Reactions of 3-Chloro-2*H*-thiete 1,1-Dioxide[1]

Thomas C. Sedergran, Masataka Yokoyama, and Donald C. Dittmer*

Department of Chemistry, Syracuse University, Syracuse, New York 13210

Received December 20, 1983

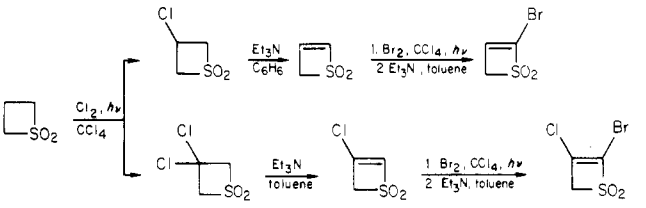
3-Chloro-2*H*-thiete 1,1-dioxide, prepared by dichlorination of thietane 1,1-dioxide followed by dehydrochlorination, reacts with carbanions, amines, alcohols, and thiols to give 3-substituted thietane or 2*H*-thiete 1,1-dioxides. For example, reaction with the anion of dimethyl or diethyl malonate gives 3-[bis(alkoxycarbonyl)methylidene]thietane 1,1-dioxide. 3-Chloro-2*H*-thiete 1,1-dioxide also undergoes Diels–Alder reactions with butadiene and 1,3-diphenylisobenzofuran. 2,3-Dibromothietane 1,1-dioxide, 2,3-dibromo-3-chlorothietane 1,1-dioxide, 2-bromo-2*H*-thiete 1,1-dioxide, and 2-bromo-3-chloro-2*H*-thiete 1,1-dioxide also have been prepared.

The synthesis of functionalized thietane and thiete derivatives would be facilitated if an intermediate possessing the requisite reactivity were readily available. The only commercially obtainable four-membered sulfur heterocyclic compound is thietane.[2] This is our starting material for the synthesis of a variety of 3-substituted thietane and thiete 1,1-dioxides. Previously, 3-substituted thietanes had been prepared by cyclization of appropriately substituted acyclic intermediates, many of which are not readily available.[4] Once a convenient way has been found to introduce groups at the 3-position of the thietane sulfone ring, the introduction of substituents at the 2- (or α) position, via formation of an anion at that location, may be envisioned.[3]

Results and Discussion

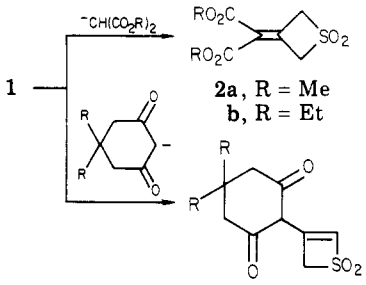
Halogen Derivatives of Thietane and Thiete 1,1-Dioxides. Oxidation of thietane with hydrogen peroxide–acetic acid catalyzed by tungsten(VI) oxide gives the sulfone which may be chlorinated in the presence of light to give either 3-chlorothietane 1,1-dioxide or 3,3-dichlorothietane 1,1-dioxide, depending on conditions. The monochloro derivative also may be converted readily to the dichloro compound. The concentration of thietane 1,1-dioxide must be around 0.3 M and a short reaction time (15 min) must be observed in order to obtain the monochloro sulfone without significant formation of the dichloro sulfone. Bromination of the 3-position with a mixture of bromine and chlorine (BrCl) has been reported previously.[5,6] We have found that this bromination reaction usually gives some of the chloride and that the purification is tedious.

Thiete 1,1-dioxide is obtained by dehydrochlorination of the monochloro sulfone,[7] and 3-chlorothiete 1,1-dioxide, 1, is obtained likewise from the dichloro sulfone. 3-Bromothiete 1,1-dioxide has been prepared similarly.[5] 2-Bromothiete 1,1-dioxide is obtained by bromination of thiete 1,1-dioxide followed by dehydrobromination. 2-Bromo-3-chlorothiete 1,1-dioxide is obtained by bromination of 1 followed by elimination of hydrogen bromide. The halogenation of thietane 1,1-dioxide occurs preferentially at the 3-position, no doubt because of the electron-withdrawing ability of the sulfone group which destabilizes the transition state for removal of a hydrogen atom from the 2-position.[8,9]



1

Additions of Carbanions. Anions of dimethyl and diethyl malonate react with 3-chlorothiete 1,1-dioxide, 1, to give exo methylene compounds **2**. However, the thietes **3** are obtained with 1,3-cyclohexanediones.



2a, R = Me
b, R = Et

3a, R = Me
b, R = H

The addition–elimination process leads to the exo methylene derivatives with malonate probably because of their greater thermodynamic stability due to the conjugation of the carbon–carbon double bond with the two ester carbonyl groups.[10] Formation of an exo methylene double bond in reactions with the anions of the 1,3-cyclohexanediones should also be favored, but as models show, an exo methylene derivative would involve unfavorable steric interactions in which the essential planarity

(1) Acknowledgment is made to the National Institutes of Health (Grant CA 08250) for the partial support of this research.

(2) Aldrich Chemical Co., Catalog 1982–83, No. 18,894-8.

(3) For examples of the reaction of electrophiles with anions of thietane 1,1-dioxides, see: Finlay, J. D.; Smith, D. J. H.; Durst, T. *Synthesis* **1978**, 579. Drozd, V. N.; Sergeichuk, V. V. *J. Org. Chem. USSR* **1977**, *13*, 353. Drozd, V. N.; Sergeichuk, V. V. *Ibid.* **1975**, *11*, 1301. Del Buttero, P.; Maiorana, S. *Synthesis* **1975**, 333. Marino, J. P. *J. Chem. Soc., Chem. Commun.* **1973**, 861.

(4) Etienne, Y.; Soulas, R.; Lumbroso, H. "The Chemistry of Heterocyclic Compounds with Three- and Four-Membered Rings", Part Two; Weissberger, A., Ed.; Interscience: New York, 1964; Chapter V. Sander, M. *Chem. Rev.* **1966**, *66*, 341. Dittmer, D. C.; Sedergran, T. C. "Small Ring Heterocyclic Compounds"; Hassner, A., Ed.; Wiley-Interscience: New York, Vol. 42, Part 3, in press.

(5) Dittmer, D. C.; Nelsen, T. *J. Org. Chem.* **1976**, *41*, 3044.

(6) Lancaster, M.; Smith, D. *Synthesis* **1982**, 582.

