd for $C_{17}H_{22}ClNO_5S \cdot 1.5H_2O$: C, 49.43; H, 5.85; S, 7.75. Found: C, 49.60; H, 5.99; S, 7.76.

2a,3,5,6-Tetrahydro-2*H*-*p*-Dioxino[2,3-*e*]naphtho[1,8-*bc*]-thiophene 1,1-Dioxide (35). A solution of the hydrochloride salt of the ketal **27** (1.0 g, 2.5 mmol) in 25 mL of 6 M HCl was heated at 75 °C for 24 h under N_2. The reaction mixture was lyophilized, and the resultant powder crystallized from 95% EtOH to give compound **35** (0.4 g, 58%): mp 252–253 °C; IR (KBr) 1650 (C=C), 1300, 1130 (SO_2) cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 7.5 (s, 3, aromatic H), 4.3 (m, 4, C-5 and C-6 H), 3.8 (m, 2, C-2 H), 3.3 (m, 1, C-2a H), 2.6 (m, 2, C-3 H).

Anal. Calcd for $C_{13}H_{12}O_4S$: C, 59.08; H, 4.57; S, 12.13. Found: C, 58.84; H, 4.60; S, 11.81.

5-Oxo-4-(*N*-methyl-*N*-acetonylamino)-2,2a,3,4-tetrahydro-5*H*-naphtho[1,8-*bc*]thiophene 1,1-Dioxide Hydrochloride (33 HCl). A solution of the hydrochloride salt of the ketal **27** (1.0 g, 2.5 mmol) in 25 mL of 6 M HCl was heated at 37 °C for 5 days under N_2. The reaction mixture was lyophilized, and the resultant solid was crystallized from nitromethane to yield the hydrochloride salt of the diketone **33** (0.6 g, 70%): mp 215 °C dec; IR (KBr) 2500 (N^+H), 1730, 1700 (C=O), 1300, 1120 (SO_2) cm^{-1}; NMR (100 MHz, pyridine-d_5, D_2O) δ 8.2–7.7 (m, 3, aromatic H), 4.2–1.8 (m, 6, methylene and methine H), 3.95 (s, 2, $O{=}CCH_2NCH_3$), 2.6 (s, 3, NCH_3), 2.4 (s, 3, $CH_3C{=}O$).

The NMR spectrum recorded 1 h after dissolution of the hydrochloride salt of the diketone **33** showed complete conversion to the lactol **36:** NMR (100 MHz, pyridine-d_5, D_2O) δ 7.5 (m, 3, aromatic H), 4.1–2.0 (m, 7, methylene and methine H), 3.06 and 3.0 (two s, 3, NCH_3), 1.86 and 1.82 (two s, 3, C-6 CH_3).

Anal. Calcd for $C_{15}H_{18}ClNO_4S$: C, 52.40; S, 9.32; Cl, 10.31. Found: C, 52.17; S, 8.94; Cl, 10.30.

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Registry No.—**8,** 68950-10-7; **9,** 26461-88-1; **12,** 26458-15-1; **13,** 26458-19-5; **14,** 26458-21-9; **15,** 68950-11-8; **16,** 68950-12-9; **18,** 68950-13-0; **20,** 68950-14-1; **23,** 68950-15-2; **24,** 68950-16-3; **25,** 68950-17-4; **26,** 68965-22-0; **27** HCl, 68965-87-7; **33** HCl, 68950-18-5; **35,** 68950-19-6; **36,** 68950-20-9; (methylamino)acetone ethylene ketal, 4388-98-1.

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(21) A possible way of rationalizing the formation of **35** involves an attack on **33** by the liberated ethylene glycol to form the hemiketal **37,** dehydration to the enamine, hydrolysis to the ketone, and attack by the side chain oxygen to give **38,** which loses water to yield **35**.