(7) Dittmer, D. C.; Christy, M. E. *J. Org. Chem.* **1961**, *26*, 1324.

(8) Chlorination of sulfolane and tetrahydrothiapyran 1,1-dioxide occurs only at the β- and γ-positions: Tabushi, I.; Tamaru, Y.; Yoshida, Z. *Tetrahedron* **1974**, *30*, 1457.

(9) Walling, C. "Free Radicals in Solution"; Wiley: New York, 1957; p 365.

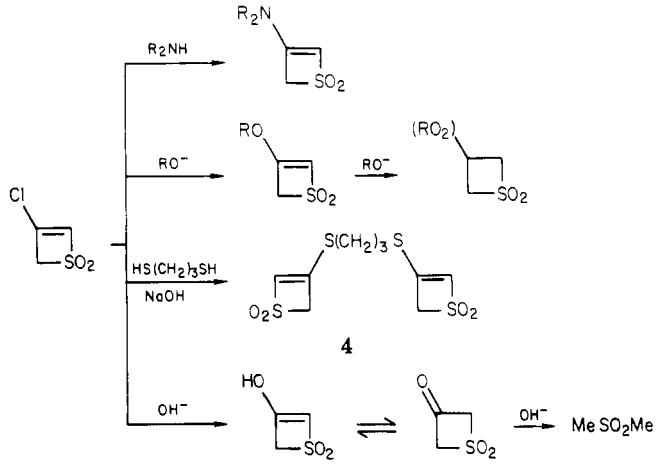
(10) Isomerization of a double bond toward two *gem*-ethoxycarbonyl groups is observed in the addition–elimination reaction of malonate anions with (phenylsulfonyl)ketene dimethyldithioacetal monoxide: Veenstra, G. E.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 202.

0022-3263/84/1949-2408$01.50/0

of the carbon framework about the carbon–carbon double bond results in nonbonding repulsions between the oxygen atoms of the dione and the α-methylene protons of the thietane sulfone ring. Thiete derivatives **3a,b** apparently do not exist as enols since no strong absorption was observed in the OH stretching region of the infrared spectra nor were any OH absorptions seen in the NMR spectra.

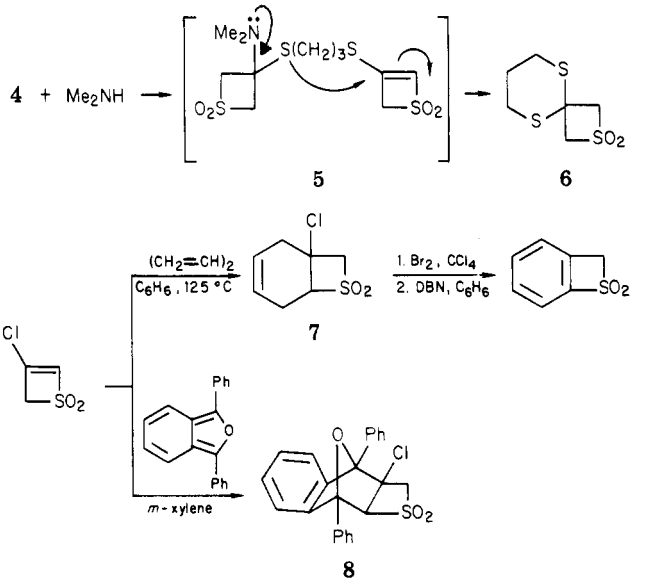
Treatment of thiete 1,1-dioxide with anions of diethyl malonate or ethyl acetoacetate gives normal Michael adducts. The anions of nitroethane[11] and *tert*-butyl *o*-tolyl sulfone[12] previously have been reported to add similarly to thiete 1,1-dioxides. Amines, cyanide, alkoxides, and thiols also are known to add to thiete 1,1-dioxides.[13]

Additions of Amines, Alcohols, and Thiols. The addition–elimination reaction of secondary amines, alkoxides, and thioalkoxides with 3-chlorothiete 1,1-dioxide proceeds well to give 3-substituted thiete derivatives. Some alkoxides react further in a Michael fashion with the initially formed 3-alkoxythiete sulfones to give 3,3-dialkoxythietane 1,1-dioxides. Treatment of 3-chlorothiete 1,1-dioxide with sodium hydroxide resulted in the formation of dimethyl sulfone presumably via the formation of 3-thietanone 1,1-dioxide. The reaction with imidazole requires the presence of a base, e.g., triethylamine, before addition will occur. 3-Aminothiete sulfones previously had been prepared by cycloadditions of sulfenes to various ketene *N,N*-, *N,O*-, or *N,S*-acetals[14] and to ynamines.[15] 3,3-Dialkoxythietane 1,1-dioxides also have been prepared by addition of sulfene to ketene acetals.[16] The ready availability of 1 makes its use in the synthesis of these derivatives an attractive alternative.



Treatment of adduct **4** with dimethylamine gave the dithioketal **6** possibly via the dimethylamino derivative **5**. Compound **6** also was obtained by treatment of 3,3-dibromothietane 1,1-dioxide with 1,3-propanedithiol in aqueous sodium hydroxide.

Diels–Alder Reactions. 1,3-Butadiene reacts with 3-chlorothiete 1,1-dioxide at 125 °C in a sealed tube to give the bicyclic derivative **7**. A similar reaction had been



reported previously for 3-bromothiete 1,1-dioxide.[5] Adduct **7** can be converted to benzothiete 1,1-dioxide in the same way as the butadiene–3–bromothiete 1,1-dioxide adduct. The reaction of 3-chlorothiete 1,1-dioxide with 1,3-diphenylisobenzofuran gives adduct **8**. This diene is known to react with other thiete sulfones.[17]

Experimental Section

Melting points (uncorrected) were taken on a Mel-Temp apparatus. Spectra were taken on the following instruments: IR, Perkin-Elmer 710B; ^{1}H NMR, Varian T-60; ^{13}C NMR, Varian CFT-20. All NMR spectra are referenced to tetramethylsilane. Analyses for elements were done by Micro-Analysis Inc., Wilmington, DE. Thietane was a gift of Dr. John Norell of Phillips Petroleum Company. Tetrahydrofuran (THF) was dried over lithium aluminum hydride. Dimethylformamide (DMF), benzene, and toluene were dried over 4-Å molecular sieves.

Thietane 1,1-Dioxide. The pH of a solution of tungstic acid ($WO_3 \cdot H_2O$; Eastman Kodak, 1.1 g, 0.0044 mol) in distilled water (280 mL) was adjusted to 11.5 by addition of 10% aqueous sodium hydroxide. The white suspension of the catalyst and a mixture of glacial acetic acid (50 mL) and thietane (47.5 g, 0.641 mol) was cooled to 0 °C. Hydrogen peroxide (30%, 189 mL) was added slowly over 2 h. The reaction mixture was stirred for an additional hour, transferred to an evaporating dish, and heated on a steam bath to drive off the water and acetic acid. (Care should be taken in concentrating any mixture in which peroxides may be present. The slow evaporation in a large, open container minimizes the danger of explosion. Rapid concentration on a rotary evaporator is *not* recommended.) The resulting solid was extracted 5 times with chloroform (100-mL portions) and the catalyst was removed by filtration. The combined solutions of product in chloroform were dried ($MgSO_4$), and the solvent was removed to give thietane 1,1-dioxide as a white solid (64 g, 0.60 mol, 94%): mp 75–76 °C (lit.[18] mp 75.5–76 °C).

3-Chlorothietane 1,1-Dioxide. Carbon tetrachloride (325 mL) was added to a three-necked, 500-mL, round-bottomed flask containing thietane 1,1-dioxide (11.0 g, 0.104 mol) and fitted with a mechanical stirrer, a chlorine inlet tube, and a reflux condenser. A good hood is necessary. While a solution of thietane 1,1-dioxide (11.0 g, 0.104 mol) in carbon tetrachloride (325 mL) was irradiated (250-W sunlamp), chlorine gas was bubbled through the solution until a thick white precipitate formed (after about 15 min). The chlorine addition was stopped, the mixture was allowed to cool to room temperature, and the product was collected by filtration.

(11) Coates, J. E.; Abbott, F. S. *J. Org. Chem.* **1977**, *42*, 3506.
(12) Snyder, D. M. *Diss. Abstr. Int.* **1981**, *B42*, 223.
(13) Dittmer, D. C.; Christy, M. E. *J. Am. Chem. Soc.* **1962**, *84*, 399. Paquette, L. A.; Rosen, M. *J. Org. Chem.* **1968**, *33*, 3027. King, J. F.; DeMayo, P.; McIntosh, C. L.; Piers, K.; Smith, D. J. H. *Can. J. Chem.* **1970**, *48*, 3704. Abbott, F. S.; Haya, K. *Ibid.* **1978**, *56*, 71. Dittmer, D. C.; Davis, F. A. *J. Org. Chem.* **1967**, *32*, 3872.
(14) (a) Hasek, R. H.; Meen, R. H.; Martin, J. C. *J. Org. Chem.* **1965**, *30*, 1495. (b) Petukhova, N. P.; Aristova, N. E.; Stepanyants, A. U.; Prilezhaeva, E. N. *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **1976**, *25*, 119.
(15) Truce, W. E.; Bavry, R. H.; Baily, P. S., Jr. *Tetrahedron Lett.* **1968**, 5651.
(16) Truce, W. E.; Norell, J. R. *J. Am. Chem. Soc.* **1963**, *85*, 3231.
(17) Dittmer, D. C.; Takashina, N. *Tetrahedron Lett.* **1964**, 3809. Paquette, L. A.; Freedman, J. P.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 3216.
(18) Grishkevich-Trokhimovskii, E. *J. Russ. Phys. Chem. Soc.* **1916**, *48*, 880; *Chem. Abstr.*, **1917**, *11*, 784.

Recrystallization from chloroform gave white needles (9.0 g, 0.064 mol, 62%): mp 136–137 °C) (lit.[7] mp 136.5–137.5 °C); ^{1}H NMR ($CDCl_3$) δ 4.0–5.0 (m). The ^{13}C NMR spectrum was identical with that reported previously.[19]

3,3-Dichlorothietane 1,1-Dioxide. 3-Chlorothietane 1,1-dioxide (4.0 g, 0.028 mol) in carbon tetrachloride (325 mL) was chlorinated as above except that chlorine was added for 1 h. After the mixture was cooled to room temperature, the white crystalline product was collected by filtration. It was recrystallized from chloroform–hexane (4.0 g, 0.023 mol, 82%): mp 157–158 °C; IR (KBr) 3020, 2950, 1370 (m, SO_2), 1140 (m, SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.0 (s); ^{13}C NMR ($CDCl_3$) δ 85.8, 78.6. Anal. Calcd for $C_3H_4Cl_2O_2S$: C, 20.58; H, 2.30. Found: C, 20.81; H, 2.39.

Alternatively, thietane 1,1-dioxide (5.0 g, 0.047 mol) in carbon tetrachloride (350 mL) can be chlorinated as above. The chlorine addition takes 1–2 h. The product precipitates when the reaction mixture is cooled to room temperature (5.6 g, 0.032 mol, 68%).

3-Chlorothiete 1,1-Dioxide. Triethylamine (4.3 mL) was added dropwise by pipet (10 min) to a solution of 3,3-dichlorothietane 1,1-dioxide (5.03 g, 0.0287 mol) in benzene (189 mL) at 60 °C. The solution was stirred for 2 h at 60 °C and cooled to room temperature. The precipitate of triethylamine hydrochloride was collected by filtration and washed with hot toluene (50 mL). The toluene was removed to give a white solid which was recrystallized from chloroform–hexane (3.23 g, 0.0233 mol, 81%): mp 117–120 °C; IR (KBr) 1540 (m, C=C), 1300 (s, SO_2), 1140 (s, SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.8 (s, 1 H), 4.6 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 143.3, 142.5, 73.6. Anal. Calcd for $C_3H_3ClO_2S$: C, 26.00; H, 2.18. Found: C, 25.67; H, 2.02.

2,3-Dibromothietane 1,1-Dioxide. A solution of thiete 1,1-dioxide (3.6 g, 0.035 mol) and bromine (11.0 g, 0.069 mol) in carbon tetrachloride (50 mL) was refluxed 6 h. The solution was cooled and washed with a saturated aqueous solution of sodium bisulfite (3 × 100 mL). The carbon tetrachloride layer was dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. Recrystallization from methylene chloride–hexane gave a white, crystalline solid (6.2 g, 0.023 mol, 67%): mp 52–54 °C; IR (KBr) 3053 (s), 1320 (s, SO_2), 1140 (s, SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.68 (m, 1 H), 4.56 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 78.6, 75.4, 36.1. Anal. Calcd for $C_3H_4Br_2O_2S$: C, 13.65; H, 1.53. Found: C, 14.00; H, 1.49.

2-Bromothiete 1,1-Dioxide. Triethylamine (2.6 g, 0.026 mol) was added to a solution of 2,3-dibromothietane 1,1-dioxide (6.8 g, 0.026 mol) in toluene (100 mL) and the mixture was stirred for 2 h at 60 °C after which the triethylamine hydrobromide was removed by filtration. Removal of toluene gave a white product which was recrystallized from methylene chloride–pentane (4.6 g, 0.025 mol, 96%): mp 73–76 °C; IR (KBr) 1560 (m, C=C), 1310 (s, SO_2), 1140 (s, SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18 (t, 1 H, J = 2 Hz), 4.55 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 135.0, 127.8, 70.7. Anal. Calcd for $C_3H_3BrO_2S$; C, 19.68; H, 1.65. Found: C, 19.99, H, 1.35.

2,3-Dibromo-3-chlorothietane 1,1-Dioxide. A solution of 3-chlorothiete 1,1-dioxide (0.50 g, 0.0036 mol) and bromine (1.1 g, 0.0069 mol) in carbon tetrachloride (15 mL) was stirred and refluxed 18 h. The mixture was poured into 10% aqueous sodium bisulfite (50 mL), and the carbon tetrachloride layer was separated and dried ($MgSO_4$). Removal of the solvent gave a white solid which was recrystallized from chloroform (0.4 g, 0.001 mol, 28%): mp 92–94 °C; IR (KBr) 1330 (s, SO_2), 1150 (s, SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 83.8, 78.6, 75.1. Anal. Calcd for $C_3H_3Br_2ClO_2S$: C, 12.07; H, 1.01. Found: C, 12.34; H, 0.97.

2-Bromo-3-chlorothiete 1,1-Dioxide. Triethylamine (0.20 g, 0.0020 mol) was added with stirring to a solution of 2,3-dibromo-3-chlorothietane 1,1-dioxide (0.50 g, 0.0017 mol) in toluene (10 mL) at 60 °C. The solution was stirred for 2 h and the triethylamine hydrobromide was removed by filtration. The toluene was removed to give the white product which was recrystallized from methylene chloride–pentane (0.24 g, 0.0011 mol, 66%): mp 60–61 °C; IR (KBr) 1580 (m, C=C), 1320 (s, SO_2), 1160 (s, SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.66 (s); ^{13}C NMR ($CDCl_3$) δ 167.7, 128.1, 76.6. Anal. Calcd for $C_3H_2BrClO_2S$: C, 16.57; H, 0.93. Found: C, 16.57; H, 1.04.

3-[Bis(methoxycarbonyl)methylidene]thietane 1,1-Dioxide (2a). Dimethyl malonate (2.8 g, 0.021 mol) in dry THF (20 mL) was added under nitrogen over 30 min to sodium hydride (0.9 g, 60% oil dispersion, 0.02 mol). 3-Chlorothiete 1,1-dioxide (1.0 g, 0.0072 mol) in dry THF (10 mL) was added over 30 min and the mixture was refluxed 1 h. After the reaction had cooled to room temperature, water (50 mL) was added and the solution extracted with methylene chloride (3 × 50 mL) to remove starting materials. Acidification of the aqueous layer with 5% hydrochloric acid was followed by extraction of the product with methylene chloride (3 × 50 mL). The methylene chloride extracts were dried ($MgSO_4$) and the solvent was removed to give a white, crystalline solid (1.4 g, 0.0060 mol, 83%): mp 126–127 °C; IR (KBr) 1700 (s, CO), 1420 (m), 1280 (s), 1200 (s), 1160 (m), 1120 (m); ^{1}H NMR ($CDCl_3$) δ 5.1 (s, 4 H), 3.82 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 163.1, 140.0, 125.6, 74.5, 52.9. Anal. Calcd for $C_8H_{10}O_6S$: C, 41.02; H, 4.27. Found: C, 41.39; H, 4.31.

3-[Bis(ethoxycarbonyl)methylidene]thietane 1,1-Dioxide (2b). This was prepared as described above from diethyl malonate (1.7 g, 0.011 mol), 3-chlorothiete 1,1-dioxide (0.50 g, 0.0036 mol), and sodium hydride (0.43 g, 60% oil dispersion, 0.011 mol). A clear oil was obtained which crystallized on treatment with pentane (0.70 g, 0.0027 mol, 74%): mp 50–52 °C; IR (KBr) 1700 (s, CO), 1300 (s), 1240 (m), 1120 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.2 (s, 4 H), 4.4 (q, 4 H), 1.35 (t, 6 H); ^{13}C NMR ($CDCl_3$) δ 162.7, 138.6, 126.3, 74.4, 62.1, 14.1. An analytically pure sample was obtained by recrystallization from chloroform–hexane. Anal. Calcd for $C_{10}H_{14}O_6S$: C, 45.80; H, 5.34. Found: C, 45.54; H, 5.33.

3-[1-(4,4-Dimethyl-2,6-dioxocyclohexyl)]thiete 1,1-Dioxide (3a). 3-Chlorothiete 1,1-dioxide (0.25 g, 0.0018 mol), 5,5-dimethyl-1,3-cyclohexanedione (0.25 g, 0.0018 mol), and potassium carbonate (0.25 g, 0.0018 mol) in DMF (10 mL) were stirred overnight at room temperature. Water (20 mL) was added and the solution was extracted with methylene chloride (3 × 50 mL). The extracts were dried ($MgSO_4$) and the solvents removed under reduced pressure to give a tan solid which was recrystallized from chloroform–pentane to give white crystals (0.21 g, 0.00087 mol, 48%): mp 115–117 °C; IR (KBr) 1680 (s, br, CO), 1595 (s, br, C=C), 1370 (s, CH_3), 1297–1310 (s, SO_2), 1118 (s, br, SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.07 (s, 1 H), 5.86 (s, 1 H), 4.59 (s, 2 H), 2.36 (d, 4 H), 1.10 (s, 6 H); ^{13}C NMR ($CDCl_3$) 198.0, 125.4, 116.4, 72.6, 54.4, 45.2, 36.7, 31.9. Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.54; H, 5.82; S, 13.22. Found: C, 53.90; H, 5.73; S, 13.10.

3-[1-(2,6-Dioxocyclohexyl)]thiete 1,1-Dioxide (3b). 3-Chlorothiete 1,1-dioxide (0.25 g, 0.0018 mol), 1,3-cyclohexanedione (0.20 g, 0.0018 mol), and potassium carbonate (0.25 g, 0.0018 mol) in DMF (10 mL) were allowed to react and the mixture worked up as described above. A white solid was obtained which was recrystallized from chloroform–hexane to give white needles (0.20 g, 0.00093 mol, 52%): mp 154–155 °C; IR (KBr) 1670 (s, br, CO), 1580–1590 (s, br, C=C), 1285–1310 (s, br, SO_2), 1105 (s, br, SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.00 (s, 1 H), 5.76 (s, 1 H), 4.56 (s, 2 H), 2.65–1.95 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 180.3, 121.3, 113.5, 68.8, 46.1, 36.4, 27.6. Anal. Calcd for $C_9H_{10}O_4S$: C, 50.45; H, 4.71, S, 14.97. Found: C, 50.26; H, 4.64; S, 14.77.

3-[Bis(ethoxycarbonyl)methyl]thietane 1,1-Dioxide. Diethyl malonate (2.0 g, 0.012 mol) was added to a solution of sodium ethoxide, prepared from sodium (0.06 g, 0.003 mol) and absolute ethanol (25 mL), and the mixture was stirred for 5 min, after which thiete 1,1-dioxide[7] (1.0 g, 0.0096 mol) in absolute ethanol (10 mL) was added over 10 min. The solution was refluxed for 3 h and cooled, and water (50 mL) was added. Hydrochloric acid (10%) was added to neutralize the basic solution. Extraction with methylene chloride (3 × 50 mL), drying ($MgSO_4$), and removal of the methylene chloride under vacuum gave a white solid which was recrystallized from chloroform–hexane (1.1 g, 0.0042 mol, 44%): mp 74–76 °C; IR (KBr) 1750 (s), 1300 (s), 1210 (s), 1130 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.5–3.0 (m, 10 H), 1.4 (t, 6 H). Anal. Calcd for $C_{10}H_{16}O_6S$: 45.44; H, 6.10. Found: C, 45.22; H, 5.90.

3-[[1-Acetyl-1-(ethoxycarbonyl)]methyl]thietane 1,1-Dioxide. Ethyl acetoacetate (1.6 g, 0.012 mol) and thiete 1,1-dioxide (1.0 g, 0.0096 mol) was refluxed with sodium ethoxide as described above. The workup was the same except that more methylene chloride (3 × 100 mL) was used in the extraction of the neutralized aqueous solution. Removal of solvent gave an oil which solidified

(19) Dittmer, D. C.; Patwardhan, B. H.; Bartholomew, J. T. *Org. Magn. Reson.* **1982**, *18*, 82.

on treatment with pentane. Recrystallization from chloroform–pentane gave a white solid (1.1 g, 0.0047 mol, 49%): mp 85–87 °C; IR (KBr) 1710 (s), 1320 (s), 1290 (s), 1270 (s), 1220 (s), 1140 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.6–3.0 (m, 8 H), 2.3 (s, 3 H), 1.3 (t, 3 H). Anal. Calcd for $C_9H_{14}O_5S$: C, 46.13; H, 6.02. Found: C, 46.27; H, 5.89.

3-(Dimethylamino)thiete 1,1-Dioxide. 3-Chlorothiete 1,1-dioxide (0.50 g, 0.0036 mol) and 40% aqueous dimethylamine (0.81 g, 0.0072 mol) in benzene (10 mL) were refluxed for 2 h. The two layers were separated, and the aqueous layer was extracted with benzene (3 × 20 mL). The benzene extracts were dried ($MgSO_4$), and the solvent was removed to give white needles (0.35 g, 0.0024 mol, 66%): mp 120–122 °C (lit.[14a] mp 120–123 °C); ^1H NMR ($CDCl_3$) δ 5.3 (s, 1 H), 4.4 (s, 2 H), 3.0 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 150.1, 103.1, 66.6, 39.8.

In a similar manner, the following 3-(dialkylamino)thiete 1,1-dioxides were prepared.

3-(Diethylamino)thiete 1,1-dioxide: 95%; mp 75–76 °C (lit.[14b] mp 76–77.5 °C); ^1H NMR ($CDCl_3$) δ 5.3 (s, 1 H), 4.4 (s, 2 H), 3.3 (q, 4 H, J = 7 Hz), 1.2 (t, 6 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 148.5, 102.7, 66.4, 45.1, 13.1.

3-Piperidinothiete 1,1-dioxide: 67%; mp 142–143 °C (lit.[14a,20] mp 142–143.5 °C); ^{13}C NMR ($CDCl_3$) δ 103.4, 66.2, 48.4, 25.2, 23.1.

3-Morpholinothiete 1,1-dioxide: 59%; mp 138–139.5 °C (lit.[14a] mp 140.5–141 °C); ^{13}C NMR ($CDCl_3$) δ 148.7, 103.4, 77.1, 66.2, 47.1.

3-(N-Methylanilino)thiete 1,1-dioxide: 56%; mp 99–100 °C (lit.[14a] mp 101.5–103 °C); ^{13}C NMR ($CDCl_3$) δ 130.0, 129.8, 127.4, 124.3, 107.8, 67.5, 40.5.

3-(1-Imidazolyl)thiete 1,1-Dioxide. Imidazole (0.49 g, 0.0072 mol) and triethylamine (1.1 mL) in methylene chloride (25 mL) were stirred 10 min and 3-chlorothiete 1,1-dioxide (1.0 g, 0.0072 mol) was added. The reaction was stirred overnight, water (50 mL) was added, and the methylene chloride layer was separated and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a white solid which was recrystallized from methylene chloride–hexane (0.96 g, 0.0056 mol, 78%): mp 228–230 °C; IR (KBr) 1640 (s), 1560 (m), 1280 (s), 1235 (s), 1140 (s), 1100 (s); ^1H NMR (Me_2SO-d_6) δ 7.93 (s, 1 H, N=CHN), 7.52 (s, 1 H, SO_2CH=C), 7.00 (br s, 2 H, NCH=CHN), 4.97 (s, 2 H, CH_2); ^{13}C NMR (Me_2SO-d_6) δ 140.0, 137.7, 131.3, 125.5, 118.3, 68.4. Anal. Calcd for $C_6H_6N_2O_2S$: C, 42.35; H, 3.55; N, 16.46; S, 18.84. Found: C, 42.21; H, 3.61, N, 16.48; S, 18.91.

3-n-Butoxythiete 1,1-Dioxide. Sodium (0.080 g, 0.0035 mol) was added to n-butyl alcohol (20 mL), and when the sodium had completely reacted, 3-chlorothiete 1,1-dioxide (0.50 g, 0.0036 mol) in n-butyl alcohol (10 mL) was added. The mixture was refluxed for 2 h, cooled, and neutralized with 5% aqueous hydrochloric acid. Extraction with methylene chloride (3 × 50 mL), drying ($MgSO_4$), and removal of solvent gave the white, crystalline product which was recrystallized from chloroform–hexane (0.43 g, 0.0024 mol, 70%): mp 50–52 °C; IR (KBr) 1600 (s, C=C), 1300 (s, SO_2), 1220 (s), 1100 (s), cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.66 (s, 1 H), 4.45 (s, 2 H), 4.1 (t, 2 H), 2.1–0.8 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 160.6, 114.0, 73.5, 68.3, 30.3, 18.4, 13.6. Anal. Calcd for $C_7H_{12}O_3S$: C, 47.70; H, 6.86. Found: C, 47.64; H, 6.89.

In a similar manner the following two 3-alkoxythiete sulfones have been prepared.

3-Isobutoxythiete 1,1-dioxide: 56%; mp 60–62 °C; IR (KBr) 1600 (s, C=C), 1300 (s, SO_2), 1210 (s), 1100 (s), 990 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.66 (s, 1 H), 4.46 (s, 2 H), 3.79 (d, 2 H), 2.10 (m, 1 H), 1.03 (d, 6 H). Anal. Calcd for $C_7H_{12}O_3S$: C, 47.70; H, 6.86. Found: C, 47.55; H, 6.83.

3-Isopropoxythiete 1,1-dioxide: 61%; mp 56–58 °C; IR (KBr) 1590 (m, C=C), 1280 (s, SO_2), 1210 (s), 1140 (m), 1080 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.59 (s, 1 H) 4.36 (m, 3 H), 1.36 (d, 6 H); ^{13}C NMR ($CDCl_3$) δ 164.0, 118.1, 78.0, 68.6, 21.3. Anal. Calcd for $C_6H_{10}O_3S$: C, 44.42; H, 6.21. Found: C, 44.26, H, 6.25.

3-Phenoxythiete 1,1-Dioxide. 3-Chlorothiete 1,1-dioxide (0.50 g, 0.0036 mol) in dry THF (5 mL) was added to a solution of sodium phenoxide, prepared from phenol (10 mL) and sodium (0.09 g, 0.004 mol), under nitrogen. The mixture was stirred overnight. Water (50 mL) was added and the mixture was extracted with methylene chloride (3 × 50 mL). The combined methylene chloride extracts were washed with 5% aqueous sodium hydroxide (100 mL) and dried ($MgSO_4$), and the solvent was removed to give a yellow solid which was recrystallized from methylene chloride to give white needles (0.32 g, 0.0016 mol, 45%): mp 120–122 °C; IR (KBr) 1610 (s), 1580 (s), 1320 (s), 1190 (s), 1160 (s), 1130 (s), 1090 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H), 5.53 (s, 1 H), 4.59 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.7, 153.9, 130.4, 127.2, 119.8, 117.3, 68.0. Anal. Calcd for $C_9H_8O_3S$; C, 55.09, H, 4.11; S, 16.34. Found: C, 54.83, H, 4.38; S, 16.30.

3,3-Di-n-propoxythietane 1,1-Dioxide. Sodium (0.080 g, 0.0035 mol) was dissolved in n-propyl alcohol (20 mL) and 3-chlorothiete 1,1-dioxide (0.50 g, 0.0036 mol) was added. The mixture was refluxed for 2 h. Water (75 mL) was added, and the solution was neutralized with 5% hydrochloric acid and extracted with ether (3 × 100 mL). The combined ether extracts were dried ($MgSO_4$) and the ether was removed under vacuum to give a clear oil which solidified on scratching. The product was recrystallized from hexane as white, cubic crystals (0.51 g, 0.0023 mol, 66%): mp 48–49 °C; IR (KBr) 1300 (s), 1240 (s), 1080 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.19, (s, 4 H), 3.36 (t, 4 H), 1.59 (m, 4 H), 0.96 (t, 6 H); ^{13}C NMR ($CDCl_3$) δ 90.3, 72.6, 65.1, 22.6, 10.7. Anal. Calcd for $C_9H_{18}O_4S$: C, 48.62; H, 8.16. Found: C, 48.69, H, 8.37.

3,3-Bis(allyloxy)thietane 1,1-Dioxide. 3-Chlorothiete 1,1-dioxide (1.0 g, 0.0072 mol) was added under nitrogen to a solution of sodium allyloxide, prepared from sodium (0.33 g, 0.014 mol) and allyl alcohol (10 mL). The reaction was done as described for the diisopropoxy derivative. A colorless oil was obtained which solidified on standing. The solid was recrystallized from ether to give white plates (1.14 g, 0.0052 mol, 72%): mp 45.5–46 °C; IR (KBr) 1640 (w), 1320 (s), 1230 (s), 1200 (s), 1100 (s), 1080 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.20–5.07 (m, 6 H), 4.23 (s, 4 H), 4.92–4.04 (m, 4 H); ^{13}C NMR ($CDCl_3$) 132.8, 117.7, 90.9, 72.8, 64.8. Anal. Calcd for $C_9H_{14}O_4S$: C, 49.52; H, 6.47; S, 14.69. Found: C, 49.36; H, 6.49; S, 14.65.

3,3-Diethoxythietane 1,1-Dioxide. This was prepared from 3-chlorothiete 1,1-dioxide (1.0 g, 0.0072 mol) and 3 equiv (0.021 mol) of sodium ethoxide by the method described above. A colorless oil was obtained which solidified to a white crystalline product (0.85 g, 0.0044 mol, 69%): mp 44–45 °C (lit.[21] mp 49–50 °C); IR (KBr) 1380 (m), 1320 (s), 1225 (s), 1200 (m), 1060 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.3 (s, 4 H), 3.6 (q, 4 H), 1.4 (t, 6 H); ^{13}C NMR ($CDCl_3$) δ 90.3, 72.6, 59.0, 14.8.

3,3-Dimethoxythietane 1,1-Dioxide. This was prepared from 3-chlorothiete 1,1-dioxide (0.50 g, 0.0036 mol) and 1 equiv of sodium methoxide by the method described above. The white, crystalline product was recrystallized from chloroform–hexane (0.31 g, 0.0019 mol, 52%): mp 160–162 °C (lit.[22] mp 159.5–160.5 °C); IR (KBr) 1390 (m), 1240 (s), 1170 (s), 1080 (s), cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.20 (s, 4 H), 3.30 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 91.3, 71.9, 50.7.

1,5-Bis[1-(3,3-dioxo-3-thiacyclobutenyl)]-1,5-dithiapentane (4). A mixture of 3-bromothiete 1,1-dioxide[5] (10 g, 0.055 mol), 1,3-propanedithiol (3.0 g, 0.028 mol), and aqueous sodium hydroxide (0.16 g, 3 mL) in THF (250 mL) was refluxed for 2 h. The solvent was removed on a rotary evaporator, and the product was recrystallized from acetone–pentane to give white plates (8.0 g, 0.026 mol, 47%): mp 156–157 °C; IR (KBr) 1530 (s), 1325 (s), 1300 (s), 1220 (s), 1160 (s), 1140 (s) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.08 (s, 2 H), 4.73 (s, 4 H), 3.07 (t, 4 H), 2.07 (m, 4 H); UV (EtOH) λ_{max} 249 (ε 17 100) nm; M_r (Rast, camphor) calcd 312, found 314. Anal. Calcd for $C_9H_{12}O_4S_4$: C, 34.59; H, 3.87. Found: C, 34.42; H, 3.90. The product also was obtained in 27% yield from 3-chlorothiete 1,1-dioxide.

3-Thietanone 1,1-Dioxide Trimethylene Dithioketal (6). From 3,3-Dibromothietane 1,1-Dioxide. A mixture of 3,3-dibromothietane 1,1-dioxide[5] (0.70 g, 0.0027 mol), 1,3-propanedithiol (0.31 g, 0.0028 mol), and aqueous sodium hydroxide (0.227 g, 4 mL) in THF (25 mL) was refluxed for 1.5 h. The THF was removed to give a yellow oil which solidified on addition of ethanol. Recrystallization from ethanol gave white plates (0.55 g, 0.0026 mol, 97%): mp 134–135 °C; IR (KBr) 1380 (s), 1320 (s), 1220 (s),

(20) Opitz, G.; Schempp, H. *Liebigs Ann. Chem.* **1965**, *684*, 103.

(21) Truce, W. E.; Breiter, J. J.; Abraham, D. J.; Norell, J. R. *J. Am. Chem. Soc.* **1962**, *84*, 3030.

(22) Truce, W. E.; Abraham, D. J.; Son, P. *J. Org. Chem.* **1967**, *32*, 990.

1140 (s) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.65 (s, 4 H), 3.00 (t, 4 H), 1.90 (m, 2 H); EI-MS (70 eV) m/e (rel intensity), 210 (39), 132 (100); UV (EtOH) λ_{max} 212 (ϵ 1280), 237 (ϵ 1500) nm. Anal. Calcd for $C_6H_{10}O_2S_3$: C, 34.26; H, 4.79. Found: C, 34.33; H, 4.85.

From 4 and Dimethylamine. Dimethylamine gas (2 bubbles/s) was passed through a stirred solution of **4** (4.0 g, 0.013 mol) in THF (250 mL) at 35 °C. Stirring was continued an additional 10 h at room temperature. The THF was removed to give a yellow oil which solidified to a white solid on standing at room temperature. It was washed with cold ethanol (100 mL). Recrystallization from ethanol gave white plates (1.2 g, 0.0057 mol, 44%): mp 139–140 °C; mmp with product from 3,3-dibromothietane 1,1-dioxide 136–138 °C. The infrared and ^1H NMR spectra were identical with that product.

Desulfurization of 6. A mixture of **6** (0.50 g, 0.0028 mol) and Raney nickel[23] (20 g) in ethanol (200 mL) was refluxed for 20 h. The nickel was removed by filtration, and the solution was concentrated to give a white product which was recrystallized from carbon tetrachloride to give white prisms of thietane 1,1-dioxide (0.15 g, 0.0014 mol, 50%): mp 75–76 °C (lit.[18] mp 75.5–76 °C). Its IR and ^1H NMR spectra were identical with those of an authentic sample.

Reaction of 3-Chlorothiete 1,1-Dioxide with Sodium Hydroxide. 3-Chlorothiete 1,1-dioxide (0.50 g, 0.0036 mol) was added to aqueous sodium hydroxide (0.28 g, 15 mL), and the mixture was heated for 10 min until the sulfone dissolved. The solution was cooled, acidified to pH 1 with 10% hydrochloric acid, and extracted with methylene chloride (3 × 50 mL). The methylene chloride solution was dried ($MgSO_4$) and the solvent was removed to give dimethyl sulfone (0.23 g, 0.0015 mol, 68%): mp 105–107 °C (lit.[24] mp 109 °C). Infrared and ^1H NMR spectra were identical with those reported previously.[25]

1-Chloro-7-thiabicyclo[4.2.0]-3-octene 7,7-Dioxide (7). 1,3-Butadiene (10 mL) was added to a solution of 3-chlorothiete 1,1-dioxide (4.0 g, 0.029 mol) and hydroquinone (0.75 g) in benzene (10 mL) in a Carius tube cooled in liquid nitrogen. The tube was sealed under vacuum at liquid nitrogen temperature and heated at 125 °C for 4 days. The tube was opened, and the benzene was removed to give a residue which was dissolved in methanol (50 mL). This solution was filtered and the methanol removed to give a white solid which was recrystallized from chloroform–hexane to give white crystals (2.2 g, 0.017 mol, 59%): mp 81–82 °C; ^1H NMR ($CDCl_3$) δ 6.10 (m, 2 H), 4.7–4.3 (m, 3 H), 2.7 (m, 4 H). The product was treated with bromine (2.6 g, 0.016 mol) in refluxing carbon tetrachloride (35 mL) for 1 h. The solvent was removed and the residue was dissolved in benzene (50 mL). Diazabicyclo[4.3.0]non-5-ene (4.1 g, 0.033 mol) was added, and the mixture was refluxed for 1 h. The solution was cooled and washed with aqueous 10% hydrochloric acid (3 × 10 mL). The benzene layer was dried ($MgSO_4$), and the benzene was removed to give a yellow oil. Pentane was added to give benzothiete 1,1-dioxide as a yellow solid (1.3 g, 0.0084 mol, 50%): mp 124–127 °C (lit.[5] mp 126–128 °C). Spectroscopic properties were identical with those of an authentic sample.

2a-Chloro-3,8-oxy-3,8-diphenyl-2a,3,8,8a-tetrahydro-2*H*-naphtho[2,3-*b*]thiete 1,1-Dioxide (8). A solution of 3-chlorothiete 1,1-dioxide (1.0 g, 0.0072 mol) and 1,3-diphenylisobenzofuran (2.1 g, 0.0073 mol) in *m*-xylene (10 mL) was refluxed for 24 h. The product precipitates on cooling the mixture to room temperature. It was recrystallized from chloroform (1.04 g, 0.0025 mol, 35%): mp 223–225 °C; IR (KBr) 1330 (s), 1140 (s); ^1H NMR ($CDCl_3$) δ 8.26–6.43 (m, 14 H), 5.10 (s, 1 H), 4.23 (s, 2 H). Anal. Calcd for $C_{23}H_{17}ClO_3S$: C, 67.56; H, 4.19. Found: C, 67.67; H, 4.13.

Registry No. 1, 90344-86-8; **2a**, 90344-91-5; **2b**, 90344-92-6; **3a**, 90344-93-7; **3b**, 90344-94-8; **4**, 90345-03-2; **6**, 85069-70-1; **7**, 90345-04-3; **8**, 90367-67-2; $CH_2(CO_2Me)_2$, 108-59-8; $CH_2(CO_2Et)_2$, 105-53-3; Me_2NH, 124-40-3; Et_2NH, 109-89-7; PhNHMe, 100-61-8; $HS(CH_2)_3SH$, 109-80-8; $MeSO_2Me$, 67-71-0; $(CH_2{=}CH)_2$, 106-99-0; thietane, 287-27-4; thietane 1,1-dioxide, 5687-92-3; 3-chlorothietane 1,1-dioxide, 15953-83-0; 3,3-dichlorothietane 1,1-dioxide, 90344-85-7; 3,3-dibromothietane 1,1-dioxide, 59463-73-9; 2,3-dibromothietane 1,1-dioxide, 90344-87-9; 2-bromothiete 1,1-dioxide, 90344-88-0; 3-bromothiete 1,1-dioxide, 59463-74-0; 2,3-dibromo-3-chlorothietane 1,1-dioxide, 90344-89-1; 2-bromo-3-chlorothiete 1,1-dioxide, 90344-90-4; 5,5-dimethyl-1,3-cyclohexanedione, 126-81-8; 1,3-cyclohexanedione, 504-02-9; thiete 1,1-dioxide, 7285-32-7; 3-[bis(ethoxycarbonyl)methyl]thietane 1,1-dioxide, 82299-32-9; ethyl acetoacetate, 141-97-9; 3-[[1-acetyl-1-(ethoxycarbonyl)]-methyl]thietane 1,1-dioxide, 90344-95-9; 3-(dimethylamino)thiete 1,1-dioxide, 1599-35-5; 3-(diethylamino)thiete 1,1-dioxide, 59514-12-4; 3-piperidinothiete 1,1-dioxide, 1623-62-7; 3-morpholinothiete 1,1-dioxide, 1599-38-8; 3-(*N*-methylanilino)thiete 1,1-dioxide, 1599-21-9; 3-(1-imidazolyl)thiete 1,1-dioxide, 90344-96-0; piperidine, 110-89-4; morpholine, 110-91-8; imidazole, 288-32-4; 3-*n*-butoxythiete 1,1-dioxide, 90344-97-1; 3-isobutoxythiete 1,1-dioxide, 90344-98-2; 3-isopropoxythiete 1,1-dioxide, 90344-99-3; 3-phenoxythiete 1,1-dioxide, 90345-00-9; 3,3-di-*n*-propoxythietane 1,1-dioxide, 90345-01-0; 3,3-bis(allyloxy)thietane 1,1-dioxide, 90345-02-1; 3,3-diethoxythietane 1,1-dioxide, 18487-59-7; 3,3-dimethoxythietane 1,1-dioxide, 10099-05-5; *n*-butyl alcohol, 71-36-3; isobutyl alcohol, 78-83-1; isopropyl alcohol, 67-63-0; phenol, 108-95-2; *n*-propyl alcohol, 71-23-8; allyl alcohol, 107-18-6; ethanol, 64-17-5; methanol, 67-56-1; benzothiete 1,1-dioxide, 16065-50-2; 1,3-diphenylisobenzofuran, 5471-63-6.

(23) Mozingo, R. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 181.
(24) Baumann, E.; Walter, G. *Ber.* **1893**, *26*, 1131.
(25) Pouchert, C. J.; Campbell, J. R. "The Aldrich Library of NMR Spectra"; Aldrich Chemical Co., Inc., 1974; Vol. 10, p 2C. Pouchert, C. J. "The Aldrich Library of Infrared Spectra", 2nd ed.; Aldrich Chemical Co., 1975; p 470A.

General Synthesis of Phenanthroindolizidine, Phenanthroquinolizidine, and Related Alkaloids: Preparation of (±)-Tylophorine, (±)-Cryptopleurine, (±)-Septicine, and (±)-Julandine[1]

Hideo Iida, Yohya Watanabe, Masao Tanaka, and Chihiro Kibayashi*

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Received October 14, 1983

A general synthetic route to the pentacyclic phenanthro class and related indolizidine and quinolizidine alkaloids via β-amino ketone intermediates is reported. The synthesis of tylophorine, cryptopleurine, septicine, and julandine, in racemic forms, has been described. Synthetic steps in the preparations of these alkaloids involve 1,3-dipolar cycloadditions of the cyclic nitrones as a common feature followed by crucial ring closures by aldol reactions and photolyses.

There are biogenetic relationships between the phenanthroindolizidine and phenanthroquinolizidine groups of alkaloids, and they are characterized by their unique pentacyclic structure as well as interesting biological

0022-3263/84/1949-2412$01.50/